Novel Synthetic Routes to 8-Vinyl Chlorophyll Derivatives

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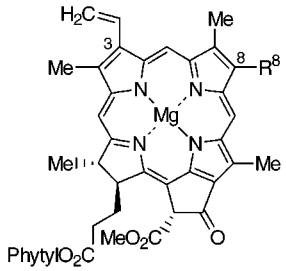
New methodology was developed toward the synthesis of 8-de-ethyl-8-vinylchlorophyll-a **1**. Such 8-de-ethyl-8-vinyl derivatives of the green plant pigment chlorophyll-a **2** have been proposed to be intermediates during biosynthesis of chlorophylls and bacteriochlorophylls. Transformation of the 8-ethyl group to an 8-vinyl group was studied on derivatives (e.g. **5**) of chlorin-e_6 trimethyl ester **9**. The reported methodology involves regioselective osmylation on ring-B, followed by dehydration of the resulting 7,8-diol (e.g. **7**). Based on a model synthesis, three partial synthetic approaches starting from **2** have been developed, using different protective groups for the 3-vinyl group. Several 8-de-ethyl-8-vinyl derivatives of **9** (e.g. **8** and its ^{13}C-labeled analogue **22**) have been synthesized. A new, mild recyclization method for fabrication of the isocyclic ring-E in chlorophylls was discovered which permits conversion of 8-de-ethyl-8-vinylchlorin-e_6 analogues **6** and **8** into the corresponding 8-de-ethyl-8-vinylpheophorbides **10** and **11**. A change from vinyl to ethyl at the 3-position in chlorophylls causes a hypsochromic shift of 10 nm or more in the optical spectrum, whereas the identity of the 8-substituent (ethyl or vinyl) appears not to affect the wavelength of the band at about 660 nm. Hence, transformation from 8-vinyl to 8-ethyl during chloroplast biogenesis is a step which does not affect the light absorption/harvesting properties of the final isolated chlorophyll chromophores.

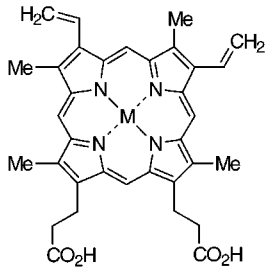
Introduction

Derivatives (e.g. **1**) of the green plant pigment chlorophyll-a **2**, bearing a vinyl instead of an ethyl group at position-8, have recently been found to be intermediates in chloroplast biogenesis in plants,[1,2] bacteria,[3] and marine organisms.[4,5] All biosynthetic transformations, starting from protoporphyrin-IX **3** (which is also a biosynthetic precursor of the red blood pigment heme **4**), are carried out on either the mono- or the divinyl substrates. Due to this remarkable biosynthetic heterogeneity[2b] in which both the 8-ethyl and the 8-vinyl derivatives of intermediates coexist in any single biosynthetic step, 8-de-ethyl-8-vinylchlorophyll-a **1** and its precursors have become valuable synthetic targets due to the need for authentic samples of divinyl derivatives.

We recently transformed mesochlorin-e_6 trimethyl ester **5**, our model compound for the divinyl synthetic approach, to its 8-de-ethyl-8-vinyl derivative **6**, in two steps.[6] Compound **5** is readily available[7] from chlorophyll-a **2** found in *Spirulina pacifica* alga.[8] The reported synthetic methodology to transform the 8-ethyl group into an 8-vinyl group involves regioselective[9] bis-hydroxylation[10,11] of **5** on ring B, followed by dehydration of the resulting 7,8-diol **7**.[12−14] Synthesis of 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **8**, which, based on Woodward's



1: R^8 = CH=CH_2
2: R^8 = Et



3: M = 2H
4: M = Fe

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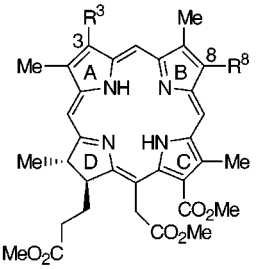
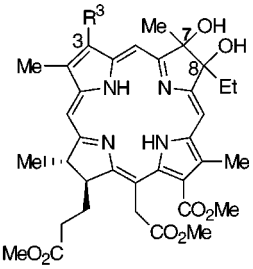
synthesis,[15] would be the key intermediate in any approach to 8-vinyl biosynthetic precursors of **2**, was expected to be more difficult. Before regioselective osmylation of the C7−C8 double bond in ring-B, the more reactive 3-vinyl group of the starting material, chlorin-e_6 trimethyl ester **9**, must be protected. Different vinyl-protection methods were tested,[6] leading to a group of novel 8-de-ethyl-8-vinylchlorin-e_6 derivatives which would be valuable as synthetic precursors for intermediates during chloroplast biogenesis.

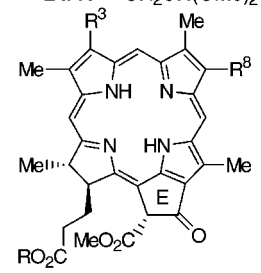
In this paper we introduce new protection/deprotection methodology leading to three approaches from chlorophyll-a **2** to derivative **8**. We also report the first syntheses of 8-de-ethyl-8-vinyl derivatives **10** and **11** of the pheophorbide-a series, which are themselves biosynthetic precursors of chlorophylls and bacteriochlorophylls during chloroplast biogenesis.





5: R^3,R^8 = Et
6: R^3 = Et, R^8 = CH=CH_2
8: R^3,R^8 = CH=CH_2
9: R^3 = CH=CH_2, R^8 = Et
12: R^3 = CH_2CH_2OH , R^8 = Et
13: R^3 = CH_2CH_2Cl, R^8 = Et
15: R^3 = CH_2CH_2Cl, R^8 = CH=CH_2
16: R^3 = CH(OH)CH_2OH, R^8 = CH=CH_2
17: R^3 = CHO, R^8 = Et
19: R^3 = $CH(OMe)_2$, R^8 = Et
21: R^3 = CHO, R^8 = CH=CH_2
22: R^3 = CH=$^{13}CH_2$, R^8 = CH=CH_2
23: R^3 = $CH_2CH(OMe)_2$, R^8 = Et
25: R^3 = $CH_2CH(OMe)_2$, R^8 = CH=CH_2
26: R^3 = CH_2CH_2OH, R^8 = CH=CH_2
27: R^3 = $CH_2CH_2SeC_6H_4$(o-NO_2), R^8 = CH=CH_2

7: R^3 = Et
14: R^3 = CH_2CH_2Cl
18: R^3 = CHO
20: R^3 = $CH(OMe)_2$
24: R^3 = $CH_2CH(OMe)_2$

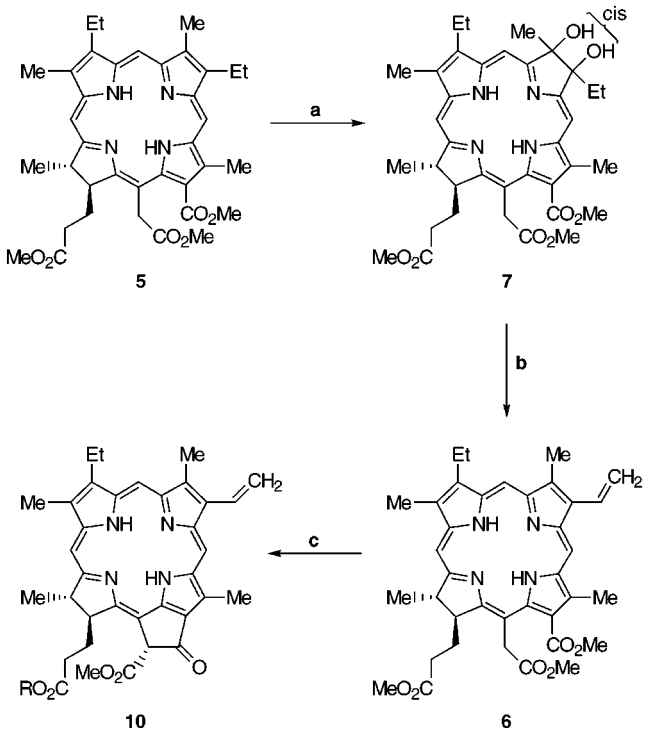


10: R = Me, R^3 = Et, R^8 = CH=CH_2
11: R = Me, R^3,R^8 = CH=CH_2
28: R = H, R^3,R^8 = CH=CH_2
29: R = Me, R^3,R^8 = Et
30: R = Me, R^3 = CH=CH_2, R^8 = Et

Results and Discussion

Model Synthesis. To achieve the desired regioselective attack of OsO_4 at the C7−C8 double bond, our starting material **9**, obtained in two steps from *Spirulina pacifica* alga,[8,16] was converted into **5** by catalytic hydrogenation with H_2 over Pd/C. This model compound, mesochlorin-e_6 trimethyl ester **5** was then converted into its 7,8-diol **7** with OsO_4/pyridine complex in THF and subsequent reduction with $NaHSO_3$. Dehydration in hot toluene containing pyridinium *p*-toluenesulfonate (PPTs) provided the 3-devinyl-3-ethyl-8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **6**, a constitutional isomer of **9**, in 60% yield (40% overall).

Scheme 1



Reagents: a, OsO_4 then $NaHSO_3$; b, PPTs, Δ; c, PPh_3, $NaN(TMS)_2$

Mild, anaerobic conditions for recyclization of ring-E are necessary in order to obtain the 8-vinyl derivatives of the pheophorbide series, e.g. **11**. Since traces of oxygen in combination with strong bases lead to undesired side products,[17] we developed a new cyclization method using triphenylphosphine as an antioxidant and sodium bis-(trimethylsilyl)amide as the base. The first methyl 3-devinyl-3-ethyl-8-de-ethyl-8-vinylpheophorbide **10** was obtained in 66% yield (Scheme 1).

Reversible Protection of the Vinyl Group. (a) Using the 2-Chloroethyl Substituent. The 2-chloroethyl substituent has been used successfully as a vinyl protecting group in a number of our syntheses.[17,18] Thus, we converted **9** into its (2-hydroxyethyl) derivative **12** using our standard procedure.[19] Conversion into the 3-(2-chloroethyl)-3-devinylchlorin-e_6 trimethyl ester **13** in 80% yield was done using trichloroacetonitrile/triphenylphosphine complex (Scheme 2).[20] This method provides better yields than the typical $SOCl_2$/DMF method in preparing **13**.[21] Compound **13** showed the same regioselectivity as **5** under osmylation conditions, yielding the 7,8-diol **14**

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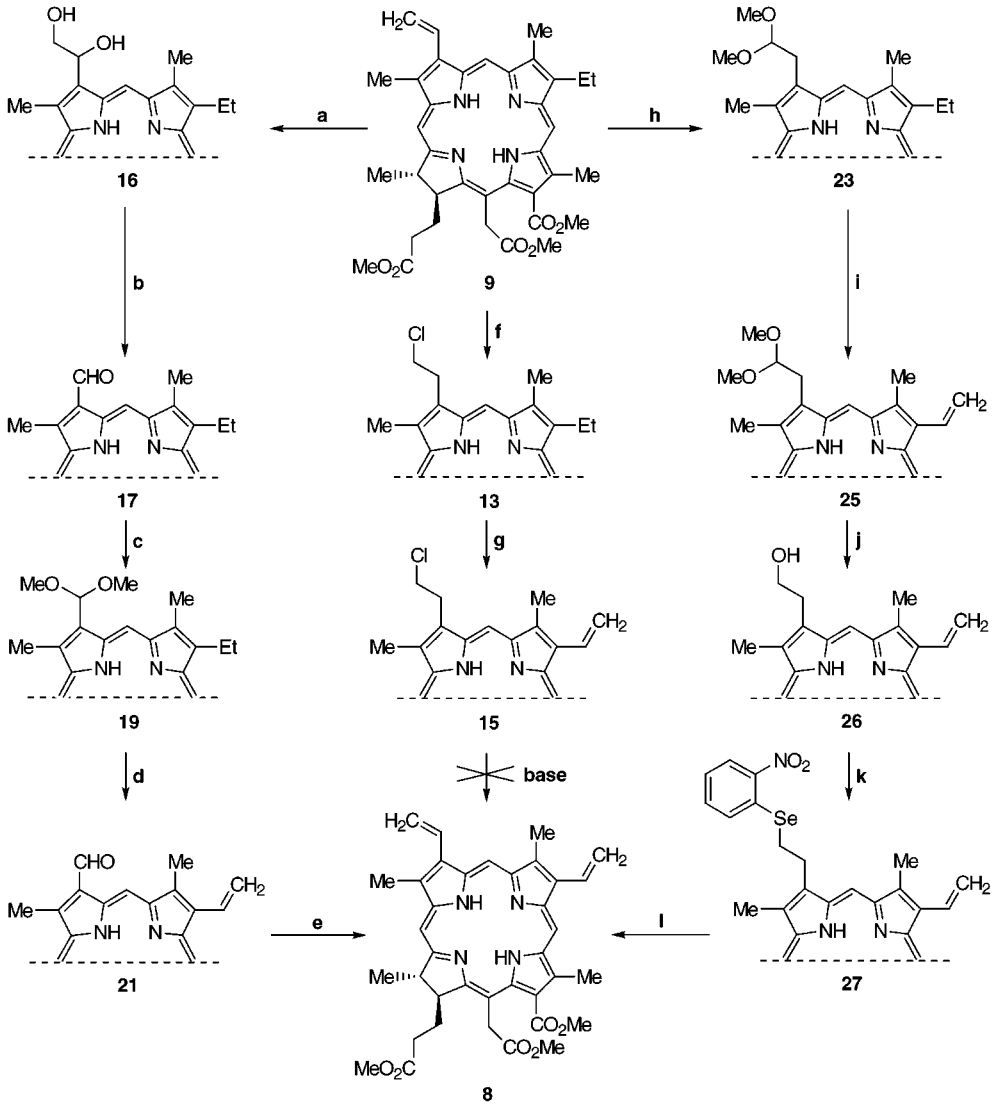
Scheme 2



Reagents: a, OsO_4/py; b, $NaIO_4$/silica gel; c, $HC(OMe)_3$, TsOH; d, OsO_4/py, then Δ; e, Ph_3PCH_2; f, $Tl(NO_3)_3$/MeOH, then H_3O^+, then $NaBH_4$, then PPh_3/Cl_3CCN; g, OsO_4 then $NaHSO_3$, then PPTs, Δ; h, $Tl(NO_3)_3$/MeOH; i, OsO_4/py, then Δ; j, H_3O^+ then $NaBH_4$; k, 2-NO_2-PhSeCN/Bu_3P; l, H_2O_2/THF

which could be easily dehydrated with PPTs in hot toluene to give the 3-devinyl-3-(2-chloroethyl)-8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **15**.

Elimination of HCl from **15** to regenerate the 3-vinyl group in the presence of a strong base, such as potassium *tert*-butoxide[17] or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) unfortunately favored the cyclization of ring-E, leading to complex product mixtures and poor yields.

(b) Vinyl cleavage: Synthesis of a ^{13}C-Labeled Analogue. Our first synthesis[6] of 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **8** involved preparation of diol **16** (Scheme 2). The 3-vinyl group of starting material **9** was reacted with OsO_4/pyridine followed by glycol cleavage, using sodium periodate on silica gel, to give the 3-formylchlorin-e_6 **17**. Unfortunately the 7,8-diol **18**, obtained from **17** via osmylation, could not be directly dehydrated due to the electron-withdrawing effect of the formyl group, which instead favored pinacol rearrangement under all dehydration conditions investigated.[6,9b,22] Thus, treatment of **17** with trimethyl orthoformate in methanol (with TsOH as catalyst) provided its dimethyl acetal **19**, from which 7,8-diol **20** could be obtained in excellent yield using OsO_4/pyridine. Dehydration of **20** was accomplished in moderate yield by heating under vacuum.[12] Under these conditions, the 8-vinyl group was formed with concomitant cleavage of the acetal to give the 3-devinyl-3-formyl-8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **21**.

A Wittig reaction[23] between **21** and methylenetriphenylphosphorane easily afforded **8**. Though the relatively high number of reaction steps in this approach appears to be a disadvantage, the Wittig reaction in the last step was found to be a valuable tool for the synthesis of ^{13}C (or ^{14}C) labeled analogues.[24] 3-(2-^{13}C−Vinyl)-8-de-

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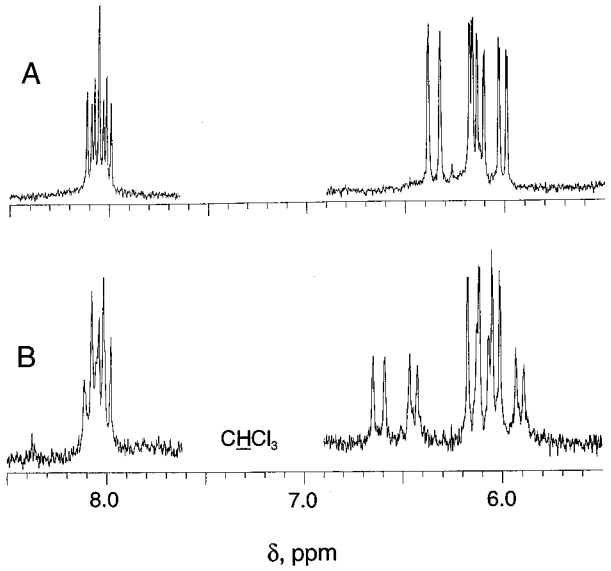

Figure 1. ^{1}H NMR spectra (300 MHz, vinyl region only) in $CDCl_3$, of (A) 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester (**8**), and (B) 3-(2-^{13}C-vinyl)-8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester (**22**).

ethyl-8-vinylchlorin-e_6 trimethyl ester **22** was obtained using ^{13}C-labeled methyltriphenylphosphonium iodide and sodium bis(trimethylsilyl)amide. Figure 1 shows the vinyl region in the proton NMR spectrum (300 MHz) of 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **8** (Figure 1A) compared with its 3^2-^{13}C-labeled analogue **22** (Figure 1B). The spectrum of **8** shows four doublets of doublets (J_{trans} = 18, J_{gem} = 1.5 Hz) in the region between 5.9 and 6.5 ppm, representing the four CH_2-protons of the 3- and 8-vinyl groups. In the spectrum of ^{13}C-labeled compound **22**, an additional ^{1}H−^{13}C coupling [J (^{13}C−^{1}H) = 160 Hz] is now observed for the 3^2-CH_2-group, whereas the signals corresponding to the 8^2-CH_2-group remain unchanged.

(c) Using the 2,2-Dimethoxyethyl Substituent: Scale-Up of the Synthetic Approach. To scale-up the synthesis of 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **8** to a 10 millimolar range, a third approach had to be developed (Scheme 2). Upon treatment of our starting material chlorin-e_6 trimethyl ester **9**, with 2 equiv of thallium(III) nitrate in methanol, followed by reductive demetalation, the 3-vinyl group is oxidized to an acetaldehyde side chain.[17] Under the reaction conditions the corresponding dimethyl acetal **23** was formed,[19] which was crystallized from the crude reaction mixture.

Instead of transforming **23** into 3-devinyl-3-(2-hydroxyethyl)chlorin-e_6 **12** according to our standard procedure,[16,17,19] **23** was now directly treated with OsO_4/pyridine to give 7,8-diol **24**. Like its homologue **20**, compound **24** could be dehydrated by heating under vacuum, yielding 3-devinyl-3-(2,2-dimethoxyethyl)-8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **25**. In this case the acetal was not cleaved under the dehydration conditions, this fact improving the yield to 50% (compared with 28% of **21** from **20**).

Treatment of acetal **25** with aqueous acid followed by reduction with sodium borohydride[17] yielded 3-devinyl-3-(2-hydroxyethyl)-8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **26**. To regenerate the 3-vinyl-group under mild, nonbasic conditions, we could successfully apply a method which we recently developed for porphyrins, using the *o*-nitrophenylselenate ligand as the leaving group.[25] Alcohol **26** was converted into its *o*-nitrophenylselenium derivative **27** with *o*-nitrophenyl selenocyanate and tributylphosphine. Compound **27** then underwent oxidative elimination when reacted with H_2O_2 in THF to yield 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **8** (Scheme 2).

A small amount of **8** also was converted into the corresponding 8-de-ethyl-8-vinylpheophorbide **11** using the previously described sodium bis(trimethylsilyl) amide/triphenylphosphine method. Compound **11**, as its free acid **28**, would be the first chlorophyll biosynthetic precursor of the divinyl series obtained by chemical synthesis.

As a result of this synthetic study, we have in hand compounds, in the chlorin-e_6 and pheophorbide-a series, with all four possible vinyl and ethyl permutations at the 3- and 8-positions. In Table 1 a comparison of the two major visible absorption maxima is shown for the derivatives **5**, **6**, **8**, and **9** in the chlorin-e_6 series and the derivatives **10**, **11**, **29**, and **30** in the pheophorbide-a series, respectively. The most remarkable observation for both series of chlorophyll derivatives is the strong influence of the substituent at the 3-position on the long wavelength absorption maximum; a change from vinyl to ethyl at the 3-position causes a hypsochromic shift of 10 nm or more, whereas the 8-substituent apparently does not affect the wavelength of the band at about 660 nm. This is an interesting observation since the substituent pattern in chlorophyll-a **2** is 3-vinyl-8-ethyl. The transformation from 8-vinyl to 8-ethyl during chloroplast biogenesis is a step which does not affect the light absorption/harvesting properties, at least of the monomeric pigments.

Conclusion

New synthetic approaches have been developed which allow the synthesis of 8-vinyl derivatives, e.g. **11**, of chlorophyll-a **2**. Regioselective osmylation on ring B, followed by dehydration of the resulting 7,8-diol, allowed transformation of the 8-ethyl group of chlorin-e_6 trimethyl ester derivatives into the 8-vinyl group. To protect the 3-vinyl group throughout the synthesis, the 2,2-dimethoxyethyl substituent appeared to be more effective than the previously preferred 2-chloroethyl substituent, because the double bond could be regenerated under mild, nonbasic conditions via the *o*-nitrophenylselenium derivative **27**. An alternative route to produce labeled compounds such as **22** involved a Wittig reaction on 3-formyl derivatives, e.g. **21**. Finally, conversion into 8-vinyl derivatives of the pheophorbide series **10**, **11** succeeded by application of mild anaerobic conditions for cyclization of ring E.

Experimental Section

General experimental techniques and analytical measurements were applied as previously described.[26] Chlorophyll-a **2** was isolated from the alga *Spirulina pacifica*, purchased from Cyanotech Corp., Kailua-Kona, HI 96740 and trans-

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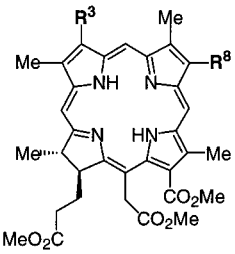
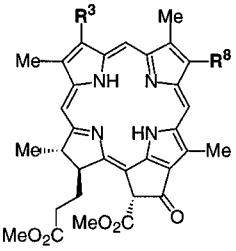
Table 1. Comparison of Electronic Absorption Maxima for Chlorin-e_6 and Pheophorbide Derivatives Bearing Different 3- and 8-Substituents



chlorophyll derivative	R^3	R^8	λ_{max}nm (ε)
5	Et	Et	399 (170 000) 650 (46 000)
9	$CH=CH_2$	Et	402 (165 000) 664 (53 000)
6	Et	$CH=CH_2$	404 (163 000) 650 (39 000)
8	$CH=CH_2$	$CH=CH_2$	410 (149 000) 662 (40 000)



chlorophyll derivative	R^3	R^8	λ_{max}nm (ε)
29	Et	Et	408 (110 000) 656 (46 000)
30	$CH=CH_2$	Et	412 (120 000) 666 (53 000)
10	Et	$CH=CH_2$	416 (122 000) 656 (40 000)
11	$CH=CH_2$	$CH=CH_2$	406 (126 000) 666 (43 000)

formed into chlorin-e_6 trimethyl ester **9** according to our standard procedures.[8] Diastereomeric mixtures, such as intermediates **7**, **14**, **16**, **18**, **20**, and **24**, are not characterized.

A. Model Synthesis. Mesochlorin-e_6 Trimethyl Ester (5). Chlorin-e_6 trimethyl ester[16] (**9**) (500 mg, 0.824 mmol) was dissolved in methyl acetate (100 mL). Palladium (10% on C, 50 mg) was added, and after degassing, the mixture was stirred for approximately 30 min under 1 atm of hydrogen gas until the complete appearance of an absorption band at 650 nm showed the reaction to be complete. The mixture was filtered through 20 g of alumina (Brockmann Grade III) and evaporated. Crystallization from CH_2Cl_2/*n*-hexane afforded 430 mg (0.671 mmol, 81%) of mesochlorin-e_6 trimethyl ester (**5**), which was identified by comparison to an authentic sample.[7]

Typical Osmylation Procedure. Mesochlorin-e_6 trimethyl ester (**5**) (430 mg, 0.671 mmol) was suspended with pyridine (0.5 mL) and a solution of osmium(VIII) oxide (175 mg, 0.688 mmol) in THF (35 mL) at 0 °C. The mixture was stirred for 30 min in the dark before the ice bath was removed, allowing the mixture to stir at room temperature in the dark. After 7 d the optical spectrum showed that 65% of the starting material **5** had reacted. An excess of $NaHSO_3$, dissolved in 50% MeOH/water was added; the mixture was stirred for 20 min, before the brown Os_2O_3 precipitate was filtered off. After separation between CH_2Cl_2 and water, the organic layer was dried over anhydrous Na_2SO_4, and the solvents were evaporated. Chromatography on silica gel (eluting with 1% MeOH/CH_2Cl_2 recovered unreacted staring material **5** (150 mg, 35%) from the green, mobile fraction, and afforded the 7,8-diol **7** (280 mg, 95%) in the bluish, polar fraction.

Isochlorin-e_6 Trimethyl Ester (6). The 7,8-diol **7** (280 mg, 0.414 mmol) and pyridinium toluene-4-sulfonate (PPTs) (28 mg, 0.111 mmol) were dissolved in dry toluene (50 mL). The mixture was heated for 30 min at 80 °C, cooled to room temperature, and then directly loaded on a column containing 50 g of alumina (Brockmann Grade III). After collecting the toluene, the product, isochlorin-e_6 trimethyl ester **6**, was eluted with CH_2Cl_2 in the least polar, green fraction. Crystallization from CH_2Cl_2/*n*-hexane afforded compound **6** (160 mg, 60%) as green plates: mp 204−206 °C; λ_{max} (CH_2Cl_2) 404 nm (ϵ 163 000), 502 (11 700), 596 (4900), 650 (39 300); δ ($CDCl_3$): −1.35, −1.30 (each br s, 1 H), 1.71−1.79 (m, 6 H), 2.15−2.30, 2.50−2.65 (each m, 2 H), 3.35, 3.43, 3.55, 3.63, 3.77, 4.25 (each s, 3 H), 3.81−3.88 (q *J* 7 Hz, 2 H), 4.32−4.45 (m, 2 H), 5.18−5.37 (q, J_{AB} 19 Hz, 2 H), 5.95−6.05, 6.08−6.17, 7.96−8.10 (each dd J_{cis} 11.5 or J_{trans} 18.0 or J_{gem} 1.5 Hz, each 1 H), 8.66, 9.42, 9.83 (each s, 1 H); MS (LSIMS) *m/e* 639 (100%, MH^+), 638 (97%, M^+). Anal. Calcd for $C_{37}H_{42}N_4O_6$: C, 69.57; H, 6.63; N, 8.77. Found: C, 69.53; H, 6.46; N, 8.50%.

Methyl Isopheophorbide-a (10). Isochlorin-e_6 trimethyl ester (**6**) (32 mg, 0.050 mmol) and triphenylphosphine (50 mg, 0.191 mmol) were dissolved in absolute THF (1.0 mL). The mixture was stirred for 20 min under Ar before a 1 M solution of sodium bis(trimethylsilyl)amide (0.032 mL) was injected. The brownish solution was stirred for 2 h at room temperature and was then quenched adding degassed citric acid/phosphate-buffer (0.5 M, pH 4, 5.0 mL). The mixture was separated between CH_2Cl_2 and water; the organic layer was dried by filtration through cotton wool and evaporated. Chromatography on silica gel with 2% methyl acetate/CH_2Cl_2 and crystallization of the dull green major fraction from CH_2Cl_2/*n*-hexane afforded the title compound (20 mg, 66%) as green needles: mp 203−205 °C; λ_{max} (CH_2Cl_2) 416 nm (ϵ 122 000), 508 (10 700), 542 (7400), 600 (8200), 656 (40 100); δ ($CDCl_3$): −1.60, 0.54 (each br s, 1 H), 1.70−1.78 (t *J* 7 Hz, 3 H), 1.79−1.85 (d *J* 8 Hz, 3 H), 2.15−2.40, 2.44−2.70 (each m, 2 H), 3.28, 3.37, 3.65, 3.60, 3.90 (each s, 3 H), 3.81−3.88 (q *J* 7 Hz, 2 H), 4.15−4.23 (m, 1 H), 4.40−4.48 (m, 1 H), 5.95−6.05, 6.08−6.20, 7.82−7.96 (each dd, J_{cis} 11.5 or J_{trans} 18.0 or J_{gem} 1.5 Hz, each 1 H), 6.22 (s, 1 H) 8.50, 9.27, 9.68 (each s, 1 H); MS (LSIMS) *m/e* 608 (16%, MH^+), 607 (43), 606 (100%, M^+). Anal. Calcd for $C_{36}H_{38}N_4O_5$: C, 71.25; H, 6.32; N, 9.24. Found: C, 71.24; H, 6.43; N, 8.87%.

B. Reversible Protection of the Vinyl Group. (1) Using the 2-Chloroethyl Substituent. 3-(2-Chloroethyl)-3-devinylchlorin-e_6 Trimethyl Ester (13). Triphenylphosphine (500 mg, 1.906 mmol) was dissolved in CCl_4 (5.0 mL). At 0 °C, trichloroacetonitrile (250 mg, 1.731 mmol) was added to form a white precipitate. After 10 min 3-(2-hydroxyethyl)-3-devinylchlorin-e_6 trimethyl ester **12** (200 mg, 0.305 mmol), obtained from **9** by our standard procedure,[17] was added to the mixture, which was then stirred for 1 h at room temperature. Direct filtration through alumina (20 g; Brockmann Grade III), eluting the major fraction with 20% petroleum ether/CH_2Cl_2, and subsequent crystallization from CH_2Cl_2/*n*-hexane afforded title compound **13** (185 mg, 90%) as green needles; this was identified by comparison with an authentic sample.[19]

3-(2-Chloroethyl)-3-de-ethyl-isochlorin-e_6 Trimethyl Ester (15). The title compound was prepared from **13** (as described for **6**), by osmylation to give **14**; subsequent dehydration of **14** with PPTs in hot toluene, chromatography on silica gel, eluting with 1% acetone/CH_2Cl_2, and crystallization from CH_2Cl_2/*n*-hexane afforded brownish needles of **15**, in a yield of 44%: mp 206−208 °C; λ_{max} (CH_2Cl_2) 406 nm (ϵ 159 000), 502 (13 700), 548 (3100), 600 (6000), 654 (42 300); δ ($CDCl_3$): −1.52, −1.36 (each br s, 1 H), 1.72−1.78 (d, 3 H), 2.15−2.30, 2.50−2.65 (each m, 2 H), 3.42, 3.44, 3.58, 3.65, 3.79, 4.28 (each s, 3 H), 4.30−4.50 (m, 6 H), 5.18−5.40 (q J_{AB} 20

Hz, 2 H), 5.98−6.05, 6.08−6.18, 7.97−8.10 (each dd, J_{cis} 11.5 or J_{trans} 19 or J_{gem} 1.5 Hz, each 1 H), 8.70, 9.40, 9.85 (each s, 1 H); MS (LSIMS) *m/e* 677 (12%), 676 (25), 675 (59), 674 (74), 673 (100, MH^+) 672 (77, M^+). Anal. Calcd for $C_{37}H_{41}ClN_4O_6$: C, 66.01; H, 6.14; N, 8.32. Found: C, 65.84; H, 6.27; N, 8.27%.

(2) Vinyl Cleavage. 3-Formyl-3-devinylchlorin-e$_6$ Trimethyl Ester (17). Chlorin-e$_6$ trimethyl ester (**9**) (1 g, 1.566 mmol) was treated with 1 equiv of OsO_4 and pyridine as described above. Working up the reaction after 30 min followed by chromatography on silica gel using 1% MeOH/CH_2Cl_2 afforded the diol intermediate **16** in quantitative yield. Compound **16** and silica gel (5.0 g) were suspended in THF (15.0 mL) before a solution of sodium metaperiodate (2 g, 9.351 mmol) in water (15.0 mL) was added. A color change from green to copper, completed within 30 min, indicated the end of the reaction. After addition of CH_2Cl_2 (20.0 mL), the mixture was filtered through cotton wool and then passed through a plug of alumina (100 g; Brockmann Grade III), eluting the brownish major fraction with CH_2Cl_2. Crystallization from CH_2Cl_2/*n*-hexane yielded the title compound **17** (845 mg, 84%) as brown needles, mp 224−226 °C; λ_{max} (CH_2Cl_2) 416 nm (ϵ 94 200), 510 (8800), 546 (9300), 636 (4900), 690 (52 600); δ ($CDCl_3$): −1.79, −1.31 (each br s, 1 H), 1.71−1.77 (d, 3 H), 2.14−2.30, 2.40−2.75 (each m, 2 H), 3.28, 3.59, 3.66, 3.79(2), 4.28 (each s, 3 H), 4.40−4.56 (m, 2 H), 5.20−5.45 (q J_{AB} 21 Hz, 2 H), 8.95, 9.67, 10.25, 11.54 (each s, 1 H); MS (LSIMS) *m/e* 641 (100%, MH^+), 613 (6), 581 (7). Anal. Calcd for $C_{36}H_{40}N_4O_7$: C, 67.48; H, 6.29; N, 8.74. Found: C, 67.68; H, 6.20; N, 8.65%.

3-(Dimethoxymethyl)-3-devinylchlorin-e$_6$ Trimethyl Ester (19). 3-Formyl-3-devinylchlorin-e$_6$ trimethyl ester (**17**) (800 mg, 1.249 mmol) and TsOH (80 mg, 0.421 mmol) were dissolved in trimethyl orthoformate (50 mL) and dry MeOH (50 mL). The brownish solution was refluxed for 30 min until the color change to green was complete. Triethylamine (100 mg, 0.988 mmol) was added, and the solvents were evaporated under vacuum. The crude product was redissolved in CH_2Cl_2 and passed through alumina (20 g; Brockmann Grade III), collecting the green major fraction, which, after crystallization from acetone/water, gave 790 mg (92%) of green spheres of the title compound **19**: mp 158−160 °C; λ_{max} (CH_2Cl_2) 399 nm (ϵ 145 000), 498 (12 700), 524 (5000), 604 (5000), 658 (45 000); δ ($CDCl_3$): −1.65, −1.38 (each br s, 1 H), 1.65−1.75 (m, 6 H), 2.15−2.35, 2.50−2.65 (each m, 2 H), 3.31, 3.53, 3.58, 3.63, 3.76, 4.26 (each s, 3 H), 3.69 (s, 6 H), 3.76−3.85 (q *J* 7 Hz, 2 H), 4.35−4.50 (m, 2 H), 5.20−5.40 (q J_{AB} 21 Hz, 2 H), 6.87 (s, 1 H), 8.77, 9.71, 9.90 (each s, 1 H); MS (LSIMS) *m/e* 689 (8%), 688 (32), 687 (86, MH^+), 686 (100%, M^+). Anal. Calcd for $C_{38}H_{46}N_4O_8 \cdot 0.5\ H_2O$: C, 65.60; H, 6.81; N, 8.05. Found: C, 65.92; H, 6.61; N, 8.02%.

3-Formyl-3-de-ethyl-isochlorin-e$_6$ Trimethyl Ester (21). 3-(Dimethoxymethyl)-3-devinylchlorin-e$_6$ trimethyl ester (**19**) (750 mg, 1.092 mmol) was converted into 7,8-diol **20** using the standard osmylation procedure described above. Chromatography on silica gel, eluting with 2% MeOH/CH_2Cl_2, recovered starting material (190 mg, 25%) in the mobile green fraction and diol **20** (560 mg, 75%) in the polar, bluish fraction. Heating the crude product **20** for 5 d at 90 °C in a vacuum oven under a vacuum of 25 Torr yielded a red-brownish product mixture, which was separated by chromatography on silica gel, eluting with 1% acetone/CH_2Cl_2. The least polar, coppertone fraction containing title compound **21** (140 mg, 28%) was collected and was crystallized from CH_2Cl_2/*n*-hexane as brown needles: mp 237−239 °C; λ_{max} (CH_2Cl_2) 422 nm (ϵ 112 000), 516 (10 800), 552 (6700), 632 (4700), 688 (50 600); δ ($CDCl_3$): −1.80, −1.30 (each br s, 1 H), 1.71−1.79 (d, 3 H), 2.20−2.40, 2.55−2.70 (each m, 2 H), 3.43, 3.56, 3.65, 3.79, 3.80, 4.28 (each s, 3 H), 4.40−4.54 (m, 2 H), 5.22−5.45 (q J_{AB} 21 Hz, 2 H), 6.01−6.06, 6.10−6.17, 7.94−8.05 (each dd J_{cis} 11.5 or J_{trans} 19 or J_{gem} 1.5 Hz, each 1 H), 8.90, 9.70, 10.28, 11.58 (each s, 1 H); MS (LSIMS) *m/e* 642 (10%), 641 (28), 640 (54), 639 (100, MH^+) 638 (86, M^+). Anal. Calcd for $C_{36}H_{38}N_4O_7$: C, 67.70; H, 6.00; N, 8.77. Found: C, 67.44; H, 6.28; N, 8.60%.

8-De-ethyl-8-vinylchlorin-e$_6$ Trimethyl Ester (8). Method A. Triphenylmethylphosphonium bromide (395 mg, 1.106 mmol) was dissolved in dry THF (1.0 mL). Under Ar a 10^{-3} M solution of sodium bis(trimethylsilyl)amide in THF (1.0 mL) was added, and the orange mixture was refluxed for 90 min. The mixture was allowed to cool to 50 °C before 3-formyl-3-de-ethyl-isochlorin-e$_6$-trimethyl ester (**21**) (5 mg, 0.008 mmol) was added. A spontaneous color change from brown to green showed the completion of the reaction, which was then quenched after 30 s by addition of degassed citric acid/phosphate buffer (5.0 mL; 0.5 M, pH4). The mixture was separated between CH_2Cl_2 and water; the organic layer was passed through cotton wool and evaporated. Chromatography on silica gel, eluting with 2% MeOAc/CH_2Cl_2, and subsequent crystallization of the green major fraction from CH_2Cl_2/*n*-hexane afforded title compound **8** (4.1 mg, 82%) as green needles:[27] mp 201−203 °C; λ_{max} (CH_2Cl_2) 410 nm (ϵ 149 000), 506 (11 000), 608 (3000), 662 (40 400); δ ($CDCl_3$): −1.46, −1.32 (each br s, 1 H), 1.72−1.78 (d, 3 H), 2.13−2.28, 2.48−2.65 (each m, 2 H), 3.44, 3.50, 3.59, 3.67, 3.78, 4.26 (each s, 3 H), 4.37−4.50 (m, 2 H), 5.17−5.39 (q J_{AB} 19 Hz, 2 H), 5.98−6.04, 6.10−6.15 (each dd J_{cis} 11.5 or J_{trans} 17.5 or J_{gem} 1.7 Hz, each 1 H), 6.13−6.19, 6.32−6.40 (each dd J_{cis} 11.5 or J_{trans} 17.8 or J_{gem} 1.4 Hz, each 1 H), 7.98−8.13 (m, 2 H), 8.74, 9.60, 9.84 (each s, 1 H); MS (LSIMS) *m/e* 640 (10%), 639 (28), 638 (53), 637 (100, MH^+) 636 (95, M^+). Anal. Calcd for $C_{37}H_{40}N_4O_6$: C, 69.70; H, 6.33; N, 8.80. Found: C, 69.56; H, 6.54; N, 8.72%.

Method B. 3-[2-(2-Nitrophenyl)selenoethyl)]-3-de-ethyl-isochlorin-e$_6$ trimethyl ester (**27**) (500 mg, 0.60 mmol) was dissolved in THF (50 mL). The solution was cooled in an ice bath, and an excess of 30% H_2O_2 (2.5 mL) was added. The reaction mixture was stirred at room temperature under Ar for 3 h before being washed with H_2O. The organic extract was passed through anhydrous Na_2SO_4, and after evaporation of the solvent, the crude material was chromatographed on silica gel, the product being eluted with 1% acetone/CH_2Cl_2. Crystallization from CH_2Cl_2/*n*-hexane provided **8** (278 mg, 73%), identical with the sample from method A.

Methyl 8-De-ethyl-8-vinylpheophorbide-a (11). 8-De-ethyl-8-vinylchlorin-e$_6$ trimethyl ester (**8**) (2.0 mg, 0.003 mmol) was treated with 1 equiv of sodium bis(trimethylsilyl)amide as described above for the preparation of **10**. After workup and chromatography on silica gel, elution with 2% MeOAc/CH_2Cl_2 gave recovered starting material (1.0 mg, 50%) in the mobile fraction and the title compound in the second, dull green fraction. Crystallization from $CHCl_3$/MeOH yielded 0.8 mg (84%) of tiny, purple spheres **11**: mp 178−180 °C; λ_{max} (CH_2Cl_2) 406 nm (ϵ 126 000), 510 (16 200), 606 (10 000), 666 (40 100); δ ($CDCl_3$): −1.68, 0.92 (each br s, 1 H), 1.82−1.85 (d *J* 8 Hz, 3 H) 2.10−2.42, 2.44−2.72 (each m, 2 H), 3.38, 3.41, 3.66, 3.58, 3.85 (each s, 3 H), 4.20−4.30 (m, 1 H), 4.44−4.55 (m, 1 H), 5.99−6.02, 6.12−6.20 (each dd J_{cis} 11.7 or J_{trans} 17.4 or J_{gem} 1.5 Hz, each 1 H), 6.21−6.33 (m, 2 H), 7.84−8.08 (m, 2 H), 6.25 (s, 1 H), 8.63, 9.50, 9.76 (each s, each 1 H); MS (LSIMS) *m/e* 606 (35%), 605 (54, MH^+), 604 (100, M^+). Anal. HRMS Calcd for $C_{36}H_{38}N_4O_5$: 604.26855. Found: 604.2673.

[3^2-^{13}C]-8-De-ethyl-8-vinylchlorin-e$_6$ Trimethyl Ester (22). 3-Formyl-3-de-ethyl-isochlorin-e$_6$-trimethyl ester (**20**) (5 mg, 0.008 mmol) was reacted with a Wittig-reagent prepared from methyl-^{13}C-triphenylphosphonium iodide (Sigma-Aldrich, 99 atom % ^{13}C) (100 mg, 0.247 mmol) as described above for compound **8**, in a yield of 65%: δ ($CDCl_3$): −1.58, −1.30 (each br s, 1 H), 1.82−1.91 (d, 3 H), 2.01−2.08, 2.24−2.41 (each m, 2 H), 3.30, 3.41, 3.47, 3.60, 3.69, 4.18 (each s, 3 H), 4.38−4.53 (m, 2 H), 4.93−5.18 (q J_{AB} 20 Hz, 2 H), 5.87−5.94, 6.06−6.16, 6.40−6.49, 6.57−6.67 (two ddd J_{cis} 11.4, J_{trans} 17.7, J_{gem} 0.9, J^{13}_{C-H} 160 Hz, each 1 H), 6.00−6.07, 6.11−6.20 (each dd J_{cis} 11.5 or J_{trans} 17.7 or J_{gem} 1.6 Hz, each 1 H), 7.95−8.15 (m, 2 H), 8.77, 9.65, 9.88 (each s, 1 H); ^{13}C, δ (C−H-dec, $CDCl_3$): δ 122.3 (s); MS (LSIMS) *m/e* 640 (30%), 639 (48), 638 (75, MH^+) 637 (100, M^+).

(27) Compound **8** was found as a byproduct upon acid treatment of an oxidized chlorin-e$_6$ phlorin and partially characterized: Inhoffen, H. H.; Kreiser, W.; Panenka, R. *Liebigs Ann. Chem.* **1971**, *749*, 117−124.

(3) Using the 2,2-Dimethoxyethyl Substituent. 3-(2,2-Dimethoxyethyl)-3-de-ethyl-isochlorin-e_6 Trimethyl Ester (25). 3-(2,2-Dimethoxyethyl)-3-devinylchlorin-e_6 trimethyl ester (**23**) (7.0 g, 10 mmol), obtained from **9** by the standard procedure[17] was reacted for 10 d with OsO_4/pyridine as described above. The reaction was quenched by bubbling H_2S gas for 3 min through the mixture. After evaporation of the solvents, the residue was redissolved in CH_2Cl_2, and passed through cotton wool to filter off the black Os_2S_3 precipitate. A chromatography on silica gel with 1% MeOH/CH_2Cl_2 eluted first starting material **23** (1.45 g, 21%) followed by 7,8-diol intermediate **24** (3.62 g, 62%). The crude **24** was redissolved in MeOAc and, after increasing the surface area by addition of glass balls (100 g, 4−5 mm diameter) and evaporation of the solvent, heated under vacuum (90 °C, 25 Torr) for 7 d. Chromatography on silica gel, eluting with 3% MeOAc/CH_2Cl_2, afforded title compound **25** (1.55 g, 45%), which was crystallized from acetone/water as green plates: mp 95−97 °C; λ_{max} (CH_2Cl_2) 404 nm (ϵ 133 000), 502 (11 900), 598 (5000), 652 (34 800); δ ($CDCl_3$): −1.43, −1.32 (each br s, 1 H), 1.69−1.80 (d, 3 H), 2.10−2.28, 2.47−2.68 (each m, 2 H), 3.37, 3.40, 3.42, 3.43, 3.58, 3.79, 3.80, 4.28 (each s, 3 H), 4.10−4.20 (d *J* 5 Hz, 2 H), 4.35−4.50 (m, 2 H), 5.00−5.07 (t *J* 5 Hz, 1 H), 5.15−5.39 (q J_{AB} 21 Hz, 2 H), 5.99−6.04, 6.05−6.10, 7.98−8.07 (each dd J_{cis} 11.5 or J_{trans} 17.8 or J_{gem} 0.5 Hz, each 1 H), 8.73, 9.52, 9.84 (each s, 1 H); MS (LSIMS) *m/e* 701 (18%), 700 (48), 699 (100, MH^+), 698 (75, M^+). Anal. Calcd for $C_{39}H_{46}N_4O_8 \cdot 0.5\ H_2O$: C, 66.18; H, 6.69; N, 7.92. Found: C, 66.52; H, 7.00; N, 7.80%.

3-(2-Hydroxyethyl)-3-de-ethyl-isochlorin-e_6 Trimethyl Ester (26). 3-(2,2-Dimethoxyethyl)-3-de-ethyl-isochlorin-e_6 trimethyl ester (**25**) (1.5 g, 2.146 mmol) was dissolved in $CHCl_3$ (25.0 mL); THF (100 mL) and 5 M HCl (5.0 mL) were added, and the mixture was refluxed for 30 min. After addition of CH_2Cl_2 (100 mL), the organic layer was washed with water and 10^{-2} M HCl and then passed through anhydrous Na_2SO_4 and evaporated under vacuum. The dry residue was redissolved in THF (10.0 mL) and treated with excess diazomethane in ether. Unreacted diazomethane was destroyed with HOAc before evaporating the solvents and redissolving the residue in CH_2Cl_2 (50 mL). A solution of $NaBH_4$ (810 mg, 21.41 mmol) in MeOH (50 mL) was added, and the solution was allowed to stir for 5 min at room temperature. Unreacted $NaBH_4$ was quenched with 1 M HCl before the organic layer was washed with satd $NaHCO_3$ and water, passed through anhydrous Na_2SO_4, and evaporated. Chromatography on silica gel, eluting with 1% MeOH/CH_2Cl_2, afforded title compound **26** (1.15 g, 82%), which crystallized from CH_2Cl_2/*n*-hexane as green needles: mp 176−178 °C; λ_{max} (CH_2Cl_2) 404 nm (ϵ 138 000), 500 (10 500), 598 (5000), 652 (35 400); δ ($CDCl_3$): −1.46, −1.40 each br s, 1 H), 1.70−1.80 (d, 3 H), 2.15−2.30, 2.50−2.70 (each m, 2 H), 3.28, 3.29, 3.56, 3.65, 3.82, 4.29 (each s, 3 H), 3.37−3.43, 3.47−3.55 (each m, 1 H), 4.06−4.13 (m, 1 H), 3.85−3.95, 4.14−4.22 (each m, 1 H), 4.38−5.50 (m, 2 H), 5.19−5.42 (q J_{AB} 20 Hz, 2 H), 5.92−6.01, 6.02−6.13, 7.87−8.02 (each dd, J_{cis} 11.4 or J_{trans} 17.8 or J_{gem} 0.5 Hz, each 1 H), 8.70, 9.26, 9.80 (each s, 1 H); MS (LSIMS) *m/e* 657 (20%), 656 (44), 655 (100, MH^+), 654 (77, M^+). Anal. Calcd for $C_{37}H_{42}N_4O_7$: C, 67.87; H, 6.47; N, 8.56. Found: C, 67.66; H, 6.52; N, 8.38%.

3-[2-(2-Nitrophenyl)selenoethyl)]-3-de-ethyl-isochlorin-e_6 Trimethyl Ester (27). Tri(*n*-butyl)phosphine (1.9 mL, 7.6 mmol) was added dropwise to a solution of 3-(2-hydroxyethyl)-3-de-ethyl-isochlorin-e_6 trimethyl ester (**26**) (1.00 g, 1.5 mmol) and *o*-nitrophenyl selenocyanate (1.73 g, 7.6 mmol) in CH_2Cl_2 (125 mL). The mixture was stirred under Ar for 1 h at room temperature before the solvent was evaporated under vacuum. Chromatography on silica gel, eluting with 1% acetone/CH_2Cl_2 yielded title compound **27** (881 mg, 70%), which was crystallized from CH_2Cl_2 *n*-hexane to give green needles: mp 200−202 °C; λ_{max} (CH_2Cl_2) 406 nm (ϵ 180 000), 502 (23 700), 600 (15 800), 654 (52 300); δ ($CDCl_3$): −1.50, (br s, 2 H), 1.70−1.80 (d, 3 H), 2.11−2.29, 2.50−2.69 (each m, 2 H), 3.16, 3.20, 3.51, 3.62, 3.80, 4.29 (each s, 3 H), 3.25−3.38 (m, 2 H) 3.79−3.90 (m, 2 H), 4.32−4.49 (m, 2 H), 5.19−5.42 (q J_{AB} 20 Hz, 2 H), 6.82−7.15 (m, 2 H), 5.80−5.99, 6.02−6.13, 7.85−8.00 (each dd J_{cis} 11.4 or J_{trans} 17.8 or J_{gem} 0.5 Hz, each 1 H), 7.26−7.30 (m, 1 H), 8.02−8.12 (dd J_{cis} 11.4 or J_{trans} 17.8 or J_{gem} 0.5 Hz, 1 H), 8.62, 9.05, 9.74 (each s, 1 H); MS (LSIMS) *m/e* 842 (39%), 841 (58), 840 (100, MH^+), 839 (88, M^+). Anal. Calcd for $C_{43}H_{45}N_5O_8Se$: C, 61.57; H, 5.41; N, 8.35. Found: C, 61.55; H, 5.41; N, 8.34%.

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