Stereoselective Synthesis of New Chlorophyll *a* Related Antioxidants Isolated from Marine Organisms

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A new class of natural antioxidants, chlorophyll *a* related chlorins **3**, **4**(S), **4**(R), **5**(R), **6**, **7**, **8**, and **9**, have been synthesized from a chlorophyll *a* degradation product, pheophorbide *a* methyl ester (**1**). Claisen-type intramolecular condensation of pyropheophorbide *a* methyl ester (**2**) afforded the common intermediate enol **3**. Chlorin **1** and enol **3** have a propensity to undergo exocyclic ring opening by ionic bases. The organic base DBU was found to be an efficient reagent for promoting the asymmetric hydroxylation of these chlorins, using *N*-sulfonyloxaziridines, without cleavage of the exocyclic rings. Model studies for hydroxylactonization have shown that periodate oxidation of hydroxy ketone **10** stereoselectively and predominantly forms hydroxy lactone **17**(S). Periodate oxidation of α-hydroxy 1,3-diketone **4**(R) and/or **4**(S) to furnish hydroxy lactone **5**(R) and diketone **7** was found out to be regioselective, and the site of reaction depends on the appropriate choice of reaction media. ^{1}H NMR spectra have provided information on the absolute configuration of diastereomers at the C-13^2 or C-15^1 position.

Introduction

Of the natural prosthetic groups the most biologically important and the most widespread are the metalated complexes of tetrapyrrolic macrocycles such as hemes and chlorophylls.[1] The coordinated metal ions in these macrocycles play a significant role on fine tuning of the electronic and redox properties of the molecules.[2] In this way, these coordination compounds have developed unique reactivity and biological interaction with their various molecular enviroments in cells. However, despite the diversity of the metal-containing cofactors, metal-free natural tetrapyrroles having special biological functions may not be the exception rather than the rule, since the number of related compounds isolated in metal-free form from marine organisms is rapidly increasing. In addition to the well-known pigment bonellin[3] (a chlorin) that controls the sex of larvae of the Mediterranean sea worm, *Bonnelia viridis*, another new class of chlorins with strong antioxidative activity has also recently been discovered.[4] Of this new class of chlorins, 13^2,17^3-cyclopheophorbide *a* enol (**3**) was the first to be isolated from the sponge *Darwinella oxeata* in 1986.[5] The rest of the antioxidative chlorins, which can be considered as further oxidized products of enol **3**, 13^2(*S*)-hydroxychlorophyllone *a* [**4**(S)] ("*S*" or "*R*" denotes the absolute configuration at C-13^2 or C-15^1 position where appropriate.), 13^2(*R*)-hydroxychlorophyllone *a* [**4**(R)], 15^1(*R*)-chlorophyllone *a* lactone [**5**(R)], chlorophyllonic acid *a* methyl ester (**6**), 13^2-oxopyropheophorbide *a* (**7**), purpurin-18 (**8**), and purpurin-18 methyl ester (**9**), were recently found in marine animals such as the short-necked clam, *Ruditapes philippinarum*, in the viscera of the scallop, *Pactinopecten yessoensis*, and in attached and wafting diatoms.[4]

These novel antioxidative chlorins share a similar structural framework and molecular substitution pattern to chlorophyll *a* and are most likely to be biogenetically related to it. The structural difference between **3** and chlorophyll *a* is in the formation of an additional exocyclic ring (VI). In nature, antioxidants were evolved in many organisms and microorganisms as a defense against the detrimental effects of oxygen once photosynthetic organisms began releasing oxygen into the primitive atmosphere 3.5 billion years ago.[6] Other than the common antioxidants, hydroxylated and polyhydroxylated aromatic and heterocyclic compounds such as vitamin A (retinol), vitamin C (ascorbic acid), and vitamin E (α-tocopherol),[7] it is interesting and typical that nature chose to modify the very molecule (chlorophyll) that was producing oxygen in order to protect against unwanted oxidation processes.[8] As can be deduced from their occurrence in animals, these pigments have no photosynthetic activity.

The rich stereostructural diversity of these antioxidative chlorins and their important biological activity have attracted our interest. In this contribution we report the synthesis of these new chlorins and their related derivatives. The chemical reactivities inherent in these novel structures are also addressed.

Results and Discussion

A. Synthesis of Enol 3 and Subsequent Asymmetric Hydroxylation. Our basic strategy for the

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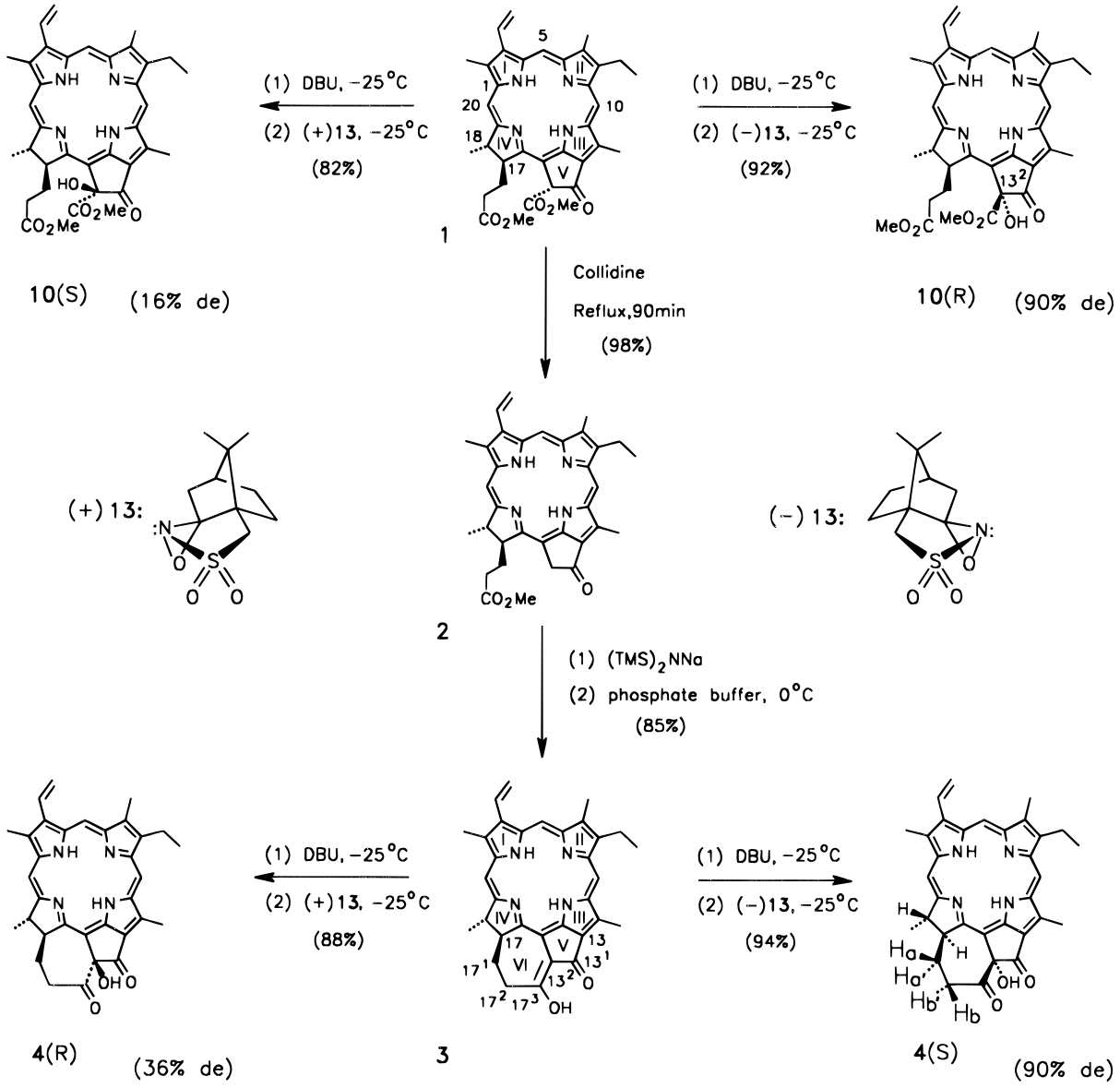
0022-3263/96/1961-2501$12.00/0

Scheme 1



synthesis of hydroxy diketones **4**(S) and **4**(R) is shown in Scheme 1. A degradation product of chlorophyll *a*, pheophorbide *a* methyl ester (**1**), was used as starting material since it is stable and readily obtained from *Spirulina maxima* alga.[9] Decarbomethoxylation of pheophorbide *a* methyl ester (**1**) in collidine afforded a 98% yield of pyropheophorbide *a* methyl ester (**2**).[9] Modification of Eschenmoser's method,[10] treatment of **2** with 7 equiv of $(TMS)_2NNa$ in THF for 3 min followed by flash chromatography on deactivated silica resulted in a Claisen-type intramolecular condensation and gave $13^2,17^3$-cyclopheophorbide *a* enol (**3**) in 85% yield.[11] Enol **3** is a common intermediate to the new chlorophyll *a* related chlorins and exists only in the enolic form in solution and in the crystalline state.[5,11]

To bring about the conversion of enol **3** to 13^2-hydroxychlorophyllone *a* (**4**), a number of methods were investigated, which included aerial and iodine oxidation. None of them were successful since decomposition and overoxidation readily occurred in these procedures. For example, aerial oxidation of **1** during chromatography on silica, especially on a TLC plate, was used by Senge *et al.*[12] to prepare 13^2-hydroxypheophorbide *a* methyl ester (**10**) [a diastereomeric mixture of **10**(R) and **10**(S)]. Unfortunately, it is not suitable for enol **3** since the molecule is so unstable that it decomposes when being subjected to chromatography on silica gel plates. Attempts at aerial oxidation of enol **3** in an alcoholic solution of zinc acetate also failed in our hands. Although this method of aerial oxidation was used in the preparation of 13^2-hydroxychlorin **10** from **1** in 30% yield,[13] it did not work for **3**, which gave back neither **3** nor zinc-metalated **3** but an overoxidized green mixture which has not been identified. Hydroxylation of **3** using molecular iodine in the presence of sodium acetate in aqueous THF solution was partially successful[14,15] and gave a mixture (19% yield) of 13^2-hydroxychlorophyllone *a* (**4**) and 13^2-

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Table 1. Selected ^{1}H NMR Spectral Data ($CDCl_3$, 400 MHz)

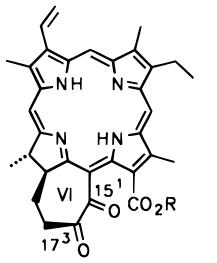
	compound									
proton	**1**[a]	**3**[a]	**4**(S)[a]	**4**(R)[b]	**5**(R)[b]	**6**[b]	**10**(S)[a]	**10**(R)[b]	**17**(S)[a]	**20**[b]
H-10	9.52 (s)	8.64 (s)	9.40 (s)	9.47 (s)	9.68 (s)	9.70 (s)	9.62 (s)	9.53 (s)	9.77 (s)	9.90 (s)
H-5	9.39 (s)	8.43 (s)	9.35 (s)	9.35 (s)	9.50 (s)	9.49 (s)	9.48 (s)	9.47 (s)	9.55 (s)	9.86 (s)
H-20	8.57 (s)	7.38 (s)	8.70 (s)	8.52 (s)	8.78 (s)	8.60 (s)	8.63 (s)	8.61 (s)	8.80 (s)	9.00 (s)
H-18	4.47 (q)	2.93 (dq)	4.33 (dq)	4.75 (dq)	4.38 (dq)	4.40 (dq)	4.49 (q)	4.49 (q)	4.43 (q)	4.68 (dq)
H-17	4.20 (dd)	2.58 (m)	4.90 (ddd)	3.82 (ddd)	4.42 (ddd)	4.53 (ddd)	4.15 (dd)	4.69 (dd)	4.05 (dd)	5.16 (ddd)
H_a-17^1	2.62 (dt)	1.71 (m)	2.23 (dddd)	3.71 (dddd)	2.19 (dddd)	2.38 (dddd)	2.92 (m)	2.13 (m)	2.46 (m)	2.78 (m)
$H_{a'}$-17^1	2.31 (dt)	1.71 (m)	2.88 (dddd)	2.65 (dddd)	2.85 (dddd)	2.90 (dddd)	2.28 (m)	2.46 (m)	2.18 (m)	2.36 (m)
H_b-17^2	2.50 (t)	2.45 (t)	2.78 (ddd)	3.83 (ddd)	3.49 (ddd)	3.83 (ddd)	2.55 (m)	2.09 (m)	2.45 (m)	2.67 (m)
$H_{b'}$-17^2	2.24 (t)	2.45 (t)	4.31 (ddd)	2.95 (ddd)	3.01 (ddd)	3.05 (ddd)	2.26 (m)	2.29 (m)	1.80 (m)	2.32 (m)
13^2-OH/H	6.27 (s)		4.56 (br s)	4.14 (br s)			5.43 (s)	5.32 (s)		
15^1/17^3-OH		13.24 (s)			5.86 (br s)				6.05 (br s)	

[a] Concentration 1.5 mg/0.6 mL. [b] Concentration 1.0 mg/0.6 mL.

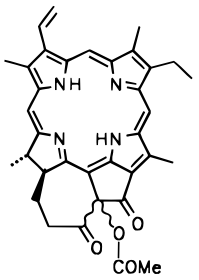
acetoxychlorophyllone *a* (**11**). However, in both cases (**4** and **11**) no epimeric enrichment was noted and no attempts have been made to separate optically-pure **4**.

Due to the unacceptable low yield and stereoselectivity of the above method, alternative methods for introduction of a 13^2-hydroxy group were therefore sought. Thus, we turned out attention to the oxidation of enolates with *N*-sulfonyloxaziridines, a method introduced by Davis and co-workers.[16] Following the standard procedure,[17] treatment of enol **3** with $(TMS)_2NNa$ or LDA followed by oxidation with 1-phenyl-*N*-(phenylsulfonyl)oxaziridine[18] at −78 °C for 30 min failed to give the desired product **4** after the standard workup, but resulted in a very polar yellowish-green mixture. The visible spectrum (672 nm, 404 nm) of this mixture indicated cleavage of the exocyclic rings. Treatment of this mixture with diazomethane gave chlorin p_6 trimethyl ester (**12**) (24% yield from **3**). The amount of base and/or oxaziridine as well as reaction conditions were varied in order to avoid the cleavage of the exocyclic rings, but all were largely unsuccessful. These results suggested that the two exocyclic rings of **3** could not withstand strong ionic bases such as $(TMS)_2NNa$ and LDA.

Therefore, the matter of choosing a suitable base which would not ring-open enol **3** had to be attended to before attempting the asymmetric hydroxylation. Toward this end, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a strong "non-nucleophilic" [19] organic base, was used which was found to be very efficient at promoting the reaction.[8] Reaction of **3** with DBU followed by oxidation with commercially-available (−)-(1*R*)-(10-camphorsulfonyl)oxaziridine [(−)**13**] at −25 °C for 12 h gave a 94% yield of 13^2-hydroxychlorophyllone *a* (**4**), obtained as an (*S*,*R*) mixture of 95% 13^2(*S*)-hydroxychlorophyllone *a* [**4**(S)] and 5% 13^2(*R*)-hydroxychlorophyllone *a* [**4**(R)] according to reversed-phase HPLC analysis.[8,11] Reaction of **3** with (+)-(1*S*)-(10-camphorsulfonyl)oxaziridine [(+)**13**], the enantiomer of (−)**13**, under similar conditions afforded a 88% yield of **4** as a (*R*,*S*) mixture of 68% **4**(R) and 32% **4**(S). The above mixtures were purified by preparative HPLC to furnish diastereomerically pure **4**(S) and **4**(R) (Scheme 1). Structural assigments for **4**(S) and **4**(R) were based on the anisotropic effect of the newly introduced 13^2-OH groups which cause downfield shifts in the ^{1}H NMR of nearby protons [H-17, $H_{a'}$-17^1, $H_{b'}$-17^2 in **4**(S) and H-18, H_a-17^1, H_b-17^2 in **4**(R)] (see Table 1).



6 R=Me
22 R=H



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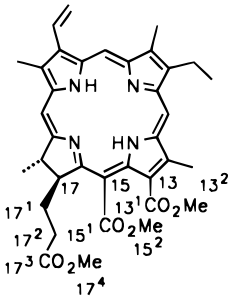

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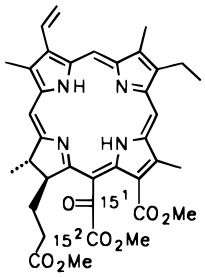

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The stereoselective difference in the reaction of **3** with (−)**13** and (+)**13** can be rationalized as resulting from the effects of the 17-propionic group, which hinders the bulky electrophile (+)**13** from approaching the *re* face of the chlorin enolate.[11] A similar preparation of optically-pure 13^2-hydroxy pheophorbide *a* methyl ester (**10**)[8,11] was readily accomplished (Scheme 1). Reaction of pheophorbide *a* methyl ester (**1**) with (−)**13** gave a diastereomeric mixture (92% yield) of 95% 13^2(*R*)-hydroxypheophorbide *a* methyl ester [**10**(R)] and 5% 13^2-(*S*)-hydroxypheophorbide *a* methyl ester [**10**(S)] while reaction of **1** with (+)**13** gave a mixture (82% yield) of 58% **10**(S) and 42% **10**(R). An HPLC separation of the above (*R*,*S*) diastereomers gave optically-pure **10**(R) and **10**(S). The effectiveness of the preparative separation was confirmed by 400 MHz ^{1}H NMR spectroscopy and further HPLC analysis. The reason for preparation of these monoexocyclic systems, **10**(R) and **10**(S), will become evident in the following discussion.

B. Model Studies for Hydroxylactonization. 15^1-(*R*)-Hydroxychlorophyllone *a* lactone [**5**(R)] and diketone **7** are the mono-oxidized products, at different exocyclic rings, of 13^2-hydroxychlorophyllone *a* (**4**). Purpurin-18 (**8**) results from their further oxidation. Therefore, with

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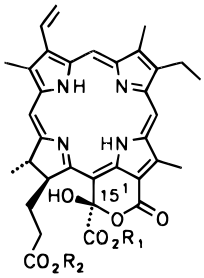
(15) Smith, K. M.; Simpson, D. J. *J. Chem. Res., Synop.* **1987**, 64.
(16) Davis, F. A.; Chen, B. *Chem. Rev.* **1992**, *92*, 919.
(17) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.
(18) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774.
(19) Ma, L.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1995**, 2251 and references therein.

Table 2. Selected ^{1}H−^{1}H Coupling Constants (Hz, $CDCl_3$)

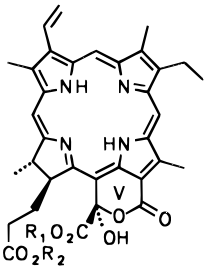
	compound									
protons	**1**	**3**	**4**(S)	**4**(R)	**5**(R)	**6**	**10**(S)	**10**(R)	**17**(S)	**20**
3^1,3^2(*E*)	17.1	18.0	18.1	18.1	17.6	17.4	18.3	18.2	17.6	18.5
3^1,3^2(*Z*)	11.6	11.6	11.4	11.6	11.2	12.1		11.9	11.5	12.4
3^2(*E*),3^2(Z)		1.6	1.2	1.0	1.0	1.0	0.8	1.0	1.2	1.3
8^1,8^2	7.8	7.9	8.1	7.2	7.9	7.7	7.6	7.7	8.0	7.7
18^1,18	7.1	7.2	7.4	7.0	7.5	7.3	7.3	7.0	6.8	7.6
18,17	1.7		3.8	8.3	1.6	1.7				1.3
17,17^1	3.1		13.3	11.0	11.5	12.3	2.2	1.7	2.4	2.9
17,$17^1{}_{a'}$	9.3		3.5	1.6	5.3	6.6	10.2	8.5	10.4	8.8
$17^1{}_a$, $17^1{}_{a'}$	13.3		12.4	13.1	12.8	12.3				
$17^1{}_a$, $17^2{}_b$	7.1		2.1	6.2	8.3	10.0				
$17^1{}_a$, $17^2{}_{b'}$	6.2		14.0	12.8	2.5	1.4				
$17^1{}_{a'}$, $17^2{}_b$	9.3		4.4	1.5	9.0	10.0				
$17^1{}_{a'}$, $17^2{}_{b'}$	5.3		3.5	5.2	9.6	8.3				
$17^2{}_b$, $17^2{}_{b'}$	15.1		11.7	15.0	11.5	12.7				

sufficient amounts of **4** at hand, our next objective was directed toward generation of these further oxidized products. Initially, because 13^2-hydroxychlorophyllone *a* (**4**) possesses two similar carbonyl groups which are both reactive (though the carbonyl at the 17^3-position appeared to be less sterically encumbered and less conjugated), the monoketone 13^2-hydroxypheophorbide *a* methyl ester (**10**) was used as a model for the hydroxylactonization reaction.

The first hydroxy lactonechlorin **14**, a diastereomeric mixture of hydroxy lactones **14**(S) and **14**(R), was prepared by Fischer,[14] via aerial oxidation of pheophorbide *a* methyl ester (**1**) in the presence of pyridine and alkali, in the 1930s. This mixture, called "unstable chlorin" due to its extreme instability, is the precursor to many chlorophyll *a* degradation products.[20] The "unstable chlorin" monomethyl ester **15** [a diastereomeric mixture of **15**(R) and **15**(S)] is more stable and was obtained by Fischer after $KMnO_4$ oxidation of pheophorbide *a* followed by acid fractionation.[14]



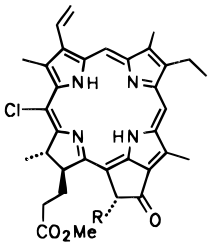
14 (S). R_1=R_2=H
15 (S). R_1=Me, R_2=H
17 (S). R_1=R_2=Me



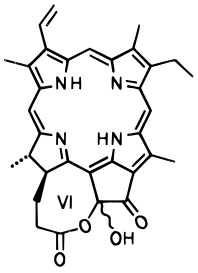
14 (R). R_1=R_2=H
15 (R). R_1=Me, R_2=H
17 (R). R_1=R_2=Me

Treatment of (95%*R*, 5%*S*) 13^2-hydroxypheophorbide *a* methyl ester (**10**) with methanolic alkali at room temperature for 12 h under N_2 resulted in the hydrolytic cleavage of ring V, generating "unstable chlorin" **14**, a result similar to the alkaline aerial oxidation of pheophorbide *a* methyl ester (**1**). Attempts to purify "unstable chlorin" **14** were unsucessful due to its ready decomposition. However, purpurin-7 trimethyl ester (**16**) (45% yield from **10**) was obtained after treatment of the "unstable chlorin" (**14**) with diazomethane. Attempts to prepare "unstable chlorin" dimethyl ester (**17**) [a diastereomeric mixture of **17**(R) and **17**(S)] by partial esterification (via Et_3N/MeOH) of **14** were also unsuccessful since methylation of the hydroxy lactone is fast and readily proceeds without selective differentiation of the 17^3-carboxylic acid. Rather than expend further efforts on optimizing this process, it was decided to establish whether this route was suitable for the oxidation of 13^2-(*S*)-hydroxychlorophyllone *a* [**4**(S)]. Treament of the (95%*S*, 5%*R*) mixture of 13^2-hydroxychlorophyllone *a* (**4**) with KOH/MeOH under N_2 for 10 h led to the cleavage of both exocyclic rings and gave chlorin p_6 trimethyl ester (**12**) after methylation with diazomethane.

Formally, the transformation of hydroxy ketone **4** to hydroxy lactone **5**(R) is oxygen atom insertion, and Sakata *et al.*[4] have suggested that this transformation is achieved biogenetically via a Baeyer−Villiger type oxidation. With this in mind, we also investigated the oxidation of chlorins with peroxycarboxylic acids. Unfortunately, reaction of **4** (95%*S*, 5%*R*) or **10** (95%*R*, 5%*S*) with MCPBA or CF_3COOOH in the dark resulted in overoxidation and no products could be identified. Conversely, treatment of the non-hydroxylated chlorins, pheophorbide *a* methyl ester (**1**) and pyropheophorbide *a* methyl ester (**2**), with the above oxidants gave no reactions if electrophiles were not present in solution. Instead of oxidation, electrophilic substitution at the H-20 positions of **1** and **2** occurred when only a trace amount of electrophile was present. For example, traces of HCl present in solvent chloroform will bring about the formation of 20-chloropheophorbide a methyl ester (**18**) and 20-chloropyropheophorbide *a* methyl ester (**19**). This higher susceptibility of 20 position to electrophiles in pheophorbides has been observed before.[21]



18. R=COOMe
19. R=H



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The only method which worked in our hands was found to be periodate oxidation, which occurred only under acidic conditions. Periodic acid (0.1 N) in aqueous dioxane was found to be the most satisfactory, and 15^1-hydroxypurpurin-7 lactone dimethyl ester (**17**) was isolated in 79% yield. Under these conditions **17** was obtained as a diastereomeric mixture of 84% **17**(S) and 16% **17**(R) (from signal integration of the 400 MHz ^{1}H NMR). Either epimer of **10** was found to give the same diastereomeric mixture of **17** under the above oxidation conditions. The reason for this is that hydroxy lactone **17** is very sensitive to both acid and base which give rise to epimerization via the reversible opening of the hydroxy lactone ring. Equilibration under acidic conditions predominantly favors formation of the thermodynamically more stable epimer **17**(S) in which the methoxycarbonyl moiety at position 15^1 is on the side opposite to that of the bulky 17-propionic group. Therefore, in subsequent

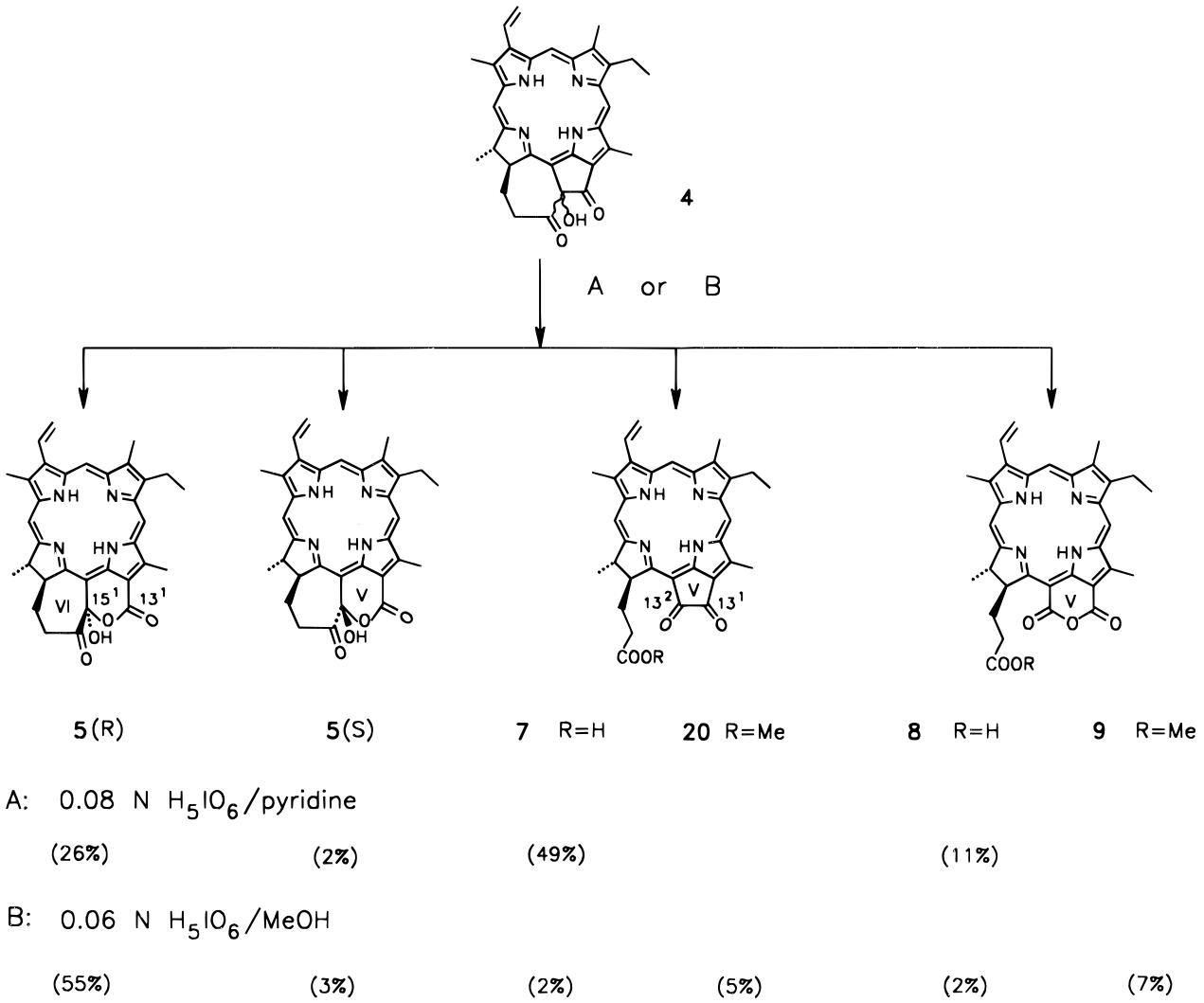
(20) Kenner, G. W.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2517.

(21) Scheer, H.; Inhoffen, H. H. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. II, pp 45−90.

Table 3. Selected ^{13}C NMR Spectral Data ($CDCl_3$)

	compound								
carbon	**1**	**3**	**4**(S)	**4**(R)	**5**(R)	**6**	**10**(S)	**10**(R)	**20**
C-17[3]	173.36	167.35	208.00	206.21	203.62	196.90	172.83	173.46	174.87
C-13[1]	189.63	191.78	195.44	193.39	162.57	166.90	192.00	191.93	192.79
C-13[2]	64.71	116.83	93.43	92.66		52.31	88.94	89.09	185.19
C-17	52.88	52.47	51.91	53.71	49.84	50.16	51.75	50.75	52.67
C-18	51.70	49.33	51.51	50.31	51.18	51.20	50.29	50.16	51.63
C-17[2]	29.86	34.00	40.12	43.17	34.17	36.25	31.40	30.99	29.70
C-17[1]	31.06	25.03	37.99	22.71	31.37	29.47	31.11	30.18	31.50
C-15[1]					104.68	192.38			
C-18[1]	23.10	19.06	22.37	16.99	23.56	23.62	22.65	22.69	23.85

Scheme 2



reactions, we used the (95%*S*, 5%*R*) **4** instead of using epimerically-pure compounds. Reaction of **17** with an excess of ethereal diazomethane caused almost quantitative conversion to purpurin-7 trimethyl ester (**16**).

C. Periodate Oxidation of α-Hydroxy 1,3-Diketone 4. When the initial experiment utilizing the above periodate oxidation was used to make hydroxy lactone **5** and 1,2-diketone **7**, only a low yield (<10%) of the desired products was obtained, the major product (>50%) being the bis-oxidized product purpurin-18 (**8**). This indicated that the "mono-oxidized products" **5** and **7** were more reactive than the starting material **4**, and this was confirmed by following oxidations of **5** and **7** with periodic acid, where both more rapidly gave purpurin-18 (**8**).

Subsequent work showed that regioselective oxidation of one of the two carbonyl groups can be modestly achieved by using different solvent systems. Addition of pyridine to the periodic acid solution resulted in the formation of 13^2-oxopyropheophorbide *a* (**7**) (49%) and two minor products, a 28% yield of 15^1-hydroxychlorophyllone *a* lactone (**5**) and an 11% yield of purpurin-18 (**8**) isolated after preparative TLC on deactivated silica (condition A in Scheme 2).[8] Structural assignments are based on visible and ^1H and ^{13}C NMR spectroscopy (see Experimental Section). This procedure preferentially oxidized the seven-membered exocyclic ring and allowed for the preparation of 13^2-oxopyropheophorbide *a* (**7**) from pheophorbide *a* methyl ester (**1**) in 4 steps in ~40% overall yield.

Another procedure which oxidizes the exocyclic ring V over ring VI results from replacement of pyridine with methanol as a component in the reaction medium with

periodic acid. Under these conditions, (95%*S*, 5%*R*) **4** was predominantly converted into 13^2-hydroxychlorophyllone *a* lactone (**5**) (57%), together with four minor products, 13^2-oxopyropheophorbide *a* (**7**) (1.8%), purpurin-18 (**8**) (2.7%), purpurin-18 methyl ester (**9**) (7.2%), and 13^2-oxopyropheophorbide *a* methyl ester (**20**) (5.4%) (condition B in Scheme 2). Separation was achieved by preparative TLC on deactivated silica gel. Two purple-red compounds, **8** (the second least mobile band) and its methyl ester **9** (the most mobile band), could be readily identified from their different R_f values and their identical visible spectra (700, 404 nm) while the two yellow compounds, **7** (the least mobile band) and its methyl ester **20** (the second most mobile band) displayed the same visible spectra (678, 420, 390 nm). The gray-green major band (**5**) was shown by 400 MHz ^{1}H NMR to be a diastereomeric mixture of 94% 15^1(*R*)-hydroxychlorophyllone *a* lactone [**5**(R)] and 6% 15^1(*S*)-hydroxychlorophyllone *a* lactone [**5**(S)]. Hydroxy lactone **5** was found, like the model hydroxy lactone **17**, to be very sensitive to acid and base which give rise to epimerization via the reversible opening of its hydroxy lactone ring. Nevertheless, the principal product **5**(R) has an α (down) 15^1-OH group rather than a β-OH as in the model hydroxy lactone **17**(S). The reversed orientation of the 15^1-OH in **5**(R) is due to the conformation at the C-15^1 position which reduces the serious steric congestion with the carbonyl group at C-17^3. Optically-pure **5**(R) was obtained by subjecting the above diastereomeric mixture to preparative TLC separation on deactivated silica gel. The synthetic **5**(R) exhibits identical spectra to those of the natural product (see Experimental Section). This procedure produces an efficient synthesis of 15^1(*R*)-hydroxychlorophyllone *a* lactone [**5**(R)] from pheophorbide *a* methyl ester (**1**) in four steps in ~45% overall yield.

As expected, reaction of the (94%*R*, 6%*S*) 15^1-hydroxychlorophyllone *a* lactone (**5**) with an excess of ethereal diazomethane gave a good yield (82%) of chlorophyllonic acid *a* methyl ester (**6**). Attempts to isolate **21**, the lactonized isomer of 13^2-oxopyropheophorbide *a* (**7**), by using milder oxidation conditions failed. In addition, attempts to obtain a pure sample of chlorophyllonic acid *a* (**22**), a non-lactonized isomer of 15^1-hydroxychlorophyllone lactone *a* (**5**), were also unsuccessful. These observations, and a consideration of the peripheral overcrowding, indicate that formation of the six-membered hydroxy lactone ring (as in **5**, **8**, and **17**) is predominant and cyclization to the eight-membered hydroxy lactone ring (as in **21**) is unfavored under our reaction conditions.[22]

Although chlorins **6** and **20** are 1,2-diketones, their oxidation by periodic acid was found to be even faster than for the α-hydroxy 1,3-diketone **4**, a difference mainly attributed to the ring strain of the 1,2-diketone twisted conformation in **6** and **20** and the obviously more encumbered conformation of **4**.

Conclusions

In summary, syntheses of new chlorophyll *a* related chlorins from chlorophyll *a* have been accomplished in a way that parallels their probable biogenesis. The key stereochemical issues were addressed via DBU-promoted asymmetric hydroxylation with the expectation that the rigid exocyclic ring VI (in **5**) would provide an exploitable diastereofacial bias for ensuing hydroxylactonization to the desired epimer **5**(R). DBU as a base for promoting hydroxylation reactions is certain to be applicable to other 1,3-diketonic systems, particularly those sensitive to ionic bases. Periodate oxidations of either epimer of **4** were found to give similar products, i.e., a mixture of mono- and bis-oxidized products **5**, **7**, and **8**, which coincidently parallels all the antioxidant chlorins isolated from the short-necked clam, *R. philippinarum*.[4] This observation suggests that **5**(R), **7**, and **8** were probably biosynthesized by "periodate type" oxidation of **4**(S). These new chlorophyll *a* related chlorins also provide strong structural evidence to support the hypothesis that the antioxidative chlorins synthesized in this work are precursors to the so-called "disturbing petroporphyrins" [23] characterized by exocyclic rings, which are molecular fossils of chlorophyll *a* derivatives in marine sediment.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were recorded using a Bruker WH-400 spectrometer, and ^{13}C NMR spectra were run on a Varian XL-300 or a Bruker AMX-500 spectrometer. Silica gel 60 (70−230 mesh, Merck; usually silica III, deactivated with 6% water or silica V, deactivated with 15% water) was used for column chromatography. Preparative thin layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck G_{254} silica gel (0.5 mm, 1 mm thick); the plates were deactivated by a blank development with 10% methanol in dichloromethane followed by air drying before use. Electronic absorption spectra were measured in chloroform or/and methanol using a HP 8452A diode array spectrophotometer. Analytical HPLC chromatograms were obtained using a Waters Novapak C_{18} 4 μm 60 Å (3.9 mm × 15 cm) column. Semipreparative HPLC separations were performed on a Waters 600E HPLC system using a Waters C_{18} 10 μm 125 Å (7.8 mm × 30 cm) column with a flow rate at 3 mL min^{-1} and detection at 410 nm. Mass spectra were recorded by fast atom bombardment (FAB) and electron impact (EI). Elemental analyses were carried out in the departmental microanalytical laboratory at UBC. Reactions were monitored by TLC and spectrophotometry and were carried out under nitrogen and in the dark. Pheophorbide *a* methyl ester (**1**) was obtained from *S. maxima* alga using a literature method.[9] Pyropheophorbide *a* methyl ester (**2**) was obtained (98% yield) from decarboxylation of pheophorbide *a* methyl ester (**1**) in collidine.[9] 1-Phenyl-*N*-(phenylsulfonyl)-oxaziridine was prepared by following the literature procedure.[18] (−)-(1*R*)-(10-Camphorsulfonyl)oxaziridine and (+)-(1*S*)-(10-camphorsulfonyl)oxaziridine were purchased from Aldrich. Tetrahydrofuran (THF) and dioxane were dried overnight with calcium hydride and distilled from sodium wire and benzophenone; other solvents were of reagent grade.

13^2,17^3-Cyclopheophorbide *a* Enol (3). To a solution of pyropheophorbide *a* methyl ester (**2**) (546 mg, 1 mmol) in THF (60 mL) under an atmosphere of nitrogen was added $(TMS)_2$-NNa (7.0 mL, 7.0 mmol, 1.0 M in THF). The yellow solution was stirred at room temperature for 3 min and then poured onto a deoxygenated (N_2) mixture of dichloromethane (800 mL), saturated NaH_2PO_4 (200 mL), and ice (200 g). The mixture was shaken until the yellow color turned to bright-green. After the aqueous phase was separated, the organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo*. The residue was purified by chromatography on silica V, eluting with dichloromethane. The product was crystallized from dichloromethane/hexane under nitrogen, giving the title product 438 mg (85%) as lustrous dark green needles: mp >300 °C [lit.[10] mp >300 °C, lit.[5] mp >360 °C]; ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) δ 13.24 (s, 1H), 8.64 (s, 1H), 8.43 (s, 1H), 7.38 (s, 1H), 7.70 (dd, J = 18.0, 11.6 Hz, 1H), 6.12 (dd, J = 18.0, 1.6 Hz, 1H), 6.04 (d, J = 11.6, 1.6 Hz,

(22) Woodward, R. B.; *et al. Tetrahedron* **1990**, *46*, 7599.

(23) Callot, H. J. In *Chlorophylls*; Scheer, H., Ed.; CRC Press: Boca Raton, 1991; p 339. Lash, T. D. *Energy Fuels* **1993**, *7*, 166. Lash, T. D.; Balasubramaniam, R. P. *Tetrahedron Lett.* **1990**, *31*, 7545.

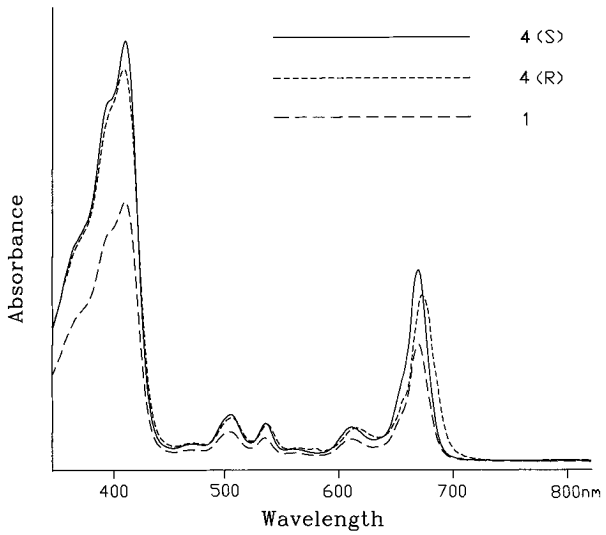


Figure 1. UV−vis spectra ($CHCl_3$) of pheophorbide *a* methyl ester (**1**), 13^2(*S*)-hydroxychlorophyllone *a* [**4**(S)], and 13^2(*R*)-hydroxychlorophyllone *a* [**4**(R)].

1H), 3.31 (q, J = 7.9 Hz, 2H), 3.08 (s, 3H), 3.02 (s, 3H), 2.94 (s, 3H), 2.93 (q, J = 7.2 Hz, 1H), 2.58 (m, 1H), 2.45 (t, 2H), 1.71 (m, 2H), 1.80 (d, J = 7.1 Hz, 3H), 1.52 (t, J = 7.9 Hz, 3H), 0.30 (br s, 1H), −1.72 (br s, 1H); ^{13}C NMR (75 MHz, 18.0 mg/0.6 mL $CDCl_3$) δ 191.78, 169.63, 167.35, 157.77, 154.65, 150.04, 144.15, 143.21, 141.27, 136.35, 135.95, 135.04, 134.99, 130.80, 128.93, 127.78, 127.52, 121.80, 116.83, 104.10, 104.02, 96.74, 91.02, 52.47, 49.33, 34.00, 25.03, 19.06, 17.24, 16.69, 11.69, 11.58, 10.90; UV−vis λ_{max} ($CHCl_3$) 364 nm (ϵ 67 200), 430 (66 000), 456 (47 200), 592 (5 200), 630 (4 800), 690 (33 400) [lit.[10] λ_{max} (CH_2Cl_2) 361 nm (ϵ 65 500), 429 (64 000), 455 (44 400), 629 (9 000), 688 (33 000); lit.[5] λ_{max} 359 nm (ϵ 63 000), 426 (63 000), 452 (50 000), 626 (10 000), 686 (32 000)]; EIMS *m/z* 516 (M^+,100%), 501 (28); HREIMS $C_{33}H_{32}N_4O_2$ (M^+) calcd 516.2525, obsd 516.2534. Anal. Calcd for $C_{33}H_{32}N_4O_2$: C, 76.72; H, 6.24; N, 10.84. Found: C, 76.91; H, 6.19; N, 10.37.

13^2(*S*)-Hydroxychlorophyllone *a* [4(S)]. A cold (−25 °C) solution of 13^2,17^3-cyclopheophorbide *a* enol (**3**) (103 mg, 0.2 mmol) in THF (60 mL) was blanketed with N_2 and stirred vigorously while DBU (1.0 mL) was injected dropwise via a syringe. After 15 min at this temperature, a solution of (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (50 mg, 0.22 mmol) in cold (−25 °C), dry THF (12 mL) was transferred into the reaction vessel via a cannula. This mixture was stirred at −25 °C for 12 h, and the reaction was quenched with saturated NH_4Cl. The aqueous phase was extracted with dichloromethane (2 × 100 mL), and the combined organic phases were dried over sodium sulfate, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica V, eluting with dichloromethane. The product was crystallized from methanol, giving 100 mg (94%) of a blue microcrystalline powder, which was analyzed by reversed-phase HPLC as a diastereomeric mixture of 95% 13^2(*S*)-hydroxychlorophyllone *a* [**4**(S)] and 5% 13^2(*R*)-hydroxychlorophyllone *a* [**4**(R)]: mp >300 °C. Anal. Calcd for $C_{33}H_{32}N_4O_3$: C, 74.41; H, 6.06; N, 10.52. Found: C, 74.65; H, 6.10; N, 10.19. After semipreparative HPLC separation (12 mg) with a mobile phase, 75% (0.1% TFA in CH_3CN)/25% (0.1% TFA in water), 13^2(*S*)-hydroxychlorophyllone *a* [**4**(S)] (10 mg) was obtained. After treatment with methanol, the optically-pure title compound (9.1 mg) was collected as a dark green solid: mp >300 °C; ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) δ 9.40 (s, 1H), 9.35 (s, 1H), 8.70 (s, 1H), 7.96 (dd, J = 18.1, 11.4 Hz, 1H), 6.28 (dd, J = 18.1, 1.2 Hz, 1H), 6.18 (d, J = 11.4, 1.2 Hz, 1H), 4.90 (ddd, J = 13.3, 3.8, 3.5 Hz, 1H), 4.56 (br s, 1H), 4.33 (dq, J = 7.4, 3.8 Hz, 1H), 4.31 (ddd, J = 14.0, 11.7, 3.5 Hz, 1H), 3.60 (s, 3H), 3.59 (q, J = 8.1 Hz, 2H), 3.39 (s, 3H), 3.20 (s, 3H), 2.88 (dddd, J = 12.4, 4.4, 3.5, 3.5 Hz, 1H), 2.78 (ddd, J = 14.0, 11.7, 2.1 Hz, 1H), 2.23 (dddd, J = 14.0, 13.3, 12.4, 2.1 Hz, 1H), 2.19 (d, J = 7.4 Hz, 3H), 1.64 (t, J = 8.1 Hz, 3H), 0.41 (br s, 1H), −2.05 (br s, 1H); ^{13}C NMR (125 MHz, 7.0 mg/0.6 mL $CDCl_3$) δ 208.00, 195.44, 172.68, 163.20, 154.53, 150.92, 147.72, 144.88, 142.16, 138.19, 136.38, 136.31, 135.75, 131.58, 129.13, 129.08, 127.77, 122.85, 105.36, 104.06, 98.10, 93.43, 92.87, 51.92, 51.51, 40.12, 37.99, 22.37, 19.24, 17.29, 12.20, 12.08, 11.14; UV−vis λ_{max} ($CHCl_3$) 416 nm (ϵ 111 000), 506 (12 500), 536 (10 200), 612 (9 200), 670 (50 900), λ_{max} (CH_3OH) 408 nm (ϵ 103 000), 504 (11 600), 534 (9 000), 608 (8 300), 666 (47 600) [lit.[4] λ_{max} (CH_3OH) 408 nm, 503, 534, 608, 665]; FABMS *m/z* 533 ($[MH]^+$, 100%), 532 (37), 531 (17); HRFABMS $C_{33}H_{33}N_4O_3$ ($[MH]^+$) cacld 533.2552, obsd 533.2540.

13^2(*R*)-Hydroxychlorophyllone *a* [4(R)]. The same hydroxylation procedure as for **4**(S) was employed by reacting 13^2,17^3-cyclopheophorbide *a* enol (**3**) (52 mg, 0.1 mmol) with (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine (27 mg, 0.118 mmol). The product was purified as described above and gave a blue solid (45.9 mg, 88%) after treatment with methanol. A reversed-phase HPLC analysis showed the product to be a diastereomeric mixture of 68% 13^2(*R*)-hydroxychlorophyllone *a* [**4**(R)] and 32% 13^2(*S*)-hydroxychlorophyllone *a* [**4**(S)]: mp >300 °C. Anal. Calcd for $C_{33}H_{32}N_4O_3$: C, 74.41; H, 6.06; N, 10.52. Found: C, 74.13; 6.14; N, 10.44. After semipreparative HPLC separation (9 mg) with a mobile phase, 75% (0.1% TFA in CH_3CN)/25% (0.1% TFA in water), 13^2(*R*)-hydroxychlorophyllone *a* [**4**(R)] (4.5 mg) was obtained. After treatment with methanol, the optically-pure title compound (4.2 mg) was collected as a dark green solid: mp >300 °C; ^{1}H NMR (400 MHz, 1.0 mg/0.6 mL $CDCl_3$) δ 9.47 (s, 1H), 9.35 (s, 1H), 8.52 (s, 1H), 7.96 (dd, J = 17.6, 11.2 Hz, 1H), 6.29 (dd, J = 17.6, 1.0 Hz, 1H), 6.18 (dd, J = 11.2, 1.0 Hz, 1H), 3.82 (ddd, J = 11.0, 8.3, 1.6 Hz, 1H), 4.14 (br s, 1H), 4.75 (dq, J = 8.3, 7.0 Hz, 1H, H-18), 3.68 (s, 3H), 3.68 (q, J = 7.2 Hz, 2H), 3.35 (s, 3H), 3.20 (s, 3H), 2.95 (ddd, J = 15.0, 12.8, 5.2 Hz, 1H), 2.65 (dddd, J = 13.1, 5.2, 1.6, 1.5 Hz, 1H), 3.83 (ddd, J = 15.0, 6.2, 1.5 Hz, 1H), 3.71 (dddd, J = 13.1, 12.8, 11.0, 6.2 Hz, 1H), 2.20 (d, J = 7.0 Hz, 3H), 1.68 (t, J = 7.2 Hz, 3H), 0.90 (br s, 1H), −1.56 (br s, 1H); ^{13}C NMR (75 MHz, 4.0 mg/0.6 mL $CDCl_3$) δ 206.21, 193.39, 172.36, 162.82, 154.68, 150.80, 149.43, 144.95, 142.44, 138.18, 136.32, 136.26, 135.89, 131.60, 129.55, 128.93, 127.11, 122.83, 105.73, 104.73, 98.29, 92.66, 91.73, 53.71, 50.31, 43.17, 22.71, 19.36, 17.39, 16.99, 12.25, 12.01, 11.16; UV−vis λ_{max} ($CHCl_3$) 416 nm (ϵ 113 000), 508 (15 500), 538 (11 100), 616 (10 000), 674 (48 300), λ_{max} (CH_3OH) 408 (ϵ 119 000), 504 (13 500), 534 (11 000), 612 (10 500), 670 (50 000) [lit.[4] λ_{max} (CH_3OH) 408 nm, 505, 535, 612, 670]; EIMS *m/z* 532 (M^+, 100%), 501 (21); HREIMS $C_{33}H_{32}N_4O_3$ (M^+) calcd 532.2474, obsd 532.2474.

Chlorin p_6 Trimethyl Ester (12). (a) A cold (−78 °C) solution of 13^2,17^3-cyclopheophorbide *a* enol (**3**) (30 mg, 58 μmol) in THF (15 mL) was blanketed with N_2 and stirred vigorously while a similarly cold solution of $(TMS)_2NNa$ in THF (0.18 mL of 1.0 M, 0.18 mmol) was introduced dropwise via a syringe. After 15 min at this temperature, a solution of 1-phenyl-*N*-(phenylsulfonyl)oxaziridine[18] (20.8 mg, 79 μmol) in cold (−78 °C), dry THF (1 mL) was transferred into the reaction vessel via a cannula. This mixture was stirred at −78 °C for 30 min before the reaction was quenched with saturated NH_4Cl. The aqueous phase was extracted with dilchloromethane (3 × 30 mL), and the combined organic phases were dried over sodium sulfate, filtered, and evaporated *in vacuo*. TLC analysis showed that the product did not move on TLC even with development by 5% methanol in dichloromethane. The residue was dissolved in THF and acidified with 1 M HCl. The aqueous layer was reextracted with dichloromethane before the organic layer was treated with an excess of ethereal diazomethane. The evaporated residue was purified by chromatography on silica gel, eluting with dichloromethane. The product was crystallized from dichloromethane/methanol, giving the title compound (8.8 mg, 24%) as small dark green needles: mp 237 °C [lit.[24] mp 235−236 °C, lit.[25] mp 236 °C]; ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) δ 9.70 (s, 1H), 9.49 (s, 1H), 8.77 (s, 1H), 8.00 (dd, J = 16.8, 12.0 Hz, 1H), 6.31 (dd, J = 16.8, 1.2 Hz, 1H), 6.15 (dd, J = 12.0, 1.2 Hz, 1H), 5.15 (dd, J = 9.2, 2.8 Hz, 1H), 4.38 (q, J = 7.6 Hz, 1H), 4.22 (s, 3H), 4.14 (s, 3H), 3.72 (q, J = 7.7 Hz, 2H), 3.63 (s, 3H), 3.52 (s, 3H), 3.40 (s, 3H), 3.23 (s, 3H), 2.38 (m, 1H), 2.20 (m, 1H),

2.05 (m, 1H), 1.87 (m, 1H), 1.84 (d, J = 7.6 Hz, 3H), 1.69 (t, J = 7.7 Hz, 3H), −0.82 (br s, 1H), −1.00 (br s, 1H); ^{13}C NMR (75 MHz, 7.5 mg/0.6 mL $CDCl_3$) δ 173.54, 172.84, 170.72, 167.23, 167.02, 154.93, 148.89, 145.24, 141.19, 137.75, 135.98, 135.80, 135.71, 135.46, 130.87, 129.53, 129.06, 122.44, 122.34, 104.64, 103.08, 100.33, 93.60, 52.67, 52.56, 52.14, 51.48, 49.39, 31.43, 31.25, 23.56, 19.56, 17.64, 12.54, 12.04, 11.20; UV−vis λ_{max} ($CHCl_3$) 404 nm (ϵ 158 500), 500 (12 000), 532 (7 300), 616 (6 200), 672 (44 900) [lit.[24] λ_{max} (CH_2Cl_2) 402 nm (ϵ 137 000), 498 (9 900), 532 (5 500), 614 (4 900), 668 (40 900)]; FABMS m/z 625 ([MH]$^+$, 100%), 567 (23); HRFABMS $C_{36}H_{41}N_4O_6$ ([MH]$^+$) calcd 625.3026, obsd 625.3043. Anal. Calcd for $C_{36}H_{40}N_4O_6$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.75; H, 6.38; N, 8.80.

(b) A solution of the foregoing (95%*S*, 5%*R*) mixture of 13^2-hydroxychlorophyllone *a* (**4**) (15 mg, 0.0282 mmol) in THF (15 mL) was blanketed with N_2 and stirred vigorously while KOH (0.5 g) in CH_3OH (5 mL) was added. This mixture was stirred at room temperature in the dark for 10 h before the mixture was acidified to pH 3 by 2 N HCl and extracted with dichloromethane. The organic layer was washed with water three times before being treated with an excess of ethereal diazomethane. The material was purified as described in section a (above) to give chlorin p_6 trimethyl ester (**12**) (8.0 mg, 46%).

13^2(*R*)-Hydroxypheophorbide *a* Methyl Ester [10(R)]. The same hydroxylation procedure as for **4**(S) was employed by reacting pheophorbide *a* methyl ester (**1**) (61 mg, 0.1 mmol) with (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (27 mg, 0.118 mmol). The product was purified as described for hydroxychlorin **4**(S) and, after treatment with methanol, gave a blue powder (57 mg, 92%) which was analyzed by reversed-phase HPLC as a diastereomeric mixture of 95% 13^2(*R*)-hydroxypheophorbide *a* methyl ester [**10**(R)] and 5% 13^2(*S*)-hydroxypheophorbide *a* methyl ester [**10**(S)]: mp >300 °C. Anal. Calcd for $C_{36}H_{38}N_4O_6$: C, 69.44; H, 6.15; N, 9.00. Found: C, 69.10; H, 6.16; N, 8.70. After semipreparative HPLC separation (10 mg) with a mobile phase, 85% (0.1% TFA in CH_3CN)/15% (0.1% TFA in water), 13^2(*R*)-hydroxypheophorbide *a* methyl ester **10**(R) (7.5 mg) was obtained. After treatment with methanol, the optically-pure title compound (7.0 mg) was collected as shiny blue plates: mp >300 °C; ^{1}H NMR (400 MHz, 1.0 mg/0.6 mL $CDCl_3$) δ 9.53 (s, 1H), 9.47 (s, 1H), 8.61 (s, 1H), 7.96 (dd, J = 18.2, 11.9 Hz, 1H), 6.29 (dd, J = 18.2, 1.0 Hz, 1H), 6.17 (dd, J = 11.9, 1.0 Hz, 1H), 5.32 (s, 1H), 4.69 (dd, J = 8.5, 1.7 Hz, 1H), 4.49 (q, J = 7.0 Hz, 1H), 3.70 (q, J = 7.7 Hz, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H), 3.18 (s, 3H), 2.46 (m, J = 8.5 Hz, 1H), 2.29 (m, 1H), 2.13 (m, J = 1.7 Hz, 1H), 2.09 (m, 1H), 1.68 (d, J = 7.0 Hz, 3H), 1.65 (t, J = 7.7 Hz, 3H), 0.39 (br s, 1H), −1.74 (br s, 1H); ^{13}C NMR (75 MHz, 7.0 mg/0.6 mL $CDCl_3$) δ 191.93, 173.46, 173.42, 172.71, 161.80, 155.46, 150.88, 150.19, 145.15, 142.09, 137.68, 136.40, 136.35, 136.24, 131.87, 129.56, 128.96, 126.22, 122.31, 107.58, 104.15, 97.79, 93.40, 89.09, 53.77, 51.33, 50.75, 50.16, 30.99, 30.18, 22.69, 19.35, 17.41, 12.27, 12.08, 11.15; UV−vis λ_{max} ($CHCl_3$) 416 nm (ϵ 136 600), 506 (15 500), 538 (11 600), 560 (4 200), 612 (11 500), 670 (62 100); FABMS m/z 623 ([MH]$^+$, 100%), 695 (19), 563 (12); HRFABMS $C_{36}H_{39}N_4O_6$ ([MH]$^+$) calcd 623.2869, obsd 623.2874.

13^2(*S*)-Hydroxypheophorbide *a* Methyl Ester [10(S)]. The same hydroxylation procedure as for **10**(R) was employed for the reaction of pheophorbide *a* methyl ester (**1**) (61 mg, 0.1 mmol) with (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine (27 mg, 0.118 mmol). The product was purified as above and, after treatment with methanol, gave a blue solid (51 mg, 82%), which was analyzed by reversed-phase HPLC as a diastereomeric mixture of 58% 13^2(*S*)-hydroxypheophorbide *a* methyl ester [**10**(S)] and 42% 13^2(*R*)-hydroxypheophorbide *a* methyl ester [**10**(R)]: mp >300 °C. After semipreparative HPLC separation (10 mg) with a mobile phase, 85% (0.1% TFA in CH_3CN)/5% (0.1% TFA in water), 13^2(*S*)-hydroxy pheophorbide *a* methyl ester [**10**(S)] (4.1 mg) was separated and was treated with methanol, giving the optically-pure title product (3.9 mg) as a dark blue solid: mp >300 °C; ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) δ 9.62 (s, 1H), 9.48 (s, 1H), 8.63 (s, 1H), 8.01 (dd, J = 18.3, 11.7 Hz, 1H), 6.30 (dd, J = 18.3, 0.8 Hz, 1H), 6.20 (dd, J = 11.7, 0.8 Hz, 1H), 5.43 (s, 1H), 4.49 (q, J = 7.3 Hz, 1H), 4.15 (dd, J = 2.2, 10.2 Hz, 1H), 3.72 (s, 3H), 3.69 (q, J = 7.6 Hz, 2H), 3.64 (s, 3H), 3.59 (s, 3H), 3.41 (s, 3H), 3.23 (s, 3H), 2.92 (m, J = 2.2 Hz, 1H), 2.55 (m, 1H), 2.28 (m, J = 10.2 Hz, 1H), 2.26 (m, 1H), 1.68 (t, J = 7.6 Hz, 3H), 1.58 (d, J = 7.3 Hz, 3H), 0.31 (br s, 1H), −1.83 (br s, 1H); ^{13}C NMR (75 MHz, 3.5 mg/0.6 mL $CDCl_3$) δ 192.00, 173.96, 172.83, 172.37, 162.37, 155.35, 151.03, 149.84, 145.22, 142.03, 137.80, 136.52, 136.29, 136.21, 131.76, 129.41, 129.04, 122.89, 122.88, 107.59, 104.26, 97.97, 93.62, 88.94, 53.44, 51.78, 51.75, 50.29, 31.40, 31.11, 22.65, 19.47, 17.45, 12.30, 12.11, 11.26; UV−vis λ_{max} ($CHCl_3$) 414 nm (ϵ 141 200), 506 (9 800), 536 (15 800), 612 (11 300), 670 (63 500); EIMS m/z 622 (M$^+$, 56%), 563 (100); HREIMS $C_{36}H_{38}N_4O_6$ (M$^+$) calcd 622.2791, obsd 622.2802.

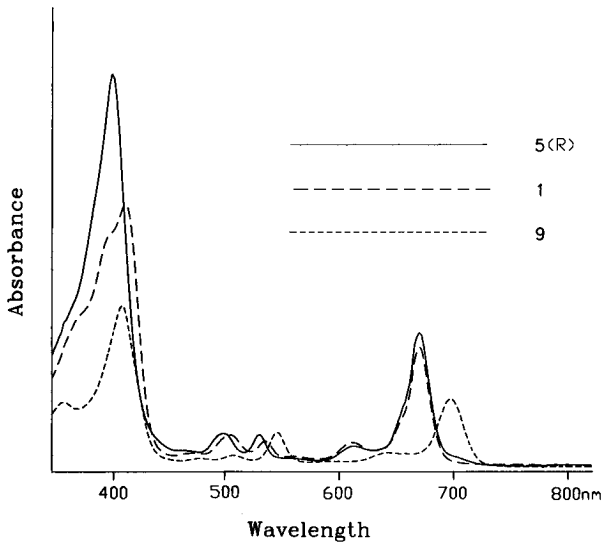


Figure 2. UV−vis spectra ($CHCl_3$) of pheophorbide *a* methyl ester (**1**), 15^1(*R*)-hydroxychlorophyllone *a* lactone [**5**(R)], and purpurin-18 methyl ester (**9**).

15^1-Hydroxypurpurin-7 Lactone Dimethyl Ester (17). A solution of the foregoing (95%*R*, 5%*S*) mixture of 13^2-hydroxypheophorbide *a* methyl ester (**10**) (30 mg, 0.05 mmol) in dioxane (20 mL) was stirred with an aqueous solution (20 mL) of periodic acid dihydrate (900 mg, 3.95 mmol) at room temperature for 20 h before the mixture was extracted with dichloromethane (2 × 40 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica III, eluting with 2% methanol in dichloromethane. The product was crystallized from dichloromethane/hexane, giving a black solid (25.2 mg, 79%), which was analyzed by ^{1}H NMR as a diastereomeric mixture of 84% 15^1(*S*)-hydroxypurpurin-7 lactone dimethyl ester [**17**(S)] and 16% 15^1(*R*)-hydroxypurpurin-7 lactone dimethyl ester [**17**(R)]: mp 217 °C; ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) [**17**(S)] δ 9.77 (s, 1H), 9.55 (s, 1H), 8.80 (s, 1H), 8.00 (dd, J = 17.6, 11.5 Hz, 1H), 6.34 (dd, J = 17.6, 1.2 Hz, 1H), 6.19 (dd, J = 11.5, 1.2 Hz, 1H), 6.05 (s, 1H), 4.43 (q, J = 6.8 Hz, 1H), 4.05 (dd, J = 10.4, 2.4 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 3.75 (q, J = 8.0 Hz, 2H), 3.51 (s, 3H), 3.40 (s, 3H), 3.26 (s, 3H), 2.46 (m, J = 2.4 Hz, 1H), 2.45 (m, 1H), 2.18 (m, J = 10.4 Hz, 1H), 1.80 (m, 1H), 1.70 (t, J = 8.0 Hz, 3H), 1.59 (d, J = 6.8 Hz, 3H), −1.10 (br s, 1H), −1.41 (br s, 1H); UV−vis λ_{max} ($CHCl_3$) 404 nm (ϵ 189 000), 502 (17 300), 530 (13 600), 562 (4 200), 614 (9 300), 672 (61 200); EIMS m/z 638 (M$^+$, 20%), 622 (80); HREIMS $C_{36}H_{38}N_4O_7$ (M$^+$) calcd 638.2740, obsd 638.2745. Anal. Calcd for $C_{36}H_{38}N_4O_7$: C, 67.70; H, 6.00; N, 8.77. Found: C, 68.00; H, 6.14; N, 8.95.

Purpurin-7 Trimethyl Ester (16). A solution of the foregoing (84%*S*, 16%*R*) mixture of 15^1-hydroxypurpurin-7 lactone dimethyl ester (**17**) (15 mg, 0.05 mmol) in dichloromethane (20 mL) was treated with an excess of ethereal diazomethane and then washed with water three times before

(24) Lee, S. H.; Jagerovic, N.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2369.

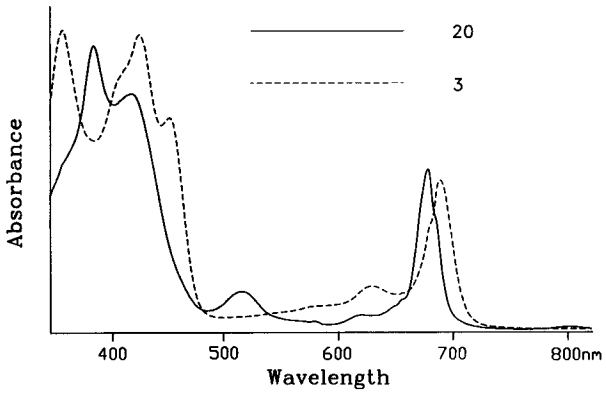


Figure 3. UV−vis spectra ($CHCl_3$) of 13^2,17^3-cyclopheophorbide *a* enol (**3**) and 13^2-oxopyropheophorbide *a* methyl ester (**20**).

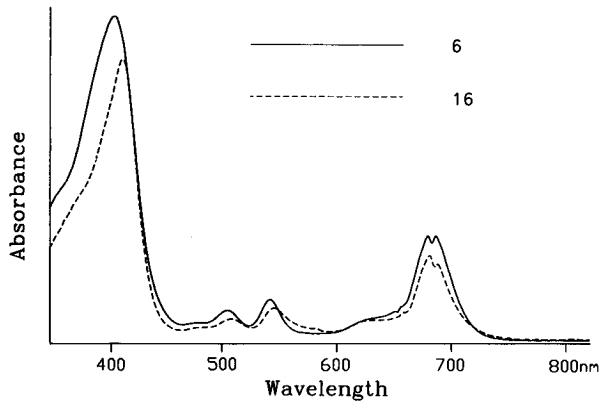


Figure 4. UV−vis spectra ($CHCl_3$) of chlorophyllonic acid *a* methyl ester (**6**) and purpurin-7 trimethyl ester (**16**).

the organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo*. The product was crystallized from dichloromethane/hexane, giving the title compound (14.8 mg, 97%) as a purple solid: mp 232 °C [lit.[25] mp 227−230 °C]; ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) δ 9.56 (s, 1H), 9.27 (s, 1H), 8.47 (s, 1H), 7.87 (dd, J = 17.9, 11.7 Hz, 1H), 6.28 (dd, J = 17.9, 1.1 Hz, 1H), 6.11 (dd, J = 11.7, 1.1 Hz, 1H), 4.66 (d, J = 7.6 Hz, 1H), 4.29 (q, J = 7.2 Hz, 1H), 4.12 (s, 3H), 3.86 (s, 3H), 3.63 (q, J = 7.6 Hz, 2H), 3.58 (s, 3H), 3.51 (s, 3H), 3.31 (s, 3H), 3.14 (s, 3H), 2.35 (t, 1H), 2.08 (m, 2H), 1.77 (d, J = 7.2 Hz, 3H), 1.75 (t, 1H), 1.64 (t, J = 7.6 Hz, 3H), −0.01 (br s, 1H), −0.09 (br s, 1H); UV−vis λ_{max} ($CHCl_3$) 410 nm (ϵ 99 500), 506 (7 500), 548 (10 000), 680 (25 300), 688 (24 800) [lit.[25] λ_{max} (CH_2Cl_2) 408 nm 504, 544, 682 (ϵ, 23 900)]; EIMS m/z 652 (M^+, 11%), 567 (15), 566 (43), 565 (100); HREIMS $C_{37}H_{40}N_4O_7$ (M^+) calcd 652.2897, obsd 652.2898. Anal. Calcd for $C_{37}H_{40}N_4O_7$: C, 68.08; H, 6.18; N, 8.58. Found: C, 67.72; H, 5.92; N, 8.36.

Oxidation of 13^2-Hydroxychlorophyllone *a* (4) by H_5IO_6 in Methanol (Condition B in Scheme 2). A solution of the foregoing (95%*S*, 5%*R*) mixture of 13^2-hydroxychlorophyllone *a* (**4**) (53 mg, 0.1 mmol) in dioxane (54 mL) and methanol (45 mL) was mixed with an aqueous solution (45 mL) of periodic acid dihydrate (2.1 g, 9.17 mmol) and stirred at room temperature for 14 h before the mixture was extracted with dichloromethane (80 mL). The organic layer was washed with water three times before it was dried over sodium sulfate, filtered, and evaporated *in vacuo*. The residue was separated by preparative TLC on deactivated silica gel (developed twice by 5% acetone, 1% methanol in dichloromethane), giving 5 distinct bands: the least mobile band (yellow, **7**), the second least mobile band (purple-red, **8**), the major band (grey-green, **5**), the second mobile band (yellow, **20**), and the most mobile band (purple-red, **9**). Unambiguous structure assignments of these compounds were accomplished by electronic absorption and ^{1}H and ^{13}C NMR spectroscopy.

15^1-Hydroxychlorophyllone *a* Lactone (5). A gray-green solid (31 mg, 57%) crystallized from dichloromethane/hexane: mp >300 °C. Anal. Calcd for $C_{33}H_{32}N_4O_4$: C, 72.24; H, 5.88; N, 10.21. Found: C, 71.89; H, 6.01; N, 10.35. ^{1}H NMR analysis showed that it is a diastereomeric mixture of 94% 15^1(*R*)-hydroxychlorophyllone *a* lactone [**5**(R)] and 6% 15^1(*S*)-hydroxychlorophyllone *a* lactone [**5**(S)]. Further purification of this diastereomeric mixture (14 mg) by preparative TLC on deactivated silica gel (developed three times by 5% acetone, 1% methanol in dichloromethane) gave the optically-pure 15^1-(*R*)-hydroxychlorophyllone *a* lactone [**5**(R)] (11.5 mg, 100% de from ^{1}H NMR) of a dark green powder after recrystallization from dichloromethane/hexane: mp >300 °C; ^{1}H NMR (400 MHz, 1.0 mg/0.6 mL $CDCl_3$) δ 9.68 (s, 1H), 9.50 (s, 1H), 8.78 (s, 1H), 8.00 (dd, J = 17.6, 11.2 Hz, 1H), 6.32 (dd, J = 17.6, 1.0 Hz, 1H), 6.20 (d, J = 11.2, 1.0 Hz, 1H), 5.86 (br s, 1H, OH), 4.42 (ddd, J = 11.5, 5.3, 1.6 Hz, 1H), 4.38 (dq, J = 7.5, 1.6 Hz, 1H), 3.79 (s, 3H), 3.69 (q, J = 7.9 Hz, 2H), 3.49 (ddd, J = 11.5, 9.0, 8.3 Hz, 1H), 3.42 (s, 3H), 3.33 (s, 3H), 3.01 (ddd, J = 11.5, 9.6, 2.5 Hz, 1H), 2.85 (dddd, J = 12.8, 9.3, 9.0, 5.3 Hz, 1H), 2.19 (dddd, J = 12.8, 11.5, 8.3, 2.5 Hz, 1H), 1.84 (d, J = 7.5 Hz, 3H), 1.69 (t, J = 7.9 Hz, 3H), −0.93 (br s, 1H), −1.45 (br s, 1H); ^{13}C NMR (75 MHz, 8.5 mg/0.6 mL $CDCl_3$) δ 203.62, 173.31, 163.85, 162.57, 155.84, 150.35, 145.68, 141.89, 138.89, 136.59, 136.39, 136.06, 134.07, 131.62, 131.45, 128.96, 123.01, 111.69, 104.68, 104.61, 100.24, 99.82, 93.44, 51.18, 49.84, 34.17, 31.37, 23.56, 19.54, 17.57, 12.44, 12.15, 11.33; UV−vis λ_{max} ($CHCl_3$) 404 nm (ϵ 147 000), 500 (12 400), 532 (11 900), 614 (7 700), 670 (50 200), λ_{max} (CH_3OH) 400 nm (ϵ 164 000), 498 (14 200), 528 (12 500), 610 (8 200), 666 (53 000) [lit.[4] λ_{max} (CH_3OH) 400 nm, 498, 529, 610, 667]; FABMS m/z 549 ([MH]$^+$, 50%), 531 (10), 520 (27); HRFABMS $C_{33}H_{33}N_4O_4$ ([MH]$^+$) calcd 549.2502, obsd 549.2506.

13^2-Oxopyropheophorbide *a* (7). Treatment of this product (1.0 mg, 1.8%) with excess ethereal diazomethane gave 13^2-oxopyropheophorbide *a* methyl ester (**20**). After crystallization from dichloromethane/hexane, this material was found to be identical to **20** as described below.

13^2-Oxopyropheophorbide *a* Methyl Ester (20). A yellow solid (3.0 mg, 5.4%) recrystallized from dichloromethane/hexane: mp 245 °C; ^{1}H NMR (400 MHz, 1.0 mg/0.6 mL $CDCl_3$) δ 9.90 (s, 1H), 9.86 (s, 1H), 9.00 (s, 1H), 8.10 (dd, J = 18.5, 12.4 Hz, 1H), 6.34 (dd, J = 18.5, 1.3 Hz, 1H), 6.26 (d, J = 12.4, 1.3 Hz, 1H), 5.16 (ddd, J = 8.8, 2.9, 1.3 Hz, 1H), 4.68 (dq, J = 7.6, 1.3 Hz, 1H), 3.72 (s, 3H), 3.70 (q, J = 7.7 Hz, 2H), 3.56 (s, 3H), 3.42 (s, 3H), 3.35 (s, 3H), 2.78 (m, J = 2.9 Hz, 1H), 2.67 (m, 1H), 2.36 (m, J = 8.8 Hz 1H), 2.32 (m, 1H), 1.87 (d, J = 7.6 Hz, 3H), 1.75 (t, J = 7.7 Hz, 3H), 0.26 (br s, 1H), −2.32 (br s, 1H); ^{13}C NMR (75 MHz, 6.2 mg/0.6 mL $CDCl_3$) δ 192.79, 185.19, 174.87, 173.67, 166.86, 153.87, 152.58, 151.30, 144.71, 142.33, 137.77, 137.40, 136.32, 134.51, 131.29, 130.34, 128.95, 126.42, 123.65, 105.05, 104.41, 101.50, 95.59, 52.67, 52.67, 51.63, 31.50, 29.70, 23.85, 19.38, 17.51, 12.60, 12.22, 11.32; UV−vis λ_{max} ($CHCl_3$) 390 nm (ϵ 49 500), 420 (42 900), 518 (6 900), 622 (3 300), 678 (29 000), λ_{max} (CH_3OH) 386 nm (ϵ 40 000), 514 (7 200), 622 (4 700), 676 (20 800) [lit.[4] λ_{max} (CH_3OH) 386 nm, 514, 618, 676]; EIMS m/z 562 (M^+, 100%), 475 (96); HREIMS $C_{34}H_{34}N_4O_4$ (M^+) calcd 562.2580, obsd 562.2589. Anal. Calcd for $C_{34}H_{34}N_4O_4$: C, 72.58; H, 6.09; N, 9.96. Found: C, 72.09; H, 6.01; N, 9.80.

Purpurin-18 (8). Treatment of this product (1.5 mg, 2.7%) with an excess of ethereal diazomethane gave purpurin-18 methyl ester (**9**). After being crystallized from dichloromethane/methanol, the product was found to be identical to **9** as described below.

Purpurin-18 methyl ester (9): 4.2 mg (7.2%) of purple red small shiny flakes recrystallized from dichloromethane/methanol; mp 267 °C [lit.[24] mp >270 °C; lit.[25] mp >260 °C dec]; ^{1}H NMR (400 MHz, 1.0 mg/0.6 mL $CDCl_3$) δ 9.60 (s, 1H), 9.39 (s, 1H), 8.58 (s, 1H), 7.90 (dd, J = 18.3, 11.3 Hz, 1H), 6.30 (dd, J = 18.3, 1.6 Hz, 1H), 6.20 (d, J = 11.3, 1.6 Hz, 1H), 5.20 (dd, J = 9.9, 2.5 Hz, 1H), 4.38 (dq, J = 9.9, 7.7 Hz, 1H), 3.77 (s, 3H), 3.63 (q, J = 8.3 Hz, 2H), 3.32 (s, 3H), 3.15 (s, 3H), 2.73 (m, 1H), 2.45 (m, 1H), 2.43 (m,1H), 1.99 (m, 1H), 1.73 (d, J =

(25) Inhoffen, H. H.; Jager, P.; Mahlhop, R.; Mergler, C. D. *Liebigs Ann. Chem.* **1967**, *704*, 188.

7.7 Hz, 3H), 1.65 (t, J = 8.3 Hz, 3H), 0.25 (br s, 1H), −0.08 (br s, 1H); ^{13}C NMR (75 MHz, 12.0 mg/0.6 mL $CDCl_3$) δ 177.52, 176.61, 176.61, 173.66, 164.20, 156.35, 150.17, 146.05, 144.15, 140.04, 139.15, 137.82, 136.70, 136.64, 131.87, 131.84, 131.61, 128.42, 123.75, 111.56, 107.73, 103.14, 95.01, 55.01, 51.63, 49.26, 32.55, 31.27, 23.85, 19.38, 17.43, 12.41, 11.96, 11.09; UV−vis λ_{max} ($CHCl_3$) 362 nm (ϵ 48 900), 412 (126 100), 480 (4 800), 508 (7 200), 548 (25 500), 644 (9 400), 702 (52 100) [lit.[4] λ_{max} (CH_3OH) 359 nm, 407, 478, 508, 642, 697; lit.[24] λ_{max} ($CHCl_3$) 411 nm, 478, 507, 545, 593, 64, 700 (ϵ 52 500); lit.[24] λ_{max} (CH_2Cl_2) 410 nm (ϵ 123 000), 478 (5 100), 508 (7 500), 546 (24 600), 642 (9 800), 698 (49 800)]; EIMS m/z 578 (M^+, 52%), 491 (100); HREIMS $C_{34}H_{34}N_4O_5$ (M^+) calcd 578.2529, obsd 578.2527. Anal. Calcd for $C_{34}H_{34}N_4O_5$: C, 70.57; H, 5.92; N, 9.68. Found: C, 70.95; H, 6.03; N, 9.70.

Oxidation of 13^2-Hydroxychlorophyllone *a* (4) by H_5IO_6 in Pyridine (Condition A in Scheme 2). A solution of the foregoing (95%*S*, 5%*R*) mixture of 13^2-hydroxychlorophyllone *a* (**4**) (27 mg, 0.05 mmol) in dioxane (20 mL) and pyridine (15 mL) was stirred with an aqueous solution (20 mL) of periodic acid dihydrate (1 g, 4.38 mmol) at room temperature for 18 h before the mixture was extracted with dichloromethane (60 mL). The organic layer was washed with water three times before it was dried over sodium sulfate, filtered, and evaporated *in vacuo*. The residue was separated by preparative TLC on deactivated silica gel (developed twice by 5% acetone, 1% methanol in dichloromethane), giving three distinct bands: the most mobile band (grey-green, **5**), the second mobile band (purple-red, **8**), and the least mobile band (yellow, **7**).

15^1-Hydroxychlorophyllone *a* lactone (5): 7.7 mg (28%), mp >300 °C. This material was analyzed by ^{1}H NMR as a diastereomeric mixture of 92% 15^1(*R*)-hydroxychlorophyllone *a* lactone [**5**(R)] and 8% 15^1(*S*)-hydroxychlorophyllone *a* lactone [**5**(S)].

Purpurin-18 (8). Treatment of this product (3.2 mg, 11.3%) with excess ethereal diazomethane gave purpurin-18 methyl ester (**9**). After crystallization from dichloromethane/methanol, the product was found to be identical to **9** as described previously.

13^2-Oxopyropheophorbide *a* (7). Treatment of this product (13.4 mg, 49%) with excess ethereal diazomethane gave 13^2-oxopyropheophorbide *a* methyl ester (**20**) (12.7 mg) after crystallization from dichloromethane/hexane. This material was found to be identical to the product **20** as described previously.

Chlorophyllonic Acid *a* Methyl Ester (6). A solution of the foregoing (94%*R*, 6%*S*) mixture of 15^1-hydroxychlorophyllone *a* lactone (**5**) (8 mg, 0.0146 mmol) in dichloromethane (20 mL) was treated with an excess of ethereal diazomethane and then washed with water three times, dried over sodium sulfate, filtered, and evaporated *in vacuo*. The product was crystallized from dichloromethane/hexane, giving the title compound (6.7 mg, 82%) as a grey-brown solid: mp 219 °C; ^{1}H NMR (400 MHz, 1.0 mg/0.6 mL $CDCl_3$) δ 9.70 (s, 1H), 9.49 (s, 1H), 8.60 (s, 1H), 7.96 (dd, J = 17.4, 12.1 Hz, 1H), 6.30 (dd, J = 17.4, 1.0 Hz, 1H), 6.15 (d, J = 12.1, 1.0 Hz, 1H), 4.53 (ddd, J = 12.3, 6.6, 1.7 Hz, 1H), 4.40 (dq, J = 7.3, 1.0 Hz, 1H), 4.03 (s, 3H), 3.83 (ddd, J = 12.7, 10.0, 10.0 Hz, 1H), 3.70 (q, J = 7.7 Hz, 2H), 3.60 (s, 3H), 3.38 (s, 3H), 3.21 (s, 3H), 3.05 (ddd, J = 12.7, 8.3, 1.4 Hz, 1H), 2.90 (dddd, J = 12.3, 10.0, 8.3, 6.6 Hz, 1H), 2.38 (dddd, J = 12.3, 12.3, 10.0, 1.4 Hz, 1H), 1.73 (d, J = 7.3 Hz, 3H), 1.67 (t, J = 7.7 Hz, 3H), −0.68 (br s, 2H); ^{13}C NMR (75 MHz, 6.5 mg/0.6 mL $CDCl_3$) δ 196.90, 192.38, 173.24, 166.90, 164.07, 155.22, 149.61, 145.48, 142.09, 138.42, 136.38, 136.31, 135.61, 135.07, 130.82, 130.12, 128.85, 122.77, 121.12, 108.52, 105.87, 101.48, 93.41, 52.31, 51.20, 50.16, 36.25, 29.47, 23.62, 19.49, 17.56, 12.57, 12.00, 11.17; UV−vis λ_{max} ($CHCl_3$) 408 nm (ϵ 163 000), 504 (14 500), 544 (20 000), 628 (10 500), 680 (53 000), 688 (53 000), λ_{max} (CH_3OH) 400 nm (ϵ 170 000), 504 (15 400), 540 (20 000), 610 (sh 8 400), 628 (11 000), 678 (52 400), 686 (sh 46 300) [lit.[4] λ_{max} (CH_3OH) 400 nm, 504, 540, 610, 677]; FABMS m/z 563 ($[MH]^+$, 55%), 534 (20), 503 (16); HRFABMS $C_{34}H_{35}N_4O_4$ ($[MH]^+$) calcd 563.2658, obsd 563.2665. Anal. Calcd for $C_{34}H_{34}N_4O_4$: C, 72.58; H, 6.09; N, 9.96. Found: C, 72.19; H, 5.92; N, 9.85.

Oxidation of 15^1-Hydroxychlorophyllone *a* lactone (5) by H_5IO_6. A solution of the foregoing (94%*R*, 6%*S*) mixture of 15^1-hydroxychlorophyllone *a* lactone (**5**) (5.5 mg, 0.01 mmol) in dioxane (10 mL) was stirred with an aqueous solution (10 mL) of periodic acid dihydrate (50 mg, 0.22 mmol) at room temperature for 8 h before the mixture was extracted with dichloromethane (30 mL). The organic layer was washed with water three times before it was dried over sodium sulfate, filtered, and evaporated *in vacuo*. The residue was redissolved in dichloromethane and treated with an excess of ethereal diazomethane. The product was purified by chromatography on silica gel, eluting with dichloromethane. After recrystallization from dichloromethane/methanol, purpurin-18 methyl ester (**9**) (4.5 mg, 78%) was obtained as a purple-red shiny flakes, identical to the material prepared from the methods described above.

Oxidation of 13^2-Oxopyropheophorbide *a* Methyl Ester (20) by H_5IO_6. A solution of the foregoing 13^2-oxopyropheophorbide *a* methyl ester (**20**) (3.5 mg, 6.2 μmol) in dioxane (5 mL) was stirred with an aqueous solution (4 mL) of periodic acid dihydrate (25 mg, 0.11 mmol) at room temperature for 6 h before the mixture was extracted with dichloromethane (20 mL). The organic layer was washed with water three times before it was dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with dichloromethane. The product was crystallized from dichloromethane/methanol, giving purpurin-18 methyl ester (**9**) (3.0 mg, 84%) as a purple-red shiny flakes, identical to the material prepared from previous methods.

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