Chemical modification of chlorophyll *a*: synthesis of new regiochemically pure benzoporphyrin and dibenzoporphyrin derivatives

Lifu Ma and David Dolphin

Abstract: Starting from pheophorbide *a* methyl ester (**5**), a degradation product of chlorophyll *a*, routes for the preparation of 3-vinylporphyrins **6** and **9** and of an [A,C]-divinylporphyrin **16** are described. These porphyrins were obtained as a result of chemical modification of **5** on ring D and the exocyclic ring E. Diels–Alder reactions of these (di)vinylporphyrins with dimethyl acetylenedicarboxylate, to afford new regiochemically pure benzoporphyrin derivatives **29** and **30** and dibenzoporphyrin derivative **33** for potential use as sensitizers in photodynamic therapy of tumors, were also investigated.

Key words: Diels–Alder, (di)vinylporphyrins, (di)benzoporphyrins, photodynamic therapy, chlorophyll.

Résumé : On décrit des voies de synthèse pour la préparation des 3-vinylporphyrines **6** et **9** et d'une [A,C]-divinylporphyrine (**16**) à partir de l'ester méthylique de l'acide phéophorbide *a* (**5**). On a obtenu ces porphyrines par modification chimique du cycle D et du cycle exocyclique E du produit **5**. On a aussi examiné les réactions de Diels–Alder de ces (di)vinylporphyrines avec l'acétylènedicarboxylate de diméthyle pour préparer les dérivés benzoporphyrines **29** et **30** et le dérivé dibenzoporphyrine **33** régiochimiquement purs, qui pourraient s'avérer utiles comme sensibilisateurs dans la thérapie photodynamique des tumeurs.

Mots clés : Diels–Alder, (di)vinylporphyrines, (di)benzoporphyrines, thérapie photodynamique, chlorophylle.

[Traduit par la rédaction]

Introduction

Among long-wavelength absorbing photosensitizers, chlorins and bacteriochlorins have received increasing attention as potential candidates for use in photodynamic therapy (PDT) since they absorb strongly in the red region (>670 nm) and thereby enable deeper penetration of light through tissues (1). Some naturally occurring chlorins and bacteriochlorins have previously been reported as effective photosensitizers both in vitro and in vivo (2). However, these compounds, by virtue of their di- and tetrahydro reduction states, can be readily oxidized back to the parent porphyrin accompanied by the loss of their long-wavelength absorption bands (3). This potential lack of stability has led us to examine other ways of producing chlorin-like and bacteriochlorin-like chromophores.

A number of years ago Johnson and co-workers (4) reported a facile synthesis of compounds possessing the chlorin-like chromophore by using the Diels–Alder reaction on vinylporphyrins. We extended this methodology to vinyl- and [A,C]-divinylporphyrins and prepared a series of benzoporphyrin derivatives (BPD) (5) and dibenzoporphyrin derivatives (DBPD) (6) (bacteriochlorins). In the BPD series, benzoporphyrin derivative monoacid A (BPD-MA) (**1**), a second-generation photosensitizer that has shown promising photophysical properties, is currently in Phase II clinical trials and has been proposed as a possible alternative to Photofrin™, a commercial variant of hematoporphyrin derivative, used in the clinic for the treatment of solid tumors (7). Preliminary biological evaluation also indicated that the dibenzoporphyrin (**2**) is highly photocytotoxic and has potential as a useful therapeutic compound (8).

Further biological investigation of DBPD (**2**) as a potential phototoxin in PDT was complicated by problems associated with the availability of the [A,C]-divinylporphyrin **3** since the total synthesis of **3**, via a stepwise route from pyrrolic precursors using the MacDonald dipyrromethane approach, requires a large number of steps and therefore considerable effort in order to obtain the quantities required for biological investigations (6, 9). For the synthesis of BPD-MA (5), protoporphyrin IX dimethyl ester (**4**) is reacted with dimethyl acetylenedicarboxylate (DMAD) in refluxing toluene (Scheme 1). The ring A Diels–Alder adduct (i.e., 1,4-cyclohexadiene derivative) is then separated by crystallization from the ring B adduct and is subsequently rearranged with base (DBU). The rearranged

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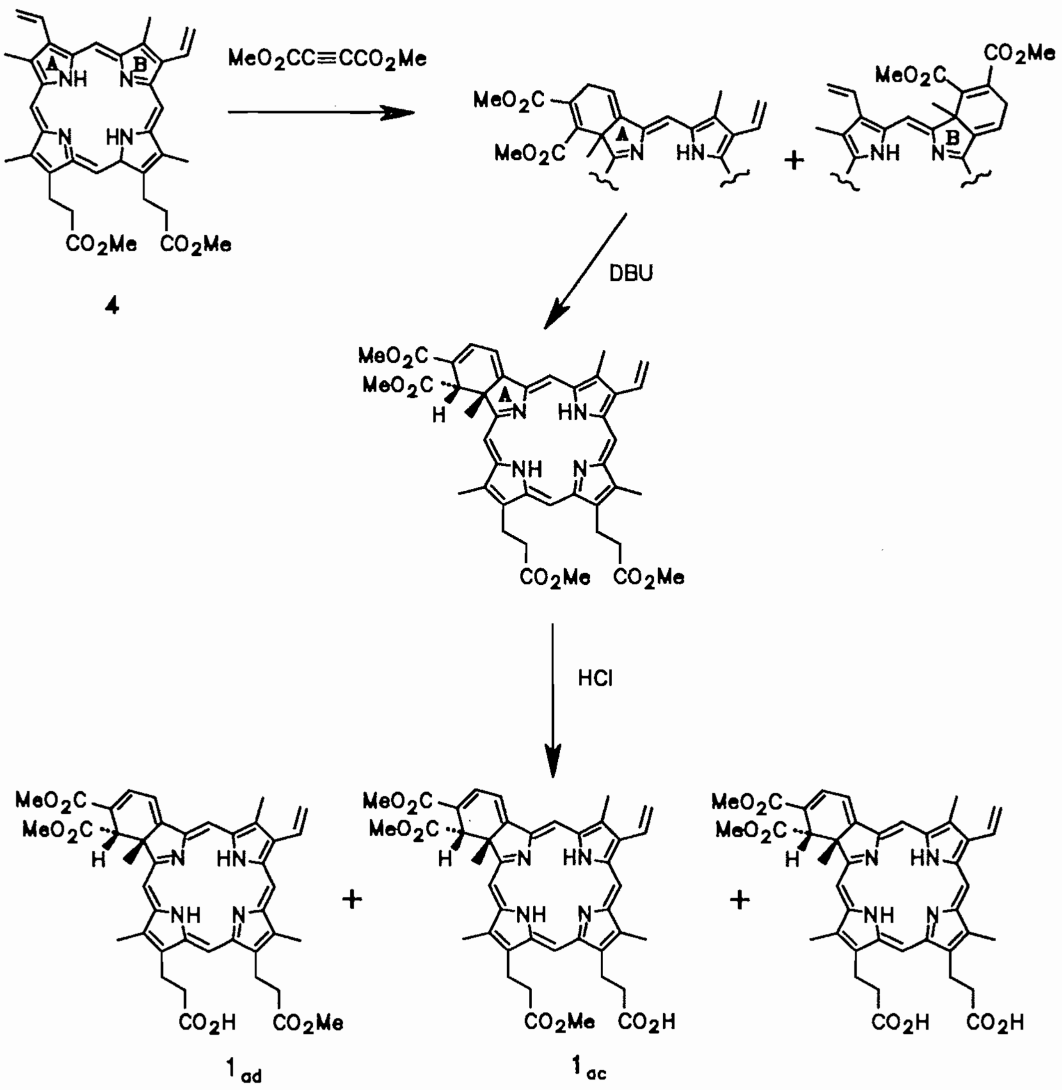
Scheme 1



ring “A” 1,3-cyclohexadiene derivative is then partially hydrolyzed to afford, after purification, the two regioisomers, $\mathbf{1}_{ac}$ and $\mathbf{1}_{ad}$, which are used for biological studies (5). From the biological data reported so far, photodynamic activity is maximized for BPD when: (*a*) “ring A” of the porphyrin nucleus is modified by the Diels–Alder cycloaddition – base rearrangement procedure; (*b*) only one of the two methyl propionate groups is hydrolyzed to the free acid (7).

To eliminate the problem of regioisomer formation in the preparation of BPD-MA, we sought to acquire vinylporphyrins that contain one vinyl group (in ring A) and one propionic side chain. Similar studies were recently reported by Pandey et al. after the submission of this paper (10). These vinylporphyrins should thus afford regiochemically pure BPD-MA derivatives and would subsequently lead to less ambiguity at the biological screening stage. Further, it was envisioned that performing a partial synthesis of [A,C]-divinylporphyrins, from readily available natural tetrapyrroles, might facilitate and greatly simplify the synthetic sequence to [A,C]-divinylporphyrins.

Results and discussion

With our recent progress on chemical modifications of chlorophyll derivatives on ring D and the exocyclic ring E (11–15), the way was opened for synthesis of vinylporphyrins and [A,C]-divinylporphyrins from a chlorophyll degradation product. More specifically, these studies demonstrated the feasibility of transforming pheophorbide *a* methyl ester (**5**), readily available from the blue alga, *Spirulina maxima*, into 3-vinylporphyrin **6** (13). This substance, with a vinyl group at position 3, will produce only a ring “A” chlorin (after the Diels–Alder reaction) and only one propionic ester side chain, which can be hydrolyzed to the corresponding monocarboxylic acid at the final step of the synthesis, and serves as an ideal precursor to a regiochemically pure BPD-MA derivative. As a continuation of our research on chemical modifications of chlorophyll *a*, pheophorbide *a* methyl ester (**5**) was chosen as the key intermediate in this work.

A. Preparation of 3-vinylporphyrins 6 and 9

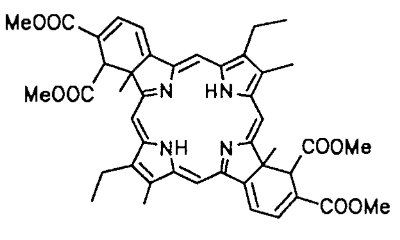
3-Vinylporphyrin **6** was obtained by the direct transformation of 13^1-hydroxychlorin **7** using a procedure described in a recent report (13). Demethoxycarbonylation of pheophorbide *a* methyl ester (**5**) in collidine afforded pyropheophorbide *a* methyl ester (**8**), which was reduced by NaBH4 to give a diastereomeric mixture of 13^1-deoxo-13^1-hydroxypyropheophorbide *a* methyl ester (**7**). Reaction of **7** with 1.2 equivalents benzoyl chloride in DMF gave vinylporphyrin **6** in 73% yield after recrystallization from dichloromethane–hexane.

3-Vinylrhodoporphyrin XV dimethyl ester (**9**), another substrate suitable for the synthesis of regiochemically pure BPD derivatives, was prepared from the oxidation of purpurin-7 trimethyl ester (**10**) (16), which was obtained from two routes. Thus, pheophorbide *a* methyl ester (**5**) was transformed into **10** by dissolution in pyridine, dilution with ether, and addition of KOH in *n*-propanol. After aeration for 30 min Fischer's "unstable chlorin" was obtained (16). Esterification of "unstable chlorin" (**11**) with diazomethane gave purpurin-7 trimethyl ester (**10**). The overall yield from **5** was 58%. Deglyoxylation and concomitant oxidation of purpurin-7 trimethyl ester in collidine furnished a 76% yield (44% overall yield from **5**) of 3-vinylrhodoporphyrin XV dimethyl ester (**9**).

One important characteristic of the above method is that **11** was somewhat unstable and had a tendency to oxidize further in the aerial oxidation step. The esterification with diazomethane therefore produced both purpurin-18 methyl ester (**12**) in addition to the desired purpurin-7 trimethyl ester (**10**). Separation of purpurin-18 methyl ester from purpurin-7 trimethyl ester by chromatography is difficult due to their very close structures and polarities. Based on our synthetic methods (11, 12, 14) developed in the research of natural antioxidative chlorins, an alternate route to synthesize purpurin-7 trimethyl ester (**10**) was via 15^1-hydroxypurpurin-7-lactone methyl ester (**13**). Hydroxylation (14) of pheophorbide *a* methyl ester (**5**) using commercially available (−)-(1*R*)-(10-camphorsulfonyl)oxaziridine and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (17) gave 13^2*R*-hydroxypheophorbide *a* methyl ester (**14**(*R*)) (90% d.e.) in 94% yield. Periodate oxidation of 13^2*R*-hydroxypheophorbide *a* methyl ester to 15^1-hydroxypurpurin-7-lactone methyl ester, followed by esterification with diazomethane, gave purpurin-7 trimethyl ester (**10**) in 79% yield (73% overall yield from **5**). This route has the advantages of higher yield and facile separations although it necessitates two extra steps compared to the original aerial oxidation of pheophorbide *a* methyl ester.

B. Synthesis of [A,C]-divinylporphyrin 16 via 3-vinylpurpurin 15

Attention was then focused on the development of a new and efficient route to obtain an [A,C]-divinylporphyrin from a chlorophyll derivative. To keep the number of chemical modifications involved in this sequence to a minimum, 3-vinylpurpurin **15** was chosen as the required precursor to an [A,C]-divinylporphyrin. With a 3-vinyl group at ring A and a 13-formyl group at ring C, purpurin **15** was subjected to a Wittig olefination reaction on the 13-formyl group to form a second vinyl group at ring C and, after further decarboxylation and oxidation, to give the desired target [A,C]-divinylporphyrin **16**. It was reasoned that the glyoxylic ester group at position 15 of the purpurin **15** could be lost with concomitant oxidation of the chlorin macrocycle into the porphyrin **17** in a one-pot procedure as was used in the transformation of purpurin-7 trimethyl ester (**10**) into



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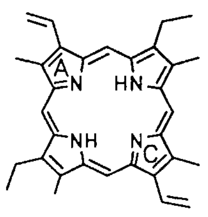

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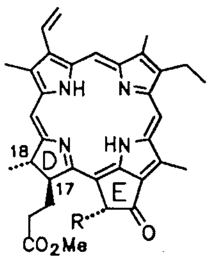
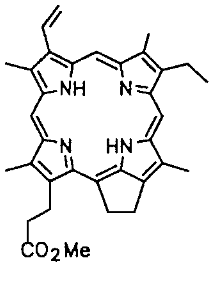


5. R=COOMe
8. R=H



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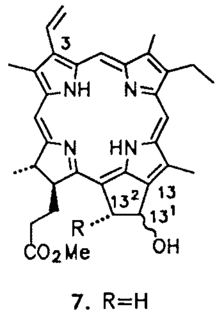
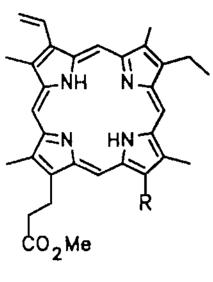
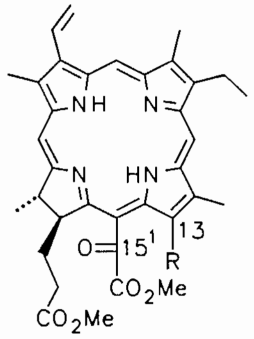


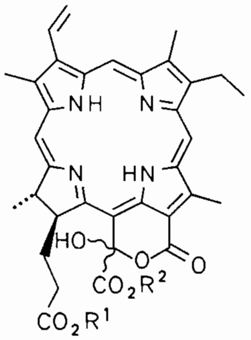
7. R=H
20. R=COOMe



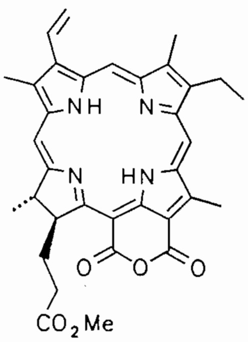
9. R=COOMe
17. R=CHO



10. R=COOMe
15. R=CHO



11. $R^1=R^2=H$
13. $R^1=R^2=Me$



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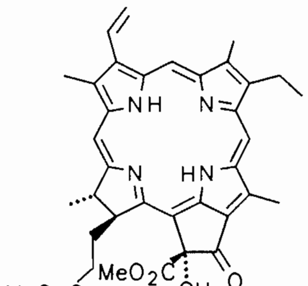
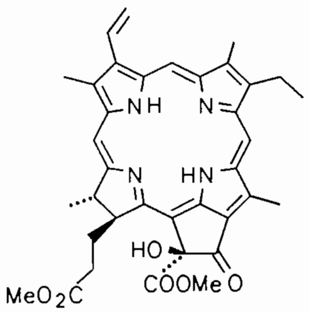
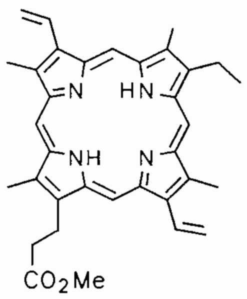


14 *(R)*



14 *(S)*



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3-vinylrhodoporphyrin XV dimethyl ester (**9**) (18) in collidine at 170°C. Further, Wittig olefination of the resulting **17** with methylene triphenylphosphorane would furnish the desired [A,C]-divinylporphyrin **16**. Alternatively the [A,C]-divinylporphyrin **16** may be formed first by a Wittig olefination of the purpurin **15**, to furnish the [A,C]-divinylpurpurin **18**, followed by deglyoxylation of the ester and oxidation in situ in refluxing collidine. Both pathways appeared plausible because of the known transformation procedures and the ready availability of the starting material **15** from the synthetic method described above.

For the preparation of 3-vinylpurpurin **15**, two synthetic pathways were investigated and the one giving the higher overall yield was subsequently used to make **15** on a 400 mg scale. Initially, 3-vinylpurpurin **15** was derived from the photooxidation of 13^1-deoxo-13^1,13^2-dehydropheophorbide *a* methyl ester (**19**) (13). In this synthetic approach, the first step was $NaBH_4$ reduction of pheophorbide *a* methyl ester (**5**) to give a diastereomeric mixture of 13^1-deoxo-13^1-hydroxypheophorbide *a* methyl ester (**20**) (13, 19), followed by elimination of a molecule of trifluoroacetic acid (via proton sponge), to provide the desired compound **19** in 80% yield. Although **19** (mp >300°C) has high thermal stability, it is extremely photosensitive, and reaction (in dichloromethane solution) in air with sunlight (20 min) oxidatively cleaved the 13^1-13^2 double bond to quantitatively give vinylpurpurin **15**. In a second method, 3-vinylpurpurin **15** was derived from the periodate oxidation of the diastereomeric mixture, 13^2-deoxo-13^1-hydroxy-13^2*R*-hydroxypheophorbide *a* methyl ester (**21**), which was in turn obtained from the $NaBH_4$ reduction of 13^2*R*-hydroxypheophorbide *a* methyl ester (**14**(*R*)) (13). Using this second method, purpurin **15** has been obtained in 67% overall yield from pheophorbide *a* methyl ester (**5**), in contrast to an 80% overall yield from **5** in the first method by means of photooxidation.

When purpurin **15** was heated in collidine at 170°C for 45 min, 13-decarboxy-13-formyl-3-vinylrhodoporphyrin XV methyl ester (**17**) was obtained in only 15% yield; the remainder of the starting material decomposed or was overoxidized under these conditions. Attempts to avoid these side reactions by reducing reflux time and temperature (using pyridine instead of collidine) were all unsuccessful. The problem seemed to be due to the susceptibility of the 13-formyl group, which led to overoxidation during the purpurin-into-porphyrin conversion. Protection of the 13-formyl function to circumvent this unwanted side reaction was therefore considered next. The ethylene acetal **22** was readily formed in 90% yield by heating purpurin **15** with ethylene glycol in THF and *p*-toluenesulfonic acid as catalyst. The salient features of the electronic spectrum of acetal **22** (λ_{max} = 660 nm), which looks similar to such hydroxychlorins as **7** and **20**, are the hypsochromic shift of its Q band (λ_{max} = 660 nm) in comparison with that of the purpurin **15** (λ_{max} = 686 nm) and the appearance of a strong absorption band at 496 nm, which suggested that the electron-withdrawing group at C-13 was removed.

Unfortunately, when the ethylene acetal **22** was refluxed in collidine even for 4 h, no reactions occurred and the starting material was recovered. Various attempts to achieve the purpurin-into-porphyrin conversion for the ethylene acetal **22** were all unsuccessful. It appears that an electron-withdrawing group at position 13 is required for the loss of the 15-glyoxylic ester group and concomitant oxidation of a purpurin macrocycle to a porphyrin, as observed with purpurin-7 trimethyl ester (**10**) and purpurin **15**. The key reason appears to be the dramatic change in the oxidation potential of the ethylene acetal **22** with the protection of the 13-formyl group. The presence of an electron-withdrawing group at position 13 in these purpurins seems to render the molecule easier to oxidize than the corresponding protected derivative.

The conversion of purpurin-7 trimethyl ester (**10**) into 3-vinylrhodoporphyrin XV dimethyl ester (**9**) was originally investigated by Fischer and Orth (20), who found the loss of the glyoxylic ester residue from purpurin-7 trimethyl ester (**10**) occurred upon refluxing in pyridine. Later, Kenner et al. (18) reported that the use of refluxing collidine in place of pyridine results in higher yield for the purpurin-into-porphyrin conversion, because prolonged reflux in pyridine often gives rise to decomposition products. Interestingly, we found that the presence of oxygen in the reaction medium has a beneficial effect on the conversion, but is not required, since the conversion was also observed under oxygen-free conditions.

Given the anticipated difficulty in the purpurin-into-porphyrin conversion for the [A,C]-divinylpurpurin **18**, a purpurin with a non-electron-withdrawing group (i.e., vinyl) at position 13, the planned synthetic route to [A,C]-divinylporphyrin **16** via the [A,C]-divinylpurpurin **18** was abandoned. Finally, we came back to the direct conversion of purpurin **15** and prepared sufficient 13-decarboxy-13-formyl-3-vinylrhodoporphyrin XV methyl ester (**17**) by refluxing purpurin **15** in collidine. Treatment of **17** with zinc(II) acetate in methanol–dichloromethane gave a zinc complex, which was subjected to a Wittig reaction to give, after removal of the zinc by treatment with trifluoroacetic acid, a 71% yield of the desired [A,C]-divinylporphyrin **16**. With this synthetic approach the [A,C]-divinylporphyrin **16** was obtained in six steps from pheophorbide *a* methyl ester (**5**) in 9% overall yield. Compound **16** has a very similar electronic absorption spectrum to that of the divinylporphyrin **3** reported by Dolphin and coworkers (6).

C. Synthesis of [A,C]-divinylporphyrin 16 via porphyrin 9

At this point, it was felt that the 15% yield of the formylrhodoporphyrin XV (**17**) obtained by the oxidation and deglyoxylation of purpurin **15** in collidine was unsatisfactory and should be improved upon by pursuing an alternative approach. Previous studies led us to conclude that the 13-methoxycarbonyl group and other (non-formyl) groups are advantageous in this regard. 3-Vinylrhodoporphyrin XV dimethyl ester (**9**) was chosen as the starting material since it is readily available from the oxidation of purpurin-7 trimethyl ester (**10**) as described above.

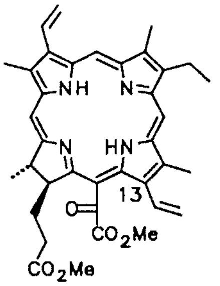
In this approach, 3-vinylrhodoporphyrin XV dimethyl ester (**9**) was hydrolyzed to its diacid form and was partially remethylated on the propionic side chain using 5% H_2SO_4 in methanol to give the 3-vinylrhodoporphyrin XV monomethyl ester (**23**) in 70% overall yield (21). The resulting monomethyl ester (**23**) was added to a solution of *N,N′*-carbonyldiimidazole in THF and heated to reflux for 30 min (22). The desired imidazolide **24** was obtained in 91% yield after flash chromatography on silica gel. The nucleophilic displacement (21) of the imidazolide **24** with the magnesium salt of methyl hydrogen malonate (23) gave the expected β-keto-ester **25** in 70% yield. This step was based on a method that was introduced by Bram and Vilkas (23) and later improved by Kenner and coworkers (21). The magnesium salt of methyl hydrogen malonate was prepared by treatment of methyl hydrogen malonate with 2 equivalents of isopropylmagnesium bromide in THF. The advantage of this procedure was its selectivity, which allowed the reaction to proceed without deprotonation of the porphyrin macrocycle to the green dianion.

With the enolizable β-keto-ester **25** in hand, we were able to attempt the decarboxylation step. A high yield of the desired acetylporphyrin **26** was obtained by modifying the decarboxylation method described by Taber et al. (24). In this reaction, the β-keto-ester **25** was stirred in a solution of 4-(dimethylamino)pyridine (4-DMAP) in phosphate buffer (pH = 7) at 90°C for 12 h under nitrogen to effect the demethoxycarbonylation (75% yield). The progress of the reaction was monitored by TLC and its completion was indicated by the disappearance of the less mobile enolizable β-keto-ester **25**. The electronic spectrum of this compound was almost the same as that of the imidazoylporphyrin **24** (oxorhodo-type spectrum). The ^{1}H NMR spectrum of porphyrin **26** showed the H-13^2 (i.e., 13-$COCH_3$) appearing as a singlet at δ 3.32 ppm. This observation indicated the presence of the desired 13-$COCH_3$ moiety.

The acetylporphyrin **26** was reduced with $NaBH_4$ in THF to give the expected hydroxyporphyrin **27**. With the absence of an electron-withdrawing group at position 13, hydroxyporphyrin **27** exhibited a rhodo-type electronic spectrum in contrast to an oxorhodo-type spectrum in the starting material **26**, suggesting that only one rhodofying group (i.e., the 3-vinyl moiety) was present in the molecule. The last step in the synthetic sequence involved the generation of the 13-vinyl group. This transformation was achieved by subjecting the hydroxyporphyrin **27** to benzoyl chloride in DMF at 105°C for 2 h (25). Under these conditions, the hydroxyporphyrin **27** was dehydrated to give the desired [A,C]-divinylporphyrin **16** in 60% yield after chromatography. This material was found to be identical to the divinylporphyrin prepared from the Wittig reaction of 13-formylporphyrin **17**. With this synthetic approach, the [A,C]-divinylporphyrin **16** was prepared in nine steps from pheophorbide *a* methyl ester (**5**) in 12% overall yield.

Diels–Alder reactions on vinylporphyrins

Porphyrin **9** was heated in degassed toluene at 110°C with a 50-fold molar excess of DMAD for 28 h and afforded the



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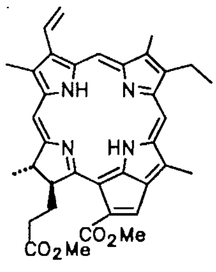

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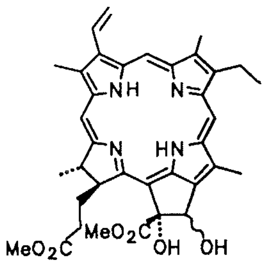

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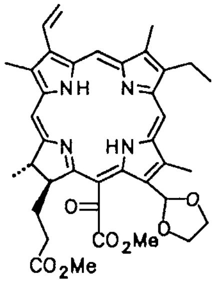

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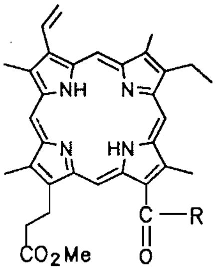
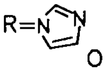
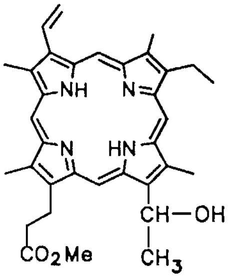


23. R=OH

24. R=

25. R=$CH_2\overset{O}{\overset{\|}{C}}OMe$

26. R=Me



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cycloadduct **28** in 50% yield. The ring A 1,4-cyclohexadiene derivative **28** was treated with DBU in dichloromethane to provide the chlorin-like BPD 1,3-cyclohexadiene dimethyl ester **29** in 90% yield after chromatography (45% overall yield from **9**). This rearrangement gave the thermodynamically more stable product, i.e., the carbomethoxy substituent attached at 2^1 and the angular methyl group located at C-2 are in a *trans* orientation. This *transoid* orientation was confirmed by a positive nOe effect observed for the C-2^1 proton (δ 5.04 ppm) and the methyl group at C-2 (δ 1.79 ppm).

The absorption spectrum (Fig. 1) of BPD **29** is characteristic of a chlorin-like chromophore but it has an unusually broad Soret band and the lowest energy absorption (Q band) at 672 nm (ε 14 600) is blue-shifted some 18 nm in comparison with that (690 nm) (5) of BPD-MA. This difference is due to the presence of an 8-vinyl group in BPD-MA, which extends the conjugation of the molecule. Pandey et al. (26) have recently exploited chemistry similar to that described above, and obtained a similar Diels–Alder adduct **29** from 3-vinylrhodoporphyrin XV dimethyl ester and DMAD. However, these authors reported a 23% overall yield (**29** from **9**) in contrast to a 45% total yield for the same reaction sequence in our hands.

For the preparation of BPD **30**, reaction of porphyrin **6** with DMAD in refluxing toluene under nitrogen gave the desired chlorin **31** in 42% yield. Compound **31** was then treated with DBU in dichloromethane to provide the fully conjugated chlorin **30** in 91% yield (36% overall yield) after chromatography. The reaction progress was monitored by UV–VIS spectroscopy, which showed a new absorbance at 686 nm (ε 37 000) (Fig. 1) and the disappearance of the peak at 648 nm of compound **31**.

As has already been mentioned, the synthetic strategy for the [A,C]-dibenzoporphyrin derivative relied on two cycloaddition reactions on an [A,C]-divinylporphyrin system. Refluxing the [A,C]-divinylporphyrin **16** with 100-fold molar excess of DMAD in toluene for 3 days gave a mixture with a strong absorption at 720 nm, a bacteriochlorin-like chromophore. The desired bis-adduct **32** was obtained as the major product along with a small amount of chlorin in which only one of the vinyl groups (either ring A and ring C) was transformed (identified by spectrophotometry). The best reaction time was found to be 80 h with a yield of ~30%, while prolonged reflux resulted in decomposition and thus gave the product **32** in a lower yield. Flash chromatography on a silica gel column followed by further purification by preparative TLC plate gave the bis-adduct **32** in 25% yield.

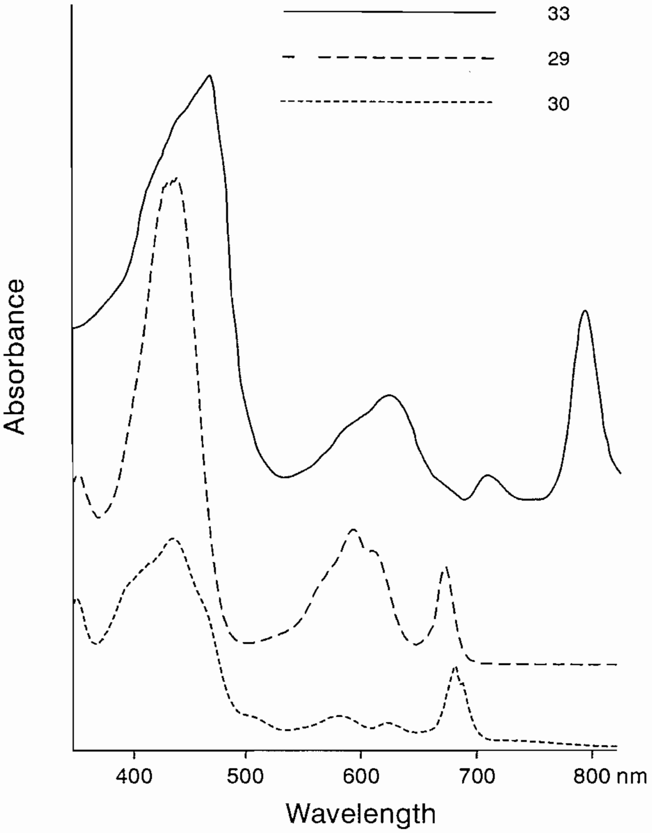


Fig. 1. UV–VIS spectra (CH_2Cl_2) of regiochemically pure benzoporphyrin derivatives **29** and **30**, and [A,C]-dibenzoporphyrin derivative **33**.

When the above bis-adduct **32** was stirred overnight with DBU at room temperature, a dramatic bathochromic shift was observed (λ_{max} = 784 nm, ε = 38 000) (Fig. 1). This [A,C]-dibenzoporphyrin derivative **33** showed almost the same electronic spectrum as the DBPD **2** reported by Dolphin and coworkers (6). The most significant features in the ^1H NMR spectrum of the new adduct **33** were the appearance of a signal at δ 4.89 ppm for the new sp^3 center generated at C-2^1 and C-12^1 and two doublets at δ 7.30 and δ 7.81 ppm for the new sp^2 centers. This observation indicated an isomerization of the double bonds in both 1,4-cyclohexadienes, thus extending the conjugation in the molecule.

As described earlier, the monocarboxylic acid analogue of benzoporphyrin derivative BPD-MA shows better photosensitizing efficacy than its corresponding diester. Therefore, to parallel the structural requirements for this biologically active benzoporphyrin derivative and to satisfy our originally planned goals, the new regiochemically pure benzoporphyrin derivatives **29** and **30**, and the [A,C]-dibenzoporphyrin derivative **33** were partially hydrolyzed with 25% HCl at the propionic ester side chain to afford the corresponding monocarboxylic acids **34**, **35**, **36** (i.e., propionic acid analogues). These monocarboxylic acids, together with their corresponding esters described herein, are being evaluated for their photodynamic ability.

Conclusion

Two series of new regiochemically pure benzoporphyrin derivatives **29** and **30** have been synthesized from Diels–Alder reactions on 3-vinylrhodoporphyrin XV dimethyl ester (**9**) and 3-vinylporphyrin (**6**) with dimethyl acetylenedicarboxylate. The corresponding monocarboxylic analogues of these new regiochemically pure BPDs have been prepared by partial hydrolysis. These new photosensitizers have characteristics that meet or exceed the promising chemical features of BPD-MA, a second-generation photosensitizer in Phase-II clinical trials. The [A,C]-divinylporphyrin **16** was synthesized via two routes and its Diels–Alder reaction with dimethyl acetylenedicarboxylate was studied. The resulting bis-adduct **33**, being a stable bacteriochlorin-like chromophore, absorbs strongly at 784 nm, a fact that, according to current thinking, renders it eminently desirable as a photosensitizer for treatment of large tumors or tumors that are deeply seated within the body.

In conclusion, the present work has led to the synthesis of a class of compounds, via chemical modifications of chlorophyll *a*, with potential as future drugs in the field of photodynamic therapy.

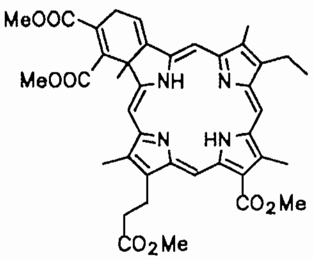
Experimental

General procedures

Melting points were measured on a Thomas–Bristoline microscopic hot stage apparatus and are uncorrected. ^1H NMR spectra were recorded using a Bruker WH-400 or Bruker AC-200 spectrometer and ^{13}C NMR spectra were run on a Varian XL-300 or a Bruker AMX-500 spectrometer (residual $CHCl_3$ as internal standard, δ_H 7.24 ppm, δ_C 77.0 ppm). Silica gel 60 (70–230 mesh, Merck; usually silica III, i.e., deactivated with 6% water, or silica V, i.e., deactivated with 15% water) or neutral alumina (usually Brockman Grade III, deactivated with 6% water, or Brockman Grade 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 deactivated silica gel plates, when necessary, were prepared by a blank development with 10% methanol in dichloromethane followed by air drying before use. Electronic absorption spectra were measured using a HP 8452A diode array spectrophotometer. 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 using a Carlo Erba elemental analyzer 1106. Reactions were monitored by TLC and spectrophotometry and were carried out under nitrogen and in the dark. Pheophorbide *a* methyl ester (**5**) was obtained from *Spirulina maxima* alga using a literature method (15). Pyropheophorbide *a* methyl ester (**8**) was obtained (98% yield) from decarboxylation of pheophorbide *a* methyl ester (**5**) in collidine (15, 27). Tetrahydrofuran (THF) and dioxane were dried overnight with calcium hydride and distilled from sodium wire and benzophenone; other solvents were of reagent grade.

Synthesis of 3-vinylporphyrins 6 and 9

13^1-Deoxo-13^1-hydroxypyropheophorbide a *methyl ester (7)*
Pyropheophorbide *a* methyl ester (**8**) (150 mg, 0.274 mmol)



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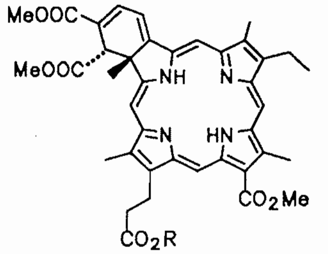
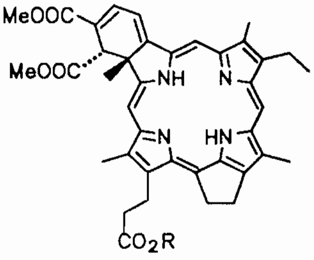
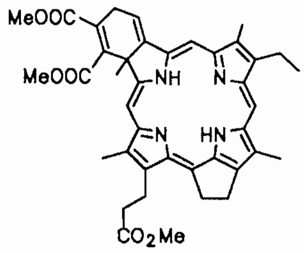


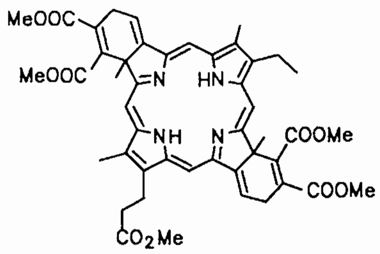
29. R=Me
34. R=OH



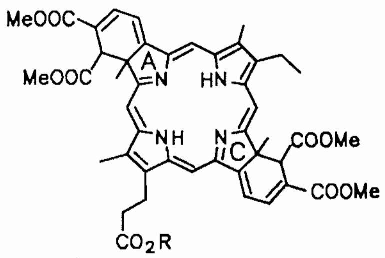
30. R=Me
35. R=OH



31



32



33. R=Me
36. R=OH

was dissolved in 100 mL of pyridine–methanol solution (pyridine:methanol = 1:1) and the solution was stirred at room temperature. $NaBH_4$ (200 mg) was added and the reaction mixture was stirred for 2 h, at which time the UV–VIS spectrum indicated no more starting material. The green reaction mixture was poured into cooled 2 N HCl and the chlorin was extracted with CH_2Cl_2. The organic layer was carefully washed once with water, twice with saturated $NaHCO_3$, three times with water, and then dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography on silica III, eluting with 1% MeOH in CH_2Cl_2. The main band was collected, evaporated, and recrystallized from CH_2Cl_2–hexane to give the title compound (129 mg, 86% yield) as a dark-green powder; mp 178–180°C; UV–VIS λ_{max} (CH_2Cl_2): 402 nm (ε 117 600), 502 (9100), 654 (32 900); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.98 (s, 1H, H-10), 9.82 (s, 1H, H-5), 9.05 (s, 1H, H-20), 8.30 (dd, 1H, H-3^1), 6.45 (dd, 1H, H-3^2(*E*)), 6.32 (s, 1H, H-3^2(*Z*)), 6.27 (dd, 1H, H-13^1), 5.30 (m, 1H, H-13^1), 4.48 (m, 2H, 13^2), 4.20 (m, 1H, H-18), 4.10 (m, 1H, H-17), 3.90 (q, 2H, H-8^1), 3.83, 3.72, 3.65, 3.40, 3.15 (5s, 12H, H-2^1, H-7^1, H-12^1, and H-17^4), 2.70 (m, 2H, H-17^1), 2.30 (m, 2H, H-17^2), 1.95 (d, 3H, H-18^1), 1.82 (t, 3H, H-8^2), −1.40 (br s, 1H, NH), −3.10 (br s, 1H, NH); LREIMS (*m*/*z*): 550 (M^+, 5%), 532 ($M^+ - H_2O$, 100%); LRFABMS (*m*/*z*): 551 ($[M + H]^+$, 100%); HREIMS, $C_{34}H_{36}N_4O_2$ ($[M - H_2O]^+$), calcd.: 532.2838; obsd.: 532.2828; HRFABMS, $C_{34}H_{39}N_4O_3$ ($[M + H]^+$), calcd.: 551.3021; obsd.: 551.3019.

3-Vinyl-13^1-deoxo-phytoporphyrin methyl ester (6)

13^1-Deoxo-13^1-hydroxypyropheophorbide *a* methyl ester (**7**) (105 mg, 0.191 mmol) was dissolved in dry DMF (50 mL) and the solution was stirred at 100°C under N_2. Benzoyl chloride (0.250 mmol) was added via a syringe and the reaction mixture (which turned red after 40 min) was stirred at this temperature for a further 120 min, at which time the UV–VIS spectrum indicated no more starting material. The reaction mixture was poured into ice-cooled 10% NaOH and the porphyrin was extracted with CH_2Cl_2. The organic layer was washed three times with water, and then dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography on silica, eluting with CH_2Cl_2. The main band was collected, evaporated, and the residue was recrystallized from CH_2Cl_2–hexane to give the title compound (74.0 mg, 73% yield) as a purple solid; mp >300°C; UV–VIS λ_{max} (CH_2Cl_2): 404 nm (ε 161 300), 504 (15 900), 540 (7800), 566 (8300), 620 (5800); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.10 (s, 1H, H-10), 9.99 (s, 1H, H-5), 9.93 (s, 1H, H-20), 8.26 (dd, 1H, H-31, *J* = 17.9 and 11.6 Hz), 6.27 (dd, 1H, H-3^2(*E*), *J* = 17.9 and 1.7 Hz), 6.11 (dd, 1H, H-3^2(*Z*), *J* = 11.6 and 1.7 Hz), 5.20 (br s, 2H, H-13^2), 4.25 (t, 2H, H-17^1, *J* = 8.3 Hz), 4.10

(q, 2H, H-8^1, J = 7.1 Hz), 3.96 (br s, 2H, H-13^1), 3.78 (s, 3H, H-12^1), 3.65 (s, 6H, H-17^4 and H-7^1), 3.59 (s, 3H, H-18^1), 3.52 (s, 3H, H-2^1), 3.03 (t, 2H, H-17^2, J = 8.3 Hz), 1.86 (t, 3H, H-8^2, J = 7.1 Hz), −3.02 (br s, 1H, NH), −3.89 (br s, 1H, NH); LREIMS (m/z): 532 (M$^+$, 100%), 459 (M$^+$ − CH$_2$COOMe, 47%); HREIMS, $C_{34}H_{36}N_4O_2$ (M$^+$); calcd.: 532.2838, obsd.: 532.2835; Anal. calcd. for $C_{34}H_{36}N_4O_2$: C 76.66, H 6.81, N 10.52%; found: C 76.50, H 6.85, N 10.58%.

*Purpurin-7 trimethyl ester (**10**) (14, 18, 28)*
Pheophorbide *a* methyl ester (**5**) (1.09 g, 1.75 mmol) was dissolved in warm pyridine (25 mL) and the solution was diluted with ether (700 mL). The solution was stirred with a stream of air passing through it, and a solution of potassium hydroxide (11.5 g) in *n*-propanol (40 mL) was added. The bright-green mixture (containing precipitated KOH) was stirred and aerated for 30 min and then extracted with water (2 × 300 mL). The ethereal solution was discarded; the aqueous extracts were combined, acidified with concentrated H_2SO_4 (11.5 mL) in water (60 mL), and then extracted with methylene chloride (2 × 350 mL). The extracts were washed with water (350 mL) and immediately treated with an excess of ethereal diazomethane. The brownish-purple solution was left at room temperature for 10 min, and then evaporated in vacuo. Chromatography (alumina V) of the residue (elution with methylene chloride) gave a major band that was collected, evaporated, and subjected to preparative TLC separation on deactivated silica plates (elution with 0.5% MeOH in CH_2Cl_2) to give the desired product (660 mg, 58% yield) after crystallization from CH_2Cl_2–hexane, along with 35 mg of a unseparated mixture of purpurin-18 methyl ester (**12**) and purpurin-7 trimethyl ester (**10**) as the other products.

*3-Vinylrhodoporphyrin XV dimethyl ester (**9**) (18)*
Purpurin-7 trimethyl ester (**10**) (450 mg, 0.69 mmol) was heated in an oil bath at 180–185°C in 2,4,6-collidine (60 mL) for 2 h. After cooling, the solvent was evaporated at 0.5 Torr (1 Torr = 133.3 Pa) and the residue was recrystallized from $CHCl_3$–CH_3OH, giving the title porphyrin (295 mg, 76%) as purple needles; mp 266–267°C (lit. (18) mp 271–272.5°C); UV–VIS λ_{max} (CH_2Cl_2): 408 nm (ε 187 000), 514 (10 000), 552 (20 000), 576 (11 000), 636 (1600); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.81, 9.89, 9.82, 9.68 (4s, 4H, H-5, H-10, H-15, and H-20), 8.12 (dd, 1H, H-3^1, J = 18.4 and 11.8 Hz), 6.23 (dd, 1H, H-3^2(*E*), J = 18.4 and 1.6 Hz), 6.10 (dd, 1H, H-3^2(*Z*), J = 11.8 and 1.6 Hz), 4.42 (s, 3H, H-13^2), 4.30 (t, 2H, H-171, J = 8.0 Hz), 3.93 (q, 2H, H-8, J = 8.0 Hz), 3.84, 3.67, 3.52, 3.50, 3.48 (5s, 15H, H-2^1, H-7^1, H-12^1, H-18^1, and H-17^4), 3.23 (t, 2H, H-17^2, J = 8.0 Hz), 1.79 (t, 3H, H-8^2, J = 8.0 Hz), −4.50 (br s, 2H, NH); LREIMS (m/z): 564 (M$^+$, 100%); Anal. calcd. for $C_{34}H_{36}N_4O_4$: C 72.32, H 6.43, N 9.92%; found: C 71.98, H 6.45, N 9.65%.

Synthesis of [A,C]-divinylporphyrin 16 via purpurin 15

13^1-Deoxo-13^1-hydroxypheophorbide a *methyl ester (**20**)*
Pheophorbide *a* methyl ester (**5**) (100 mg, 0.16 mmol) was dissolved in 50 mL of pyridine–methanol solution (pyridine:methanol = 1:1) and the solution was stirred at room temperature. $NaBH_4$ (90 mg) was added and the reaction mixture was stirred for 2 h, at which time the UV–VIS spectrum indicated that the starting material had been consumed. The reaction mixture (bright green) was poured into cooled 2 N HCl and the chlorin was extracted with CH_2Cl_2. The green organic layer was carefully washed once with water, twice with saturated $NaHCO_3$, three times with water, and then dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was chromatographed on an alumina III column, eluting with 1% MeOH in CH_2Cl_2. The main band was collected, evaporated, and recrystallized from $CHCl_3$–hexane to give the required compound (83.7 mg, 86% yield) as a dark-green powder; mp 135-136°C; UV–VIS λ_{max} (CH_2Cl_2): 400 nm (ε 124 400), 498 (12 000), 656 (35 800); ^{1}H NMR (200 MHz, $CDCl_3$) δ (the major epimer): 9.84 (s, 1H, H-10), 9.60 (s, 1H, H-5), 8.88 (s, 1H, H-20), 8.20 (dd, 1H, H-3^1), 6.63 (dd, 1H, H-13^1), 6.34 (dd, 1H, H-3^2(*E*)], 6.18 (s, 1H, H-3^2(*Z*)), 5.90 (s, 1H, H-13^2), 4.60 (m, 1H, H-18), 4.45 (m, 1H, H-17), 3.81, 3.55, 3.55, 3.39, 3.22 (5s, 15H, H-2^1, H-7^1, H-12^1, H-13^4, and H-17^4), 3.80 (q, 2H, H-8^1), 2–2.70 (m, 4H, H-17^1 and H-17^2), 1.90 (d, 3H, H-18^1), 1.75 (t, 3H, H-8^2), −1.39 (br s, 1H, NH), −3.05 (br s, 1H, NH); LREIMS (m/z): 608 (M$^+$, 100%); HREIMS, $C_{36}H_{40}N_4O_5$ (M$^+$), calcd.: 608.2999; obsd.: 608.2993; Anal. calcd. for $C_{36}H_{40}N_4O_5$: C 71.03, H 6.62, N 9.20%; found: C 70.81, H 6.79, N 8.97%.

13^1-Deoxo-13^1,13^2-dehydropheophorbide a *methyl ester (**19**)*
13^1-Deoxo-13^1-hydroxypheophorbide *a* methyl ester (**20**) (50 mg, 0.0822 mmol) was dissolved in pyridine (20 mL) and the solution stirred at 0°C under N_2. Excess trifluoroacetylimidazole (150 mg) was added via a syringe and the reaction mixture was stirred for 5 mins. After addition of proton sponge (1.81 mmol), the reaction mixture was kept at 0°C for 30 min and then at 25°C for 3 h, at which time the UV–VIS spectrum indicated no more starting material. The reaction mixture (bright green) was poured into water and the chlorin was extracted with CH_2Cl_2. The green organic layer was washed three times with water, and then dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica column eluting with CH_2Cl_2. The main band was collected, evaporated, and the residue was recrystallized from $CHCl_3$–MeOH to give the title compound (45.6 mg, 94% yield) as a dark-green powder; mp >300°C; UV–VIS λ_{max} ($CHCl_3$): 354 nm (ε 55 600), 434 (67 900), 586 (4100), 630 (11 600), 760 (4100), 820 (4100); ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) δ: 8.41(s, 1H, H-10), 8.33 (s, 1H, H-5), 7.42 (s, 1H, H-20), 7.42 (dd, 1H, H-3^1, J = 18.5 and 11.8 Hz), 7.19 (s, 1H, H-13^1), 6.01 [d, 1H, H-3^2(*E*), J = 18.5 Hz), 5.94 (d, 1H, H-3^2(*Z*), J = 11.8 Hz), 4.77 (d, 1H, H-17, J = 8.6 Hz), 3.93 (s, 3H, H-13^4), 3.77 (q, 1H, H-18, J = 8.5 Hz), 3.57 (s, 3H, H-17^4), 3.25 (q, 2H, H-8^1, J = 7.1 Hz), 2.96 (s, 3H, H-12^1), 2.91 (s, 3H, H-2^1), 2.80 (s, 3H, H-7^1), 2.44 (dd, 1H, H-17^1, J = 8.6 Hz), 2.20 (dd, 2H, H-17^2), 1.85 (dd, 1H, H-17^1), 1.69 (d, 3H, H-18^1, J = 8.5 Hz), 1.45 (t, 3H, H-8^2, J = 7.1 Hz); LREIMS (m/z): 590 (M$^+$, 100%); HREIMS, $C_{36}H_{38}N_4O_4$ (M$^+$); calcd.: 590.2893; obsd.: 590.2895; Anal. calcd. for $C_{36}H_{38}N_4O_4$: C 73.21, H 6.48, N 9.48%; found: C 72.73, H 6.53, N 9.21%.

*13^1-Deoxo-13^1-hydroxy-13^2*R*-hydroxypheophorbide* a *methyl ester (**21**)*
13^2*R*-Hydroxypheophorbide *a* methyl ester (**14**) (90% d.e.) (11, 14) (50 mg, 0.0803 mmol) was dissolved in 25 mL of

pyridine–methanol solution (pyridine:methanol = 1:1) and the solution was stirred at room temperature. $NaBH_4$ (70 mg) was added and the reaction mixture was stirred for 3 h, at which time the UV–VIS spectrum indicated the absence of starting material. The reaction mixture was poured into ice-cooled 2 N HCl and the chlorin was extracted with CH_2Cl_2. The organic layer was carefully washed once with water, twice with saturated $NaHCO_3$, three times with water, and then dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography on silica III, eluting with 1% MeOH in CH_2Cl_2. The main band was collected (44.5 mg, 89% yield) and was analyzed by ^{1}H NMR to be a diastereomeric mixture of 56% 13^1-deoxo-13^1*R*-hydroxy-13^2*R*-hydroxypheophorbide *a* methyl ester (**21*RR***) and 44% 13^1-deoxo-13^1*S*-hydroxy-13^2*R*-hydroxypheophorbide *a* methyl ester (**21*SR***). Further purification of this diastereomeric mixture (20 mg) by preparative TLC on silica (developed by 2% MeOH, 5% acetone in dichloromethane) gave the optically pure 13^1-deoxo-13^1*R*-hydroxy-13^2*R*-hydroxypheophorbide *a* methyl ester (**21*RR***) (100% d.e. from ^{1}H NMR) (8.5 mg) as a green solid after recrystallization from CH_2Cl_2–hexane; mp 180°C; UV-VIS λ_{max} (CH_2Cl_2): 400 nm (ε 114 100), 498 (10 700), 656 (33 700), 682 (6200); ^{1}H NMR (400 MHz, 1.4 mg/0.6 mL $CDCl_3$) δ: 9.80 (s, 1H, H-10), 9.65 (s, 1H, H-5), 8.80 (s, 1H, H-20), 8.20 (dd, 1H, H-3^1, J = 18.3 and 12.0 Hz), 6.42 (br s, 1H, OH-13^2), 6.33 (dd, 1H, H-3^2(*E*), J =18.3 and 1.4 Hz), 6.16 (dd, 1H, H-3^2(*Z*), J = 12.0 and 1.4 Hz), 5.60 (s, 1H, H-13^1), 4.93 (d, 1H, H-17, J = 8.2 Hz), 4.59 (q, 1H, H-18, J = 7.5 Hz), 4.48 (m, 2H, 13^2), 3.81 (q, 2H, H-8^1, J = 7.6 Hz), 3.57 (s, 3H, H-17^4), 3.55 (s, 3H, H-13^4), 3.54 (s, 3H, H-12^1), 3.53 (s, 3H, H-7^1), 3.38 (s, 3H, H-2^1), 2.45 (ddd, 1H, H-17^1), 2.32 (ddd, 1H, H-17^2), 2.10 (ddd, 1H, H-17^1), 1.96 (ddd, 1H, H-17^2), 1.74 (d, 3H, H-18^1, J = 7.5 Hz), 1.71 (t, 3H, H-8^2, J = 7.6 Hz), −1.40 (br s, 1H, NH), −3.10 (br s, 1H, NH); ^{13}C NMR (75 MHz, 12 mg/1.0 mL $CDCl_3$) δ: 176.03 (C-13^3), 173.81 (C-17^3), 167.27 (C-19), 163.05 (C-16), 150.59 (C-6), 150.48 (C-9), 143.18 (C-14), 142.49 (C-8), 139.81 (C-1), 138.18 (C-11), 136.49 (C-3), 135.63 (C-4), 134.48 (C-7), 132.21 (C-2), 129.88 (C-3^1), 128.83 (C-12), 128.41 (C-13), 121.56 (C-3^2), 108.87 (C-15), 99.75 (C-10), 99.29 (C-5), 95.00 (C-13^2), 93.46 (C-20), 82.41 (C-13^1), 53.32 (C-13^4), 51.57 (C-17^4), 50.98 (C-17), 49.95 (C-18), 30.66 (C-17^1), 29.33 (C-17^2), 23.54 (C-18^1), 19.64 (C-8^1), 17.71 (C-8^2), 12.31 (C-12^1), 11.43 (C-2^1), 11.43 (C-7^1); LREIMS (*m/z*): 624 (M$^+$, 38%); HREIMS, $C_{36}H_{40}N_4O_6$ (M$^+$), calcd.: 624.2948; obsd.: 624.2938; Anal. calcd. for $C_{36}H_{40}N_4O_6$: C 69.20, H 6.46, N 8.97%; found: C 68.97, H 6.44, N 8.70%.

13-Decarboxy-13-formyl-purpurin-7 dimethyl ester (15)

Method A: A solution of 13^1-deoxo-13^1,13^2-dehydropheophorbide *a* methyl ester (**19**) (20 mg, 0.0339 mmol) in CH_2Cl_2 (100 mL) was stirred in Vancouver sunlight for 20 min. Removal of solvent in vacuo and crystallization from CH_2Cl_2–hexane gave a brown powder of the aldehyde **15** (21 mg, 100% yield).

Method B: A solution of 13^2-deoxo-13^1-hydroxy-13^2*R*-hydroxypheophorbide *a* methyl ester (**21**) (31 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 dichloromethane. Recrystallization from dichloromethane–hexane gave the title compound as a brown powder (24.8 mg, 80%); mp 216-217°C; UV-VIS λ_{max} (CH_2Cl_2): 414 nm (ε 113 200), 508 (7400), 544 (10 600), 630 (7000), 680 (35 400), 686 (31 700); ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) δ: 10.93 (s, 1H, H-13^1), 9.50 (s, 1H, H-10), 9.20 (s, 1H, H-5), 8.45 (s, 1H, H-20), 7.90 (dd, 1H, H-3^1, J = 18.2 and 11.9 Hz), 6.30 (d, 1H, H-3^2(*E*), J = 18.2 Hz), 6.11 (d, 1H, H-3^2(*Z*), J = 11.9 Hz), 4.48 (dd, 1H, H-17, J = 9.4 Hz), 4.28 (q, 1H, H-18, J = 9.0 Hz), 3.93 (s, 3H, H-12^1), 3.66 (s, 3H, H-17^4), 3.61 (q, 2H, H-8^1, J = 7.5 Hz), 3.52 (s, 3H, H-15^3), 3.30 (s, 3H, H-2^1), 3.13 (s, 3H, H-7^1), 2.35 (m, 1H, H-17^1), 2.10 (m, 2H, H-17^2), 1.80 (m, 1H, H-17^1), 1.73 (d, 3H, H-18^1, J = 9.0 Hz), 1.65 (t, 3H, H-8^2, J = 7.5 Hz), 0.2 (br s, 2H, NH); ^{13}C NMR (75 MHz, 15 mg/1.0 mL $CDCl_3$) δ: 186.83 (C-13^1), 184.92 (C-15^1), 174.85 (C-15^2), 173.30 (C-17^3), 168.22 (C-19), 163.28 (C-16), 157.05 (C-6), 149.12 (C-9), 145.98 (C-14), 143.24 (C-8), 140.40 (C-1), 137.34 (C-11), 136.62 (C-3), 135.97 (C-4), 134.20 (C-7), 131.90 (C-2), 129.56 (C-12), 124.36 (C-13), 128.57 (C-3^1), 122.89 (C-3^2), 106.90 (C-5), 105.80 (C-15), 100.45 (C-10), 93.74 (C-20), 53.27 (C-17), 52.63 (C-15^3), 51.53 (C-17^4), 49.71 (C-18), 31.44 (C-17^2), 30.93 (C-17^1), 22.78 (C-18^1), 19.40 (C-8^1), 17.47 (C-8^2), 11.90 (C-12^1), 11.39 (C-2^1), 11.06 (C-7^1); LREIMS (*m/z*): 622 (M$^+$, 15%), 563 (M$^+$ − COOMe, 27%), 535 (M$^+$ − COOMe − CO, 27%); HREIMS, $C_{36}H_{38}N_4O_6$ (M$^+$), calcd.: 622.2791; obsd.: 622.2786; Anal. calcd. for $C_{36}H_{38}N_4O_6$: C 69.44, H 6.15, N 9.00%; found: C 69.11, H 5.93, N 8.92%.

13-Decarboxy-13-formyl-3-vinylrhodoporphyrin XV methyl ester (17)

Purpurin **15** (150 mg, 0.24 mmol) was heated in an oil bath at 180–185°C in 2,4,6-collidine (30 mL) for 45 min. After cooling, the solvent was evaporated at 0.5 Torr and the residue was recrystallized from $CHCl_3$–CH_3OH, giving the title porphyrin (19.3 mg, 15% yield) as purple needles; mp 245–246°C; UV-VIS λ_{max} (CH_2Cl_2): 414 nm (ε 189 000), 518 (9000), 560 (21 400), 582 (15 300), 636 (2500); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.40 (s, 1H, 13-CHO), 10.70, 9.92, 9.88, 9.76 (4s, 4H, H-5, H-10, H-15, and H-20), 8.15 (dd, 1H, H-3^1, J = 17.5 and 11.0 Hz), 6.29 (dd, 1H, H-3^2(*E*), J = 17.5 and 1.0 Hz), 6.15 (dd, 1H, H-3^2(*Z*), J = 11.0 and 1.0 Hz), 4.37 (t, 2H, H-17^1, J = 7.5 Hz), 4.00 (q, 2H, H-8^1, J = 8.3 Hz), 3.80, 3.69, 3.58, 3.58, 3.58 (5s, 15H, H-2^1, H-7^1, H-12^1, H-18^1, and H-17^4), 3.23 (t, 2H, H-17^2, J = 7.5 Hz), 1.80 (t, 3H, H-8^2, J = 8.3 Hz), −4.50 (br s, 2H, NH); LREIMS (*m/z*): 534 (M$^+$, 100%); HREIMS, $C_{33}H_{34}N_4O_3$ (M$^+$); calcd.: 534.2631; obsd.: 534.2634.

13-Decarboxy-13-(ethyleneacetal)-purpurin-7 dimethyl ester (22)

The foregoing purpurin **15** (20 mg, 0.032 mmol) in dry THF (50 mL) under nitrogen was stirred in a three-necked round-bottom flask equipped with a Soxhlet apparatus containing 4Å molecular sieves. Ethylene glycol (0.9 mL) and *p*-toluenesulfonic acid (2 mg) were added to the solution and the reaction mixture was brought to reflux. Progress of the reaction was followed by spectrophotometry, using the change in absorption spectrum from λ_{max} = 686 nm to λ_{max} = 660 nm; the reaction was complete after 1 h. The mixture was diluted with methylene chloride (50 mL), washed with water (3 × 50 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on alumina V (elution with methylene chloride) to give the principal green band. Removal of solvent in vacuo and recrystallization from CH_2Cl_2–hexane gave a dark-green powder of the title acetal **22** (19.2 mg, 90% yield); mp 265°C; UV–VIS λ_{max} (CH_2Cl_2): 400 nm (ε 149 000), 496 (13 000), 606 (5000), 660 (39 000); ^{1}H NMR (400 MHz, 1.5 mg/0.6 mL $CDCl_3$) δ: 10.93 (s, 1H, H-13^1), 9.75 (s, 1H, H-10), 9.68 (s, 1H, H-5), 8.80 (s, 1H, H-20), 8.12 (dd, 1H, H-3^1, J = 18.3 and 11.7 Hz), 6.33 (d, 1H, H-3^2(*E*), J = 18.3 Hz), 6.15 (d, 1H, H-3^2(*Z*), J = 11.7 Hz), 4.70 (m, 1H, 13^1-OCH_2OCH_2), 4.40 (q, 1H, H-18, J = 7.3 Hz), 4.18 (dd, 1H, H-17, J = 13.3 and 3.6 Hz), 4.06 (s, 3H, 15^1-$COOCH_3$), 4.01 (m, 3H, 13^1-OCH_2OCH_2), 3.79 (q, 2H, H-8^1, J = 7.56 Hz), 3.59 (s, 3H, H-17^4), 3.50 (s, 3H, H-12^1), 3.44 (s, 3H, H-2^1), 3.33 (s, 3H, H-7^1), 2.38 (m, 1H, H-17^1), 2.20 (m, 1H, H-17^2), 1.89 (m, 1H, H-17^1), 1.82 (d, 3H, H-18^1, J = 7.3 Hz), 1.80 (m, 1H, H-17^2), 1.73 (t, 3H, H-8^2, J = 7.6 Hz), −1.85 (br s, 1H, NH), −2.03 (br s, 1H, NH); LREIMS (*m/z*): 666 (M^+, 100%); HREIMS, $C_{38}H_{42}N_4O_7$ (M^+), calcd.: 666.3053; obsd.: 666.3061.

13-Decarboxy-3,13-divinylrhodoporphyrin XV methyl ester ***(16)***

Method A: 13-Decarboxy-13-formyl-3-vinylrhodoporphyrin XV methyl ester (**17**) (18 mg, 0.0337 mmol) was dissolved in methylene chloride (10 mL), and a saturated solution of $Zn(OAc)_2$ in methanol (0.5 mL) was added. The resulting solution was stirred at room temperature for 3 h, at which time TLC and UV–VIS spectroscopy showed full conversion to the desired compound. The solvent was removed by evaporation in vacuo and the product was redissolved in methylene chloride, filtered through a short bed of alumina V, and evaporated to dryness. The Zn(II) porphyrin was further dried, under vacuum, at 0.5 Torr, for 4 h.

Dry methyltriphenylphosphonium bromide (30 mg, 0.084 mmol) in dry THF (25 mL) and diisopropylamine (0.5 mL) were treated with *n*-butyllithium in *n*-hexane (50 mL, 1.6 M). The resulting ylide was stirred at 0°C under nitrogen gas and a THF solution (10 mL) of the above Zn(II) porphyrin was added via a cannula. After 30 min the solution was evaporated to dryness to give a residue that was taken into methylene chloride (30 mL), filtered through anhydrous sodium sulfate, and then evaporated again to dryness. The residue was dissolved in trifluoroacetic acid (3 mL) and washed twice with water (30 mL). The organic phase was evaporated to dryness and the residue was chromatographed on alumina III (elution with methylene chloride). The red eluates were evaporated to dryness to furnish a residue that was recrystallized from $CHCl_3$–hexane to give the title porphyrin (12.6 mg, 71%) as a purple-red powder.

Method B: The foregoing hydroxyporphyrin **27** (55 mg, 0.1 mmol) was dissolved in dry DMF (20 mL) and stirred at 105°C under nitrogen. Benzoyl chloride (1 mL) was added to this solution via a syringe and the mixture was kept at this temperature for 2 h. The solution was then diluted with methylene chloride (100 mL), and successively washed with 2 M sodium hydroxide (75 mL) and water (2 × 100 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was chromatographed on silica III (elution with methylene chloride) to give a major red band. The appropriate fractions were collected, evaporated, and recrystallized from CH_2Cl_2–hexane to give the title divinylporphyrin **16** (31.9 mg, 60%) as a purple-red solid. This material was found identical to the compound prepared from the Wittig reaction of 13-formylporphyrin **17**; mp 227°C; UV–VIS λ_{max} (CH_2Cl_2): 404 nm (ε 108 000), 506 (7500), 544 (9800), 572 (5600), 630 (1500); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.16, 10.15, 10.08, 10.07 (4s, 4H, H-5, H-10, H-15, and H-20), 8.27 (dd, 2H, H-3^1 and H-13^1), 6.33 (dd, 2H, H-3^2(*E*) and H-13^2(*E*)), 6.15 (dd, 2H, H-3^2(*Z*) and H-13^2(*Z*)), 4.42 (t, 2H, H-17^1, J = 7.6 Hz), 4.10 (q, 2H, H-8^1, J = 7.5 Hz), 3.69, 3.67, 3.66, 3.65, 3.63 (5s, 15H, H-2^1, H-7^1, H-12^1, H-18^1, and H-17^4), 3.26 (t, 2H, H-17^2, J = 7.6 Hz), 1.86 (t, 3H, H-8^2, J = 7.5 Hz), −3.75 (br s, 2H, NH); LRFABMS (*m/z*): 533 (M^+, 100%); HRFABMS, $C_{34}H_{37}N_4O_2$ (M^+); calcd.: 533.2916; obsd.: 533.2916.

Synthesis of [A,C]-divinylporphyrin 16 via porphyrin 9

3-Vinylrhodoporphyrin XV methyl ester (***23***) *(21)*

Vinylrhodoporphyrin XV dimethyl ester (**9**) (850 mg) in warm pyridine (175 mL) was refluxed for 4 h with a solution of potassium hydroxide (20 g) in water (25 mL) and methanol (150 mL). The solution was cooled, diluted with ice-water (1 L), acidified with concentrated sulfuric acid (15 mL) in water (100 mL), and then stirred for 10 min. The precipitated porphyrin diacid was filtered onto Celite, and washed with warm water followed by dry methanol. A mixture of dry methanol (650 mL) and concentrated sulfuric acid (20 mL) was passed slowly through the bed of Celite, thereby dissolving the porphyrin, and the resultant solution was kept at room temperature in the dark for 16 h before addition to water (1.5 L). The porphyrin was extracted with methylene chloride (3 × 500 mL) and the extracts were washed with water (1 L), dried over anhydrous $MgSO_4$, and evaporated. The residue was recrystallized from THF–benzene to give the title porphyrin monocarboxylic acid (605 mg, 70%) as a dark-red powder; mp >300°C (lit. (21) mp >300°C); UV–VIS λ_{max} (CH_2Cl_2): 408 nm (ε 154 000), 514 (7900), 554 (16 300), 578 (9500) (lit. (21) λ_{max} (pyridine): 409 nm (ε 189 000), 511(10 000), 552 (17 200), 579 (9200); λ_{max} ($CHCl_3$–HCl): 427 nm (ε 206 000), 569 (12 000), 620 (12 900); λ_{max} (0.1 M NaOMe – MeOH): 399 nm (ε 146 000), 503 (10 500), 550 (12 000), 572 (6700), 624 (1900)); ^{1}H NMR (400 MHz, CF_3COOD) δ: 11.90, 11.20, 11.00, 10.95 (4s, 4H, H-5, H-10, H-15, and H-20), 8.28 (dd, 1H, H-3^1, J = 18.3 and 11.0 Hz), 6.65 (d, 1H, H-3^2(*Z*), J = 11.0 Hz), 6.40 (d, 1H, H-3^2(*E*), J = 18.3 Hz), 4.62 (t, 2H, H-17^1), 4.25 (q, 2H, H-8^1), 4.19, 3.80, 3.78, 3.76, 3.72 (5s, 15H, H-2^1, H-7^1, H-12^1, H-18^1, and H-17^4), 3.40 (t, 2H, H-17^2), 1.82 (t, 3H, H-8^2); LREIMS (*m/z*): 550 (M^+, 100%), 506 (M^+ − CO_2, 30%); HREIMS, $C_{33}H_{34}N_4O_4$ (M^+), calcd.: 550.2580; obsd.: 550.2580; Anal. calcd. for $C_{33}H_{34}N_4O_4$: C 71.98, H 6.22, N 10.17%; found: C 71.93, H 6.16, N 9.86%.

*13-Imidazoyl-3-vinylrhodoporphyrin XV methyl ester (**24**)*

A mixture of 3-vinylrhodoporphyrin XV methyl ester (**23**) (600 mg, 1.09 mmol) and *N*,*N*′-carbonyldiimidazole (600 mg) was refluxed for 30 min in THF (125 mL). The solution was evaporated to about 60 mL and then applied to a short alumina column (Brockman Grade V; elution with methylene chloride). The appropriate eluates were evaporated and the residue was recrystallized from CH_2Cl_2–benzene to give the title porphyrin (595 mg, 91%) as a dark-red powder; mp 239°C; UV–VIS λ_{max} (CH_2Cl_2): 408 nm (ε 160 000), 514 (6900), 554 (15 300), 574 (9900); ^1H NMR (400 MHz, $CDCl_3$) δ: 10.01, 9.97, 9.88, 9.70 (4s, 4H, H-5, H-10, H-15, and H-20), 8.38 (s, 1H, H-imidazole), 8.12 (dd, 1H, H-3^1, *J* = 17.5 and 12.0 Hz), 7.95 (s, 1H, H-imidazole), 7.35 (s, 1H, H-imidazole), 6.29 (dd, 1H, H-3^2(*E*), *J* = 17.5 and 1.5 Hz), 6.15 (dd, 1H, H-3^2(*Z*), *J* = 17.5 and 1.5 Hz), 4.25 (t, 2H, H-17^1, *J* = 8.1 Hz), 4.00 (q, 2H, H-8^1, *J* = 8.0 Hz), 3.67, 3.65, 3.55, 3.53, 3.51 (5s, 15H, H-2^1, H-7^1, H-12^1, H-18^1, and H-17^4), 3.18 (t, 2H, H-17^2, *J* = 8.1 Hz), 1.80 (t, 3H, H-8^2, *J* = 8.0 Hz), −4.30 (br s, 2H, NH); LRFABMS (*m/z*): 601 ($[M + H]^+$, 73%), 533 ($M^+ - C_3H_3N2$, 100%); LREIMS (*m/z*): 533 ($M^+ - C_3H_3N_2$, 100%); HRFABMS, $C_{36}H_{37}N_6O_3$ ($[M + H]^+$); calcd.: 601.2927; obsd.: 601.2929; HREIMS, $C_{33}H_{33}N_4O_3$ ($M^+ - C_3H_3N_2$): calcd.: 533.2552; obsd.: 533.2551.

*13-Decarboxy-13-methoxycarbonylacetyl-3-vinylrhodoporphyrin XV methyl ester (**25**) (21)*

A solution of 2-PrMgBr was prepared by refluxing, under dry nitrogen, a mixture of Mg turnings (1.2 g) and 2-PrBr (4 g) in freshly distilled THF (150 mL). When the metal had dissolved, the solution was cooled to 0°C and redistilled methyl hydrogen malonate (23) (3 g) in dry THF (30 mL) was added via a cannula. The mixture was warmed to 65°C and stirred for 10 min before introduction of a solution of 13-imidazoyl-3-vinylrhodoporphyrin XV methyl ester (**24**) (400 mg) in dry THF (200 mL). Stirring was maintained for 2.5 h while heating under reflux, and glacial acetic acid (15 mL) was then added. Heating and stirring were continued for a further 15 min, after which the mixture was diluted with chloroform (1400 mL), washed with 0.1 M HCl (1100 mL) and water (2 × 800 mL), and then dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed on alumina V (elution with 5% acetone in methylene chloride) and after evaporation of the appropriate eluates the product was recrystallized from CH_2Cl_2–hexane to give the required porphyrin-β-ketoester **25** (280 mg, 70%) as a dark-red solid; mp 270–274°C (lit. (21) mp 250–254°C); UV–VIS λ_{max} (CH_2Cl_2): 410 nm (ε 140 000), 512 (7400), 552 (14 000), 576 (9200) (lit. (21) λ_{max} (CH_2Cl_2): 409 nm (ε 176 000), 512 (7200), 553 (15 400), 574 (9900), 635 (1300); λ_{max} (CH_2Cl_2–CF_3COOH): 412 nm (ε 267 000), 559 (12 200), 608 (8600); λ_{max} (0.1 M NaOMe – MeOH): 401 nm (ε 154 000), 504 (10 500), 542 (12 400), 572 (6900), 625 (2200)); ^1H NMR (400 MHz, $CDCl_3$) δ (the enol tautomer): 13.30 (s, 1H, OH), 10.62, 10.62, 10.42, 9.75 (4s, 4H, H-5, H-10, H-15, and H-20), 6.10 (s, 1H, H-13^2); δ (the ketone tautomer): 9.98, 9.97, 9.86, 9.85 (4s, 4H, H-5, H-10, H-15, and H-20), 4.70 (s, 2H, H-13^2); δ (their mixture): 8.10 (m, 1H, H-3^1), 6.25 (m, 1H, H-3^2(*E*)), 6.12 (m, 1H, H-3^2(*Z*)), 4.41 (t, 2H, H-17^1), 3.98 (q, 2H, H-8^1), 4.02–3.45 (6s, 18H, H-2^1, H-7^1, H-12^1, H-18^1, H-17^4, and 13^2-$COOCH_3$), 3.25 (t, 2H, H-17^2), 1.83 (t, 3H, H-8^2), −4.26 (br s, 1H, NH), −4.30 (br s, 1H, NH); LRFABMS (*m/z*): 607 ($[M + H]^+$, 16%); HRFABMS, $C_{36}H_{39}N_4O_5$ ($[M + H]^+$); calcd.: 607.2920; obsd.: 607.2919.

*13-Acetyl-13-decarboxy-3-vinylrhodoporphyrin XV methyl ester (**26**)*

A mixture of porphyrin-β-ketoester **25** (180 mg, 0.297 mmol), 4-(dimethylamino)pyridine (36 mg, 2.92 mmol), 1.0 M phosphate buffer (pH = 7) (40 mL), and toluene (150 mL) was stirred at 90°C for 12 h, at which time TLC analysis showed the full disappearance of the porphyrin-β-ketoester band and appearance of a more mobile red band. The reaction mixture was extracted with ethyl acetate (250 mL) and the organic layer was washed once with saturated NH_4Cl, twice with water (200 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on silica III (elution with methylene chloride) to give a major red band. The appropriate eluates were evaporated and the residue was recrystallized from CH_2Cl_2–hexane to give the title acetylporphyrin (122 mg, 75%) as purple-red small leaves; mp 284°C; UV–VIS λ_{max} (CH_2Cl_2): 410 nm (ε 147 000), 514 (7400), 554 (13 800), 576 (8600), 608 (1300); ^1H NMR (400 MHz, $CDCl_3$) δ: 10.75, 10.10, 10.07, 9.98 (4s, 4H, H-5, H-10, H-15, and H-20), 8.20 (dd, 1H, H-3^1, *J* = 17.4 and 12.5 Hz), 6.30 (d, 1H, H-3^2(*E*), *J* = 17.4 Hz), 6.12 (d, 1H, H-3^2(*Z*), *J* = 12.5), 4.43 (t, 2H, H-17^1, *J* = 7.5 Hz), 4.09 (q, 2H, H-8^1, *J* = 8.8 Hz), 3.88, 3.67, 3.65, 3.61, 3.61 (5s, 15H, H-2^1, H-7^1, H-12^1, H-18^1, and H-17^4), 3.33 (t, 2H, H-17^2, *J* = 7.5 Hz), 3.32 (s, 3H, H-13^2), 1.85 (t, 3H, H-8^2, *J* = 8.8 Hz), −3.80 (br s, 2H, NH); LRFABMS (*m/z*): 549 ($[M + H]^+$, 100%); HRFABMS, $C_{34}H_{36}N_4O_3$ ($[M + H]^+$); calcd.: 549.2865; obsd.: 549.2861.

*13-Decarboxy-13-(α-hydroxy)ethyl-3-vinylrhodoporphyrin XV methyl ester (**27**)*

To a mixture of the foregoing porphyrin **26** (100 mg, 0.182 mmol) in methylene chloride (80 mL) and methanol (15 mL) was added sodium borohydride (80 mg). The mixture was stirred for 90 min at room temperature, after which time TLC monitoring indicated reduction of the acetyl group to be complete. The reaction was quenched by slow addition of ice-cooled 1 M HCl. The organic layer was separated, washed twice with water, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on silica V (elution with 0.5% methanol in methylene chloride) to give a major red band. The appropriate eluates were evaporated and the residue was recrystallized from CH_2Cl_2–hexane to give the title hydroxyporphyrin (82 mg, 82%) as a purple solid; mp 219°C; UV–VIS λ_{max} (CH_2Cl_2): 404 nm (ε 178 000), 502 (10 600), 540 (12 000), 572 (9300), 624 (2700); ^1H NMR (400 MHz, $CDCl_3$) δ: 10.18, 10.00, 9.88, 9.88 (4s, 4H, H-5, H-10, H-15, and H-20), 8.20 (dd, 1H, H-3^1, *J* = 17.1 and 11.4 Hz), 6.31 (dd, 1H, H-3^2(*E*), *J* = 17.1 and 1.9 Hz), 6.15 (dd, 1H, H-3^2(*Z*), *J* = 12.5 and 1.9 Hz), 4.27 (t, 2H, H-17^1, *J* = 8.5 Hz), 4.00 (q, 2H, H-8^1, *J* = 8.2 Hz), 3.58, 3.58, 3.54, 3.51, 3.49 (5s, 15H, H-2^1, H-7^1, H-12^1, H-18^1, and H-17^4), 3.45 (q, 1H, H-13^1, *J* = 7.0 Hz), 3.16 (t, 2H, H-17^2, *J* = 8.5 Hz), 2.72 (br s, 1H, OH-13^1), 2.14 (d, 3H, H-13^2, *J* = 7.0 Hz), 1.81 (t, 3H, H-8^2, *J* = 8.2 Hz), −4.30 (br s, 2H, NH); LRFABMS (*m/z*): 551 ($[M + H]^+$, 100%); HRFABMS, $C_{34}H_{39}N_4O_3$ ($[M + H]^+$): calcd.: 551.3022; obsd.: 551.3011.

Diels–Alder reactions with vinylporphyrins

$2^1,2^2$-*Bis(methoxycarbonyl)-8-ethyl-13-methoxycarbonyl-17-methoxycarbonylethyl-2,7,12,18-tetramethyl-*2^3-*hydrobenzo[*b*]porphyrin (**28**)*

3-Vinylrhodoporphyrin XV dimethyl ester (**9**) (57 mg, 0.1 mmol) and DMAD (710 mg, 5 mmol) were suspended in degassed toluene (N_2) (20 mL) and the mixture heated at 110°C for 28 h. After removal of the toluene in vacuo, the residue was chromatographed on silica (methylene chloride eluant). After elution of the excess dienophile, the solvent polarity was increased to 2% methanol in methylene chloride to elute the major reaction product. After evaporation to dryness, the residue was recrystallized from CH_2Cl_2–hexane to afford the 1,4-cyclohexadiene adduct **28** as a green solid (35 mg, 50% yield); mp 244-245°C; UV–VIS λ_{max} (CH_3COCH_3): 410 nm (peak ratio, 1.40), 516 (0.119), 646 (0.138); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.75, 9.80, 9.25, 9.01 (4s, 4H, H-5, H-10, H-15, and H-20), 7.40 (dd, 1H, H-3^1, J = 7.4 and 2.1 Hz), 4.31 (t, 2H, H-17^1, J = 8.3 Hz), 3.95 (dd, 1H, H-2^3, J = 3.0 and 0.5), 3.94 (q, 2H, H-8^1, J = 7.5 Hz), 3.62 (s, 1H, H-2^3, J = 3.3 and 0.5 Hz), 3.25 (t, 2H, H-17^2, J = 8.3 Hz), 4.33, 4.02, 3.89, 3.75, 3.69, 3.45, 3.41 (7s, 21H, H-7^1, H-12^1, H-18^1, H-17^4, 2^1-$COOCH_3$, and 2^2-$COOCH_3$), 2.07 (s, 3H, 2-CH_3), 1.78 (t, 3H, H-8^2, J = 7.5 Hz), −2.26 (br s, 1H, NH), −2.30 (br s, 1H, NH); LREIMS (*m/z*): 706 (M^+, 100%), 690 ($M^+ - CH^4$, 60%).

$2^1,2^2$-*Bis(methoxycarbonyl)-8-ethyl-13-methoxycarbonyl-17-methoxycarbonylethyl-2,7,12,18-tetramethyl-*2^1-*hydrobenzo[*b*]porphyrin (**29**)*

The adduct **28** (32 mg, 0.045 mmol) was dissolved in methylene chloride and a few drops of DBU were added. The reaction mixture was stirred in the dark and monitored by visible spectroscopy (complete in 4 h). The mixture was poured into 1 M HCl and extracted with methylene chloride. The organic layer was washed twice with brine, once with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo and the compound was chromatographed on silica gel (1% MeOH in CH_2Cl_2 eluent). The pure 1,3-cyclohexadiene fraction was evaporated in vacuo yielding 29 mg (90% yield) of tiny dark-green needles after recrystallization from CH_2Cl_2–hexane; mp 248–249°C; UV–VIS λ_{max} (CH_2Cl_2): 356 nm (ε 27 000), 440 (70 400), 592 (19 900), 672 (14 600); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.70, 9.80, 9.30, 8.90 (4s, 4H, H-5, H-10, H-15, and H-20), 7.80 (d, 1H, H-2^4, J = 6.0 Hz), 7.42 (d, 1H, H-2^3, J = 6.0 Hz), 5.40 (s, 1H, H-2^1), 4.29 (t, 2H, H-17^1, J = 7.7 Hz), 3.92 (q, 2H, H-8^1, J = 7.9 Hz), 3.25 (t, 2H, H-17^2, J = 7.7 Hz), 4.34, 3.98, 3.75, 3.70, 3.43, 3.40, 2.98 (7s, 21H, H-7^1, H-12^1, H-18^1, H-17^4, 2^1-$COOCH_3$, and 2^2-$COOCH_3$), 1.79 (s, 3H, 2-CH_3), 1.76 (t, 3H, H-8^2, J = 7.9 Hz), −1.95 (br s, 1H, NH), −2.00 (br s, 1H, NH); LREIMS (*m/z*): 706 (M^+, 100%); HREIMS, $C_{40}H_{42}N_4O_8$ (M^+); calcd.: 706.3002, obsd.: 706.3010; Anal. calcd. for $C_{40}H_{42}N_4O_8$: C 67.97, H 5.99, N 7.93%; found: C 68.03, H 5.96, N 7.92%.

$2^1,2^2$-*Bis(methoxycarbonyl)-13,15-ethano-8-ethyl-17-methoxycarbonylethyl-2,7,12,18-tetra-methyl-*2^1-*hydrobenzo[*b*]porphyrin (**30**)*

3-Vinylporphyrin **6** (27 mg, 0.05 mmol) and DMAD (360 mg, 25 mmol) were suspended in degassed toluene (N_2) (20 mL) and the mixture was heated at 110°C for 30 h. After removal of the toluene in vacuo, the residue was chromatographed on silica (methylene chloride eluant). After elution of the excess dienophile, the solvent polarity was increased to 2% methanol in methylene chloride to elute the major reaction product. After evaporation to dryness, 14 mg (42% yield) of the 1,4-cyclohexadiene adduct **31** (λ_{max} = 404, 550, 650 nm) was obtained.

The adduct **31** (14 mg, 0.02 mmol) was dissolved in methylene chloride and a few drops of DBU were added. The reaction mixture was stirred in the dark and monitored by visible spectroscopy (completed in 6 h). The mixture was poured into 1 M HCl and extracted with methylene chloride. The organic layer was washed twice with brine, once with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo and the compound was chromatographed on silica gel (1% MeOH in CH_2Cl_2 eluent). The pure 1,3-cyclohexadiene fraction was evaporated in vacuo, yielding 12.7 mg (91% yield) of tiny dark-green needles after recrystallization from CH_2Cl_2–hexane; mp 258°C; UV–VIS λ_{max} (CH_2Cl_2): 354 nm (ε, 86 000), 438 (120 000), 580 (18 000), 620 (14 000), 680 (47 000), 686 (37 000); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59 (s, 1H, H-10), 9.30 (s, 1H, H-5), 8.95 (s, 1H, H-20), 7.83 (d, 1H, H-2^4, J = 5.8 Hz), 7.45 (d, 1H, H-2^3, J = 5.8 Hz), 5.20 (t, 2H, H-13^2), 5.05 (s, 1H, H-2^1), 4.30 (m, 2H, H-17^1), 3.93 (m, 2H, H-13^1), 3.93 (q, 2H, H-8^1, J = 7.9 Hz), 3.10 (t, 2H, H-17^2), 3.97, 3.78, 3.46, 3.42, 3.39, 2.92 (6s, 18H, H-7^1, H-12^1, H-18^1, H-17^4, 2^1-$COOCH_3$, and 2^2-$COOCH_3$), 1.78 (t, 3H, H-8^2, J = 7.9 Hz), 1.77 (s, 3H, 2-CH_3), −1.42 (br s, 1H, NH), −2.22 (br s, 1H, NH); LRFABMS (*m/z*): 675 ($[M + H]^+$, 100%); HRFABMS, $C_{40}H_{43}N_4O_6$ ($[M + H]^+$); calcd. 675.3182; obsd.: 675.3176.

$2^1,2^2,12^1,12^2$-*Tetrakis(methoxycarbonyl)-8-ethyl-17-methoxycarbonylethyl-2,7,12,18-tetramethyl-*$2^3,12^3$-*dihydrobenzo[*b,l*]porphyrin (**32**)*

The foregoing 3,13-divinylporphyrin **16** (30 mg, 0.0564 mmol) and DMAD (800 mg, 5.6 mmol) were suspended in degassed toluene (N2) (20 mL) and the mixture heated at 110°C for 80 h. After removal of the toluene in vacuo, the residue was chromatographed on silica (methylene chloride eluant). After elution of the excess dienophile, the solvent polarity was increased to 2% methanol in methylene chloride to elute the major reaction product. After evaporation to dryness, the resulting residue was subjected to preparative TLC on silica (1 mm thick plate; elution with 2% methanol in methylene chloride). The more mobile band was found to be the mono-adduct (exhibiting a band at 656 nm), present in a trace amount; the major band was found to be the bis-adduct, which was recrystallized from CH_2Cl_2–hexane to afford the bis-adduct **32** as a green solid (10.8 mg, 25% yield); mp 198°C; UV–VIS λ_{max} (CH_3COCH_3): 406 nm (peak ratio, 1.10), 484 (0.21), 538 (0.15), 666 (0.13), 720 (0.338); LREIMS (*m/z*): 816 (M^+, 100%).

$2^1,2^2,12^1,12^2$-*Tetrakis(methoxycarbonyl)-8-ethyl-17-methoxycarbonylethyl-2,7,12,18-tetra-methyl-*$2^1,12^1$-*dihydrobenzo[*b,l*]porphyrin (**33**)*

The bis-adduct **32** (9 mg, 0.011 mmol) was dissolved in methylene chloride and a few drops of DBU were added. The reaction mixture was stirred in the dark and monitored by visible spectroscopy (completed in 16 h). The mixture was poured into 1 M HCl and extracted with methylene chloride. The organic layer was washed twice with brine, once with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo and the compound was chromatographed on silica gel (1% MeOH in CH_2Cl_2 eluent). The pure 1,3-cyclohexadiene fraction was evaporated in vacuo, yielding 8.0 mg (90% yield) of a dark-green solid after recrystallization from CH_2Cl_2–hexane; mp 289-291°C; UV–VIS λ_{max} (CH_2Cl_2): 468 nm (ε 81 000), 620 (20 900), 700 (4700), 784 (38 000); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15, 9.15, 8.74, 8.74 (4s, 4H, H-5, H-10, H-15, and H-20), 7.82 (d, 2H, H-2^4 and H-12^4, J = 7.8 Hz), 7.35 (d, 2H, H-2^3 and H-12^3, J = 7.8 Hz), 4.95 (s, 2H, H-2^1 and H-12^1), 4.10 (t, 2H, H-17^1, J = 8.1 Hz), 3.98 (q, 2H, H-8^1, J = 7.7 Hz), 3.25 (t, 2H, H-17^2, J = 7.7 Hz), 3.90, 3.86, 3.63, 3.60, 3.32, 3.01 (6s, 18H, H-7^1, H-18^1, H-17^4, 2^1-$COOCH_3$, 2^2-$COOCH_3$, 12^1-$COOCH_3$, and 12^2-$COOCH_3$), 1.81 (s, 6H, 2-CH_3), 1.74 (t, 3H, H-8^2, J = 7.7 Hz), −1.90 (br s, 2H, NH); LRFABMS (m/z): 817 ($[M + H]^+$, 100%); HRFABMS, $C_{46}H_{49}N_4O_{10}$ ($[M + H])^+$; calcd.: 817.3455, obsd.: 817.3449.

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