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Pyrazolinyl and cyclopropyl derivatives of protoporphyrin IX and chlorins related to chlorophyll *a*

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Abstract—Diazomethane reacts regioselectively with peripheral vinyl substituents of pyropheophorbide *a* and purpurin-18 *N*-methylimide to produce corresponding 1′-pyrazolinyl-substituted derivatives as a main product. Similarly, treatment of protoporphyrin IX gave a mixture of mono- and di-substituted pyrazolinyl analogs, which were isolated as individual products. Thermolytic decomposition of the pyrazolinyl derivatives produced cyclopropyl-substituted chlorins and porphyrins. 1,3-Dipolar cycloaddition mechanisms of the formation of 1′-pyrazolinyl derivatives are discussed.

Porphyrins and related cyclic pyrrolic compounds are being studied clinically as photosensitizers in the field of photodynamic therapy (PDT) for a variety of disease indications.[1–3] A large number of potential new photosensitizers as well as those being used clinically are produced from naturally occurring porphyrins and chlorins. The synthesis of new photosensitizers from these abundant starting materials may have certain advantages for practical medicinal applications.[4] To date, all drugs approved for clinical use in the USA for PDT are related to protoporphyrin IX.[5] Most of the naturally occurring tetrapyrroles, e.g. chlorophyll *a* and protoporphyrin IX, possess at least one vinyl substituent. The modification of the vinyl group has been a focus of several researchers interested in generating new photosensitizer libraries.[5,6] One of the useful methodologies for vinyl functionalization is a reaction with 1,3-dipolar compounds via a concerted *cis*-cycloaddition mechanism.[7] It is well known that olefinic substituents can react with 1,3-dipoles such as diazoalkanes to produce 1-pyrazolines.[8] In porphyrin chemistry, ethyl diazoacetate has been employed as a specific test-reagent for vinyl-substituents.[9] While of some use in determining the presence of a vinyl group in the 1930's,[10] the reaction produces a stereoisomeric mixture of ethoxycarbonylcyclopropyl derivatives and is therefore not employed for the preparation of optically pure sensitizers.

Surprisingly, 1,3-dipolar cycloaddition reactions using other reagents, such as diazomethane, have not been reported on porphyrinic compounds. Diazomethane is one of the most reactive diazoalkanes and is widely employed in porphyrin chemistry as a fast and convenient method for methyl esterification of carboxylic acid groups in small-scale experiments.[11,12] Other applications of diazomethane include the ring-opening synthesis of chlorine 6 and purpurin 7 from pheophorbide *a*.[13,14] It is known that diazomethane can react with certain metallocomplexes of porphyrins to produce expanded analogs.[15] Formyl-substituted porphyrins on treatment with diazomethane give complex mixtures of homologated derivatives.[16] A recent publication outlines the use of diazomethane to synthesize verdinochlorins, a new class of sensitizer that possesses near-IR long wavelength absorptions of interest in PDT.[17] Similarly di- and tetraoxo-TPP derivatives were used to produce oxypyridoporphyrins and di-(oxypyrido)porphyrins via the diazomethane ring expansion reaction.[18]

Due to the extensive amount of research that has been undertaken using diazomethane in porphyrin chemistry, it is surprising that 1,3-cycloaddition reactions of diazomethane with vinyl-substituted porphyrins and chlorins has not yet been reported. Our interest in the modification of naturally occurring porphyrins and chlorins as potential photosensitizers for PDT applications led us to explore new strategies for vinyl functionalization, including the diazomethane cycloaddition methodology. In our studies, we chose pyropheophorbide *a* (**1**), purpurin-18 methylimide (**4**) and protoporphyrin IX dimethyl ester (**7**) as typical tetrapyrroles bearing vinyl substituents.

It was found that the vinyl group of pyropheophorbide *a* (**1**) in dichloromethane solution reacts slowly over a period of 48 h with ethereal diazomethane to produce a single product (a more polar band), which was isolated via chromatography on silica. Reactions were carried out at room

Keywords: diazomethane; 1,3-dipolar cycloaddition; chlorophyll derivatives; protoporphyrin IX; photodynamic therapy.

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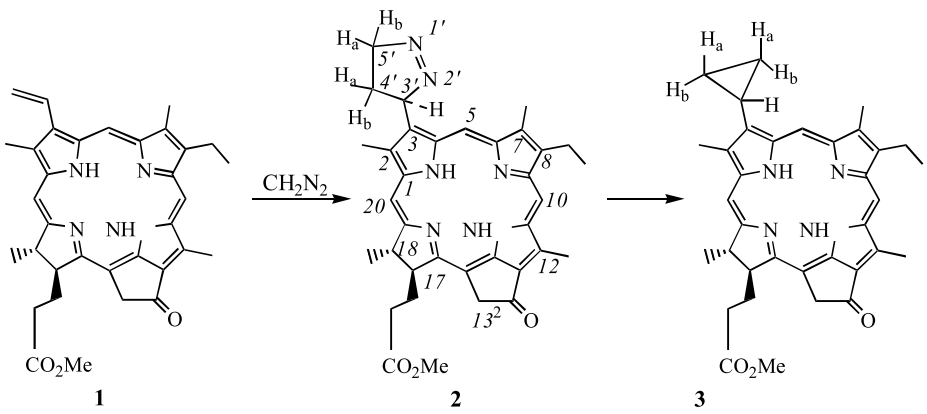


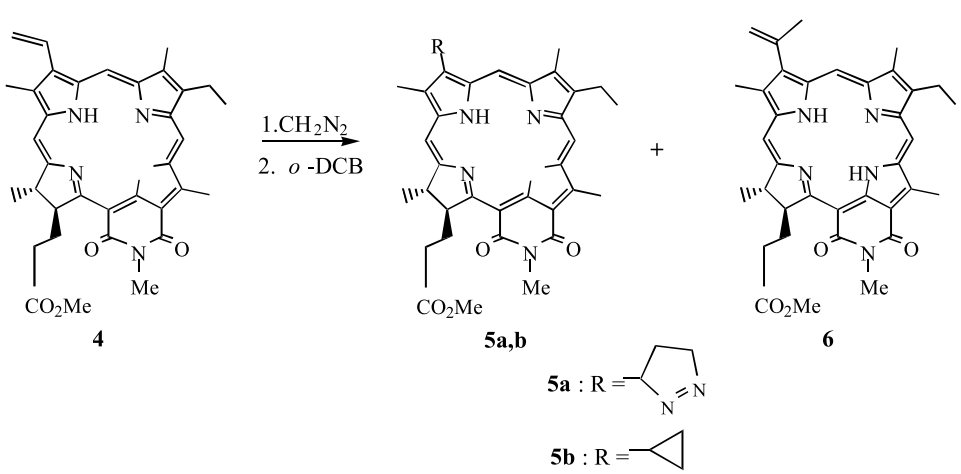
Scheme 1.

temperature in a septum-sealed flask. Different solvents did not appear to effect the reaction rate. The yield of the isolated compound was typically 35–45% after 48 h reaction time. Analysis of the compound by both LC/MS and ^{1}H NMR spectroscopy indicated that the isolated compound was the 3-[3′-(1′-pyrazolinyl)] derivative (**2**). A 2D/^{1}H NMR experiment established that the five multiplets at δ 6.70 (3′-H), 5.51 ($5'_a$-H), 4.78 ($5'_b$-H), 2.84 ($4'_a$-H) and 2.13 ppm ($4'_b$-H) corresponded to the protons of the 1′-pyrazoline ring. The presence of two (*R*,*S*)-epimers at the 3^1-chiral center was evident from the ^{1}H NMR spectrum, whereby the signals of the neighboring 5-*meso*-proton of both stereoisomers were separated and of equal intensities.

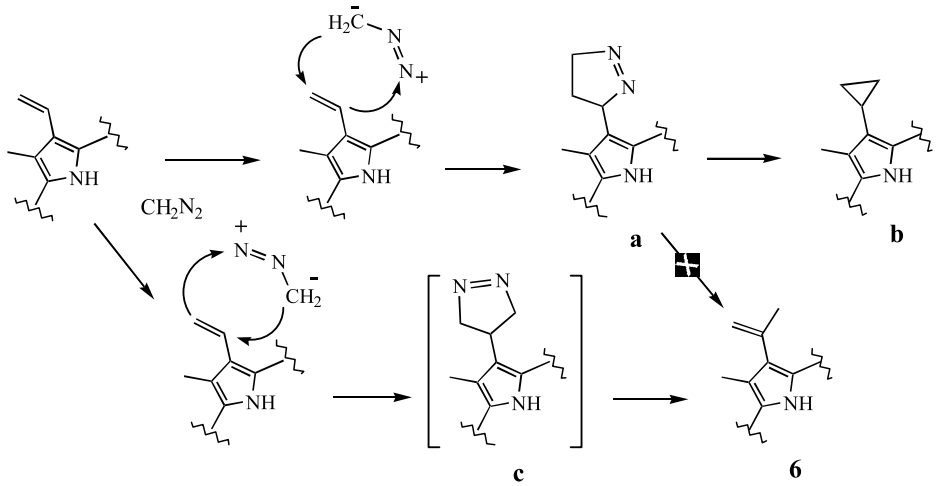
The structure of the pyrazolyl derivative (**2**) indicates that the diazomethane 1,3-dipolar cycloaddition reaction has a particular regioselective preference to produce the 'anti-Markovnikov'-type product. This is surprising, as the vinyl double bond polarization in porphyrins would be expected to produce the isomeric pyrazoline (**2c**) ring, as has been observed in styrenes.[7] Vinyl substituents on porphyrins are also known to give exclusively the products of the Markovnikov addition in A_E reactions in acidic conditions.[12] It is generally accepted that the regioselectivity of 1,3-dipolar cycloaddition reactions could be interpreted in the terms of frontier orbital interactions.[7] It appears that the regioselectivity of the diazomethane cycloaddition reaction to the vinyl substituent in pyropheophorbide *a* (**1**) is opposite to that occurring in protonated porphyrins and chlorins.[12]

It is known that 1-pyrazolines can be photolyzed or pyrolyzed to give cyclopropanes.[7] In our experiment, 3-devinyl-3-[3′(*R*,*S*)-(1′-pyrazolinyl)-pyropheophorbide *a* methyl ester (**2**) on refluxing in *o*-dichlorobenzene smoothly produced the cyclopropyl analog (**3**), isolated in 93% yield (Scheme 1). A ^{1}H NMR of (**3**) displayed cyclopropane ring protons as multiplets at δ 1.62 (3^2_a-H, 3^3_a-H), 1.32 (3^2_b-H, 3^3_b-H) and a triplet at 2.84 ppm (3^1-H).

Using a similar methodology, treatment of purpurin-18 *N*-methylimide (**4**) with diazomethane gave 1-pyrazoline (**5a**) as a main product (57%) in 72 h (Scheme 2). Surprisingly, we found that it was accompanied by a minor product, which based on mass and ^{1}H NMR data was assigned as the 3^1-methylvinyl analog (**6**) (6% yield). Mechanistically, this compound cannot originate from the 1′-pyrazolinyl derivative (**5a**) (Scheme 3), but can be formed from another regioisomer (**5c**). This compound was formed via 1,3-dipolar cycloaddition in accordance with the Markovnikov rule, as is found for styrenes. Presumably, the isomeric 1′-pyrazoline (**5c**) is not stable and decomposes at room temperature to produce the 1-methylvinyl analog (**6**). A possible explanation of the difference in the reactivity



Scheme 2.



Scheme 3.

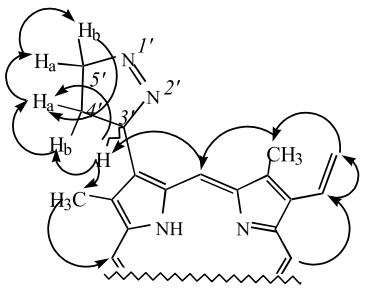


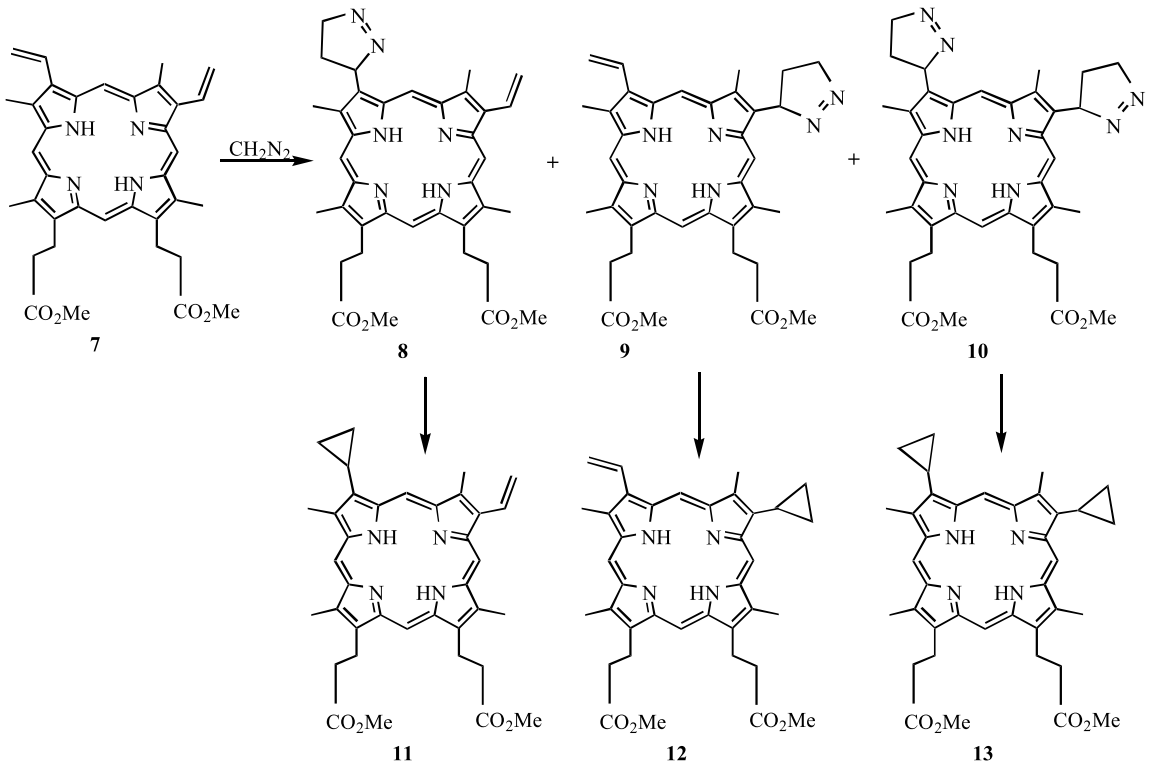
Figure 1. NOE connectivities in compound **8**.

of the vinyl substituent in (**1**) vs (**4**) could be the specific effect of the electron-withdrawing imide ring in (**4**). Pyrolysis of 3-devinyl-3-[3′(*R*,*S*)-(1′-pyrazolinyl)]-purpurin-18 *N*-methylimide (**5a**) in *o*-DCB gave 3-cyclopropylpurpurin analog (**5b**) in excellent yield (92%).

Reaction of protoporphyrin IX dimethyl ester (**7**) with excess diazomethane for 48 h produced a mixture of mono- and di-substituted pyrazolinyl analogs (**8**–**10**). These analogs were separated by column and thin-layer chromatography and isolated as individual compounds. ^{1}H NMR and mass spectrometry data on the two most mobile products confirmed their structures as the mono-(1′-pyrazolinyl)-adducts (**8**) and (**9**). Both mono-substituted analogs have proton signals of the 1′-pyrazoline ring and vinyl substituent in their ^{1}H NMR spectra. A 2D/ROESY ^{1}H NMR experiment on the fastest running band revealed it to be the 3-[3′(*R*,*S*)-(1′-pyrazolinyl)]-isomer (**8**), based on through-space interactions (Fig. 1). Hence, the second band was assigned as the structure (**9**). The third product, isolated as the most polar fraction, was identified as the di-(1′-pyrazolinyl)-substituted derivative (**10**). On longer exposure of protoporphyrin IX dimethyl ester to diazomethane (96 h), compound (**10**) became the major product isolated in 54% yield. Porphyrin (**10**) is a mixture of four (*R*/*S*)-isomers, due to the two chiral centers at the 3^1- and 8^1-carbon atoms. This isomeric mixture was clearly evident in its ^{1}H NMR spectrum, showing splitting of the resonances for the adjacent 5,10-*meso*-protons. As in the case pyropheophorbide *a*(**1**), no 3^1-methylvinyl derivatives were detected in the reaction mixture. Pyrolysis of the mono- and di-substituted 1′-pyrazolinyl derivatives (**8**–**10**) produced the corresponding cyclopropyl analogs (**11**–**13**) in 90–92% yields (Scheme 4).

1,3-Dipolar cycloaddition reactions on vinyl groups using diazomethane, have certain important advantages when compared to diazoacetic acid ester condensation. As the diazomethane reaction occurs at low temperatures, it is possible to isolate the 1′-pyrazolinyl-substituted derivatives. Such derivatives are also presumably formed as unstable intermediates during the condensation of vinyl groups with diazoacetic acid ester. Diazomethane cycloaddition with vinyl porphyrins and chlorins is a highly regiospecific reaction, producing mainly one compound. This is a first reported example of the synthesis of porphyrins and chlorins bearing 1′-pyrazoline rings. It is known that 1′-pyrazolinyl-substituted compounds have certain biological activities,[8] while the chemical reactivity of this group makes these analogs useful for a number of chemical transformations.[7] Compared to the ethoxycyclopropyl derivatives, which are a mixture of stereoisomers, pyrolysis of 1-pyrazolinyl analogs gives cyclopropyl derivatives having no asymmetric center. The introduction of cyclopropyl functionalities on a variety of organic molecules is known to elicit a large spectrum of biological activities, ranging from antibiotic, antiviral, antifungal, neurochemical, carcinogenic or antitumoral activities.[19] Preliminary results of biological testing on the cyclopropyl-substituted chlorins **3** and **5b** and several of their metallocomplexes have demonstrated significant in vitro photoactivity in a V-79 lung fibroblast cell culture model. These compounds are currently being evaluated in advanced in vivo animal models, the results of which will be reported elsewhere.

The synthetic methodology utilizing 1,3-cycloaddition reactions with vinyl-substituted tetrapyrroles lays the groundwork for important peripheral functionalization of tetrapyrrolic ring systems. Such reactions may have unique regioselective mechanisms and serve for the introduction of a number of potential biologically active functionalities.[7] These modifications may be valuable in the generation of novel photosensitizers for PDT.



Scheme 4.

1. Experimental

Melting points were determined on a Mel-Tec II apparatus and were uncorrected. Mp for 1′-pyrazolinyl derivatives were not determined, since these compounds are not stable at elevated temperatures. Preparative thin-layer chromatography was performed on Analtech 1 mm silica gel plates. Column chromatography was carried out using silica gel 60 (70–230 mesh). UV–Visible spectra were recorded on a Beckman 640-DU spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AMX-300 and a Bruker AM-400 spectrometers. Chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard. Fast atom bombardment (FAB) low- and high-resolution mass spectra were obtained on VG70E double focusing magnetic sector mass-spectrometer (UC Santa Barbara). Solvents (hplc grade) were purchased from Fisher Scientific (dichloromethane, hexane, acetone) and EM Science (diethyl ether) and used without purification. Pheophorbide *a* methyl ester was isolated from *Spirulina pacifica* alga according to a modified procedure.[20]

1.1. General procedure for preparation of pyrazolyl derivatives

All reactions were carried out in the dark. A protective shield was used during diazomethane cycloaddition. The starting chlorin/porphyrin (100 mg) was dissolved in dichloromethane (100 ml) and an ethereal solution of diazomethane (50 ml), prepared from diazald (Aldrich) (2 g), was added to the reaction mixture. The resulting solution was sealed with a rubber septum and kept at room temperature for 48–96 h. The solvent was degassed by bubbling with nitrogen and the resulting solution evaporated in vacuum. The residue was purified by chromatography on silica using 3% acetone/dichloromethane as an eluent. The product(s) was isolated as a single band(s), moving slower than the starting material.

1.2. General procedure for preparation of cyclopropyl derivatives

The (*R*,*S*)-(1′-pyrazolinyl)-derivatives (80 mg) were dissolved in *o*-diclorobenzene (40 ml) and heated at reflux for 20 min. The reaction solution was diluted with hexane (200 ml), and the formed residue was filtered and purified by chromatography on silica using 2–5% acetone/dichloromethane as an eluent. The product was crystallized from dichloromethane/hexane.

1.2.1. 3-Devinyl-3-[3′(*R*,*S*)-(1′-pyrazolinyl)]-pyropheophorbide *a* methyl ester (2). Prepared from pyropheophorbide *a*methyl ester (**1**) (200 mg). Yield: 94 mg (46%). Bluish–black solid (from dichloromethane/hexane). UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 410 (12.02), 505 (1.36), 536 (1.25), 606 (1.02), 662 (4.02); ^{1}H NMR δ 9.51 (s, 1H, 10-H), 8.98, 8.97 (two s, each 0.5H, 5-H), 8.61 (s, 1H, 20-H), 6.70 (t, 1H, 3′-H), 5.51 (m, 1H, $5'_a$-H), 5.27, 5.12 (AB, 2H, 13^2-H), 4.78 (m, 1H, $5'_b$-H), 4.52 (dq, 1H, J=7.9, 2.6 Hz, 18-H), 4.32 (dd, 1H, J=7.9, 1.8 Hz, 17-H), 3.72 (q, 2H, 8^1-CH_2), 3.70 (s, 3H, 12-CH_3), 3.63 (s, 3H, CO_2CH_3), 3.28 (s, 3H, 2-CH_3), 3.19 (s, 3H, 7-CH_3), 2.84 (m, 1H, $4'_a$-H), 2.81 (m, 1H, 17^1_a-H), 2.51 (m, 2H, $17^1_{a'}$-H, 17^2_b-H), 2.36 (m, 1H, $17^2_{b'}$-H), 2.13 (m, 1H, $4'_b$-H), 1.78 (d, 3H, 18-CH_3), 1.69 (t, 3H, 8^2-CH_3), 0.33 and −1.76 (each br s, 2H, 21-NH, 23-NH); HRFABMS $C_{35}H_{38}N_6O_3$ $[MH]^+$ calcd 591.3084, obsd 591.3087. Anal. calcd for $C_{35}H_{38}N_6O_3$: C, 71.16; H, 6.48; N, 14.23. Found: C, 71.08; H, 6.39; N, 14.38.

1.2.2. 3-Devinyl-3-cyclopropyl-pyropheophorbide *a* methyl ester (3). Prepared from 3-devinyl-3-[3′(*R*,*S*)-(1′-pyrazolinyl)]-pyropheophorbide *a* methyl ester (**2**) (80 mg). Product was crystallized from dichloromethane/hexane to give the title compound as dark bluish-green crystals. Mp 229–231°C. Yield: 74 mg (93%). UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 393 (1.08), 408 (12.42), 503 (1.16), 534 (1.07), 603 (0.82), 658 (3.86); ^{1}H NMR δ 9.56 (s, 1H, 10-H), 9.44 (d, 1H, 5-H), 8.44 (s, 1H, 20-H), 5.28, 5.15 (AB, 2H, 13^2-H), 4.46 (dq, 1H, 18-H), 4.27 (dd, 1H, 17-H), 3.70 (q, 2H, 8^1-CH_2), 3.69 (s, 3H, 12-CH_3), 3.65 (s, 3H, CO_2CH_3), 3.37 (s, 3H, 2-CH_3), 3.26 (s, 3H, 7-CH_3), 2.84 (m, 1H, 3^1-H), 2.71 (m, 1H, 17^1_a-H), 2.56 (m, 1H, $17^1_{a'}$-H), 2.36 (m, 2H, 17^2_b-H, $17^2_{b'}$-H), 1.78 (d, 3H, 18-CH_3), 1.69 (t, 3H, 8^2-CH_3), 1.62 (m, 2H, 3^2_a-H, 3^3_a-H), 1.32 (m, 2H, 3^2_b-H, 3^3_b-H), 0.62 and −1.62 (each br s, 2H, 21-NH, 23-NH); HRFABMS $C_{35}H_{38}N_4O_3$ $[MH]^+$ calcd 563.3023, obsd 563.3064. Anal. calcd for $C_{35}H_{38}N_4O_3$: C, 74.71; H, 6.81; N, 9.96. Found: C, 74.52; H, 6.69; N, 9.79.

1.2.3. 3-Devinyl-3-[3′(*R*,*S*)-(1′-pyrazolinyl)]-purpurin-18 *N*-methylimide methyl ester (5a). Prepared from purpurin-18 *N*-methylimide methyl ester (**4**) (400 mg) in 72 h. Yield: 230 mg (57%). Dark-purple solid (from dichloromethane/hexane), UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 362 (4.51), 419 (10.93), 509 (0.72), 547 (2.13), 642 (1.68), 707 (4.41); ^{1}H NMR δ 9.57 (s, 1H, 10-H), 8.95, 8.94 (two s, each 0.5H, 5-H), 8.56 (s, 1H, 20-H), 6.57 (t, 1H, 3′-H), 5.47 (m, 1H, $5'_a$-H), 5.39 (dd, 1H, 17-H), 4.75 (m, 1H, $5'_b$-H), 4.36 (dq, 1H, 18-H), 3.87 (s, 3H, N–CH_3), 3.79 (s, 3H, 12-CH_3), 3.64 (q, 2H, 8^1-CH_2), 3.60 (s, 3H, CO_2CH_3), 3.25 (s, 3H, 2-CH_3), 3.15 (s, 3H, 7-CH_3), 2.82 (m, 1H, 17^1_a-H), 2.69 (m, 1H, $4'_a$-H), 2.51 (m, 2H, $17^1_{a'}$-H, 17^2_b-H), 2.19 (m, 1H, $4'_b$-H), 1.96 (m, 1H, $17^2_{b'}$-H), 1.74 (d, 3H, 18-CH_3), 1.69 (t, 3H, 8^2-CH_3), 0.03 and −0.23 (each br s, 2H, 21-NH, 23-NH); HRFABMS $C_{36}H_{39}N_7O_4$ $[MH]^+$ calcd 634.3142, obsd 634.3097. Anal. calcd for $C_{36}H_{39}N_7O_4$: C, 67.61; H, 6.32; N, 15.77. Found: C, 67.31; H, 6.17; N, 15.36.

1.2.4. 3^1-Methyl-purpurin-18 *N*-methylimide methyl ester (6). Isolated as a minor fast brown-red band during preparation of (**5a**). Yield: 26 mg (6%). Dark-purple crystals (from dichloromethane/hexane). Mp>250°C. UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 364 (6.86), 417 (12.92), 509 (0.82), 549 (2.73), 648 (1.28), 704 (4.48); ^{1}H NMR δ 9.98 (s, 1H, 10-H), 9.83 (s, 1H, 5-H), 8.61 (s, 1H, 20-H), 7.97 (d, 1H, J=1.9 Hz, 3^2_a-H), 7.07 (d, 1H, J=1.9 Hz, 3^2_b-H), 5.35 (dd, 1H, 17-H), 4.38 (q, 1H, 18-H), 3.85 (s, 3H, N–CH_3), 3.82 (s, 3H, 12-CH_3), 3.64 (q, 2H, 8^1-CH_2), 3.59 (s, 3H, CO_2CH_3), 3.45 (s, 3H, 2-CH_3), 3.19 (s, 3H, 7-CH_3), 2.74 (m, 1H, 17^1_a-H), 2.48 (m, 2H, $17^1_{a'}$-H, 17^2_b-H), 2.06 (s, 3H, 3^1-CH_3), 1.96 (m, 1H, $17^2_{b'}$-H), 1.74 (d, 3H, 18-CH_3), 1.68 (t, 3H, 8^2-CH_3), −0.03 (br s, 2H, 21-NH, 23-NH); HRFABMS $C_{36}H_{39}N_5O_4$ $[MH]^+$ calcd 606.3079, obsd 606.3046.

1.2.5. 3-Devinyl-3-cyclopropyl-purpurin-18 *N*-methylimide methyl ester (5b). Prepared from 3-devinyl-3-[3′(*R*,*S*)-(1′-pyrazolinyl)-1-purpurin-18 *N*-methoxylimide methyl ester (**5a**) (100 mg). Yield: 91 mg (92%). Dark-purple crystals (from dichloromethane/hexane). Mp 238–241°C. UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 361 (6.38), 416 (13.12), 508 (0.86), 544 (2.67), 639 (0.98), 696 (4.69); ^{1}H NMR δ 9.53 (s, 1H, 10-H), 9.48 (s, 1H, 5-H), 8.48 (s, 1H, 20-H), 5.37 (dd, 1H, 17-H), 4.28 (dq, 1H, 18-H), 3.89 (s, 3H, N–CH_3), 3.84 (s, 3H, 12-CH_3), 3.72 (q, 2H, 8^1-CH_2), 3.60 (s, 3H, CO_2CH_3), 3.28 (s, 3H, 2-CH_3), 3.19 (s, 3H, 7-CH_3), 2.84 (m, 1H, 3^1-H), 2.81 (m, 1H, 17^1_a-H), 2.51 (m, 2H, $17^1_{a'}$-H, 17^2_b-H), 1.96 (m, 1H, $17^2_{b'}$-H), 1.74 (d, 3H, 18-CH_3), 1.68 (t, 3H, 8^2-CH_3), 1.63 (m, 2H, 3^2_a-H, 3^3_a-H), 1.35 (m, 2H, 3^2_b-H, 3^3_b-H), −0.03 and −0.26 (each br s, 2H, 21-NH, 23-NH); HRFABMS $C_{36}H_{39}N_5O_4$ $[MH]^+$ calcd 606.3079, obsd 606.3024. Anal. calcd for $C_{36}H_{39}N_5O_4$: C, 70.81; H, 6.62; N, 11.79. Found: C, 70.56; H, 6.64; N, 11.73.

1.2.6. 3-Devinyl-3-[3′(*R*,*S*)-(1′-pyrazolinyl)]-protoporphyrin IX dimethyl ester (8). Prepared from protoporphyrin IX dimethyl ester (**7**) (100 mg). Isolated using preparative TLC as the first major least polar band. Yield: 21 mg (20%). Reddish-purple solid (from dichloromethane/hexane). UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 406 (14.9), 506 (1.32), 541 (1.18), 577 (0.96), 629 (0.33); ^{1}H NMR δ 10.18 (s, 1H, 10-H), 10.06 (s, 1H, 20-H), 9.98 (s, 1H, 15-H), 9.69, 968 (two s, each 0.5H, 5-H), 8.32 (dd, 1H, J=18.0, 12.4 Hz, 8^1-H), 6.79 (t, 1H, 3′-H), 6.36 (dd, 1H, J=18.0, 1.4 Hz, 8^2_a-H), 6.16 (d, 1H, J=12.4, 1.4 Hz, 8^2_b-H), 5.51 (m, 1H, $5'_a$-H), 4.78 (m, 1H, $5'_b$-H), 4.37 (m, 4H, 13^1-CH_2, 17^1-CH_2), 3.68 (s, 6H, CO_2CH_3), 3.62 (s, 3H, 7-CH_3), 3.61 (s, 3H, 18-CH_3), 3.57 (s, 3H, 12-CH_3), 3.52 (s, 3H, 2-CH_3), 3.27 (m, 4H, 13^2-CH_2, 17^2-CH_2), 2.83 (m, 1H, $4'_a$-H), 2.13 (m, 1H, $4'_b$-H), −0.33 (br s, 2H, 21-NH, 23-NH); HRFABMS $C_{37}H_{40}N_6O_4$ $[MH]^+$ calcd 633.3189, obsd 633.3199. Anal. calcd for $C_{37}H_{40}N_6O_4$: C, 70.23; H, 6.37; N, 13.28. Found: C, 70.03; H, 6.12; N, 13.23.

1.2.7. 8-Devinyl-8-[3′(*R*,*S*)-(1′-pyrazolinyl)]-protoporphyrin IX dimethyl ester (9). Prepared from protoporphyrin IX dimethyl ester (**7**) (100 mg). Isolated using preparative TLC as second polar band. Yield: 19 mg (18%). Red-purple solid (from dichloromethane/hexane). UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 406 (14.6), 507 (1.36), 542 (1.23), 576 (0.91), 628 (0.37); ^{1}H NMR δ 10.12 (s, 1H, 5-H), 9.96 (s, 2H, 15-H, 20-H), 9.61, 9.60 (two s, each 0.5H, 10-H), 8.31 (dd, 1H, J=18.2, 12.3 Hz, 3^1-H), 6.78 (t, 1H, 3′-H), 6.38 (dd, 1H, J=18.2, 1.3 Hz, 3^2_a-H), 6.21 (dd, 1H, J=12.3, 1.3 Hz, 3^2_b-H), 5.39 (m, 1H, $5'_a$-H), 4.69 (m, 1H, $5'_b$-H), 4.39 (m, 4H, 13^1-CH_2, 17^1-CH_2), 3.69 (s, 6H, CO_2CH_3), 3.62 (s, 3H, 7-CH_3), 3.59 (s, 3H, 18-CH_3), 3.56 (s, 3H, 12-CH_3), 3.52 (s, 3H, 2-CH_3), 3.26 (m, 4H, 13^2-CH_2, 17^2-CH_2), 2.82 (m, 1H, $4'_a$-H), 2.19 (m, 1H, $4'_b$-H), −0.29 (br s, 2H, 21-NH, 23-NH); HRFABMS $C_{37}H_{40}N_6O_4$ $[MH]^+$ calcd 633.3189, obsd 633.3178. Anal. calcd for $C_{37}H_{40}N_6O_4$: C, 70.23; H, 6.37; N, 13.28. Found: C, 70.08; H, 6.21; N, 13.09.

1.2.8. 3,8-Di-[3′(*R*,*S*)-(1′-pyrazolinyl)]-deuteroporphyrin IX dimethyl ester (10). Prepared from protoporphyrin IX dimethyl ester (**7**) (100 mg) in 96 h. Isolated using preparative TLC as the most polar band. Yield: 58 mg (54%). Dark-purple solid (from dichloromethane/hexane). UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 404 (14.3), 504 (1.39), 540 (1.03), 573 (0.85), 624 (0.33); ^{1}H NMR δ 10.02 (s, 1H, 15-H), 9.98 (s, H, 20-H), 9.64, 9.63 (two s, each 0.5H, 5-H), 9.59, 9.58 (two s, each 0.5H, 10-H), 6.79 (m, 2H, 3′-H), 5.32 (m, 2H, $5'_a$-H), 4.73 (m, 2H, $5'_b$-H), 4.39 (m, 4H, 13^1-CH_2, 17^1-CH_2), 3.69 (s, 6H, CO_2CH_3), 3.65 (s, 3H, 7-CH_3), 3.62

(s, 3H, 18-CH_3), 3.57 (s, 3H, 12-CH_3), 3.50 (s, 3H, 2-CH_3), 3.29 (m, 4H, 13^2-CH_2, 17^2-CH_2), 2.85 (m, 2H, $4'_a$-H), 2.11 (m, 2H, $4'_b$-H), −0.09 (br s, 2H, 21-NH, 23-NH); HRFABMS $C_{38}H_{42}N_8O_4$ $[MH]^+$ calcd 675.3406, obsd 6759.3424. Anal. calcd for $C_{38}H_{42}N_8O_4$: C, 67.64; H, 6.27; N, 16.61. Found: C, 67.29; H, 6.12; N, 16.27.

1.2.9. 3-Devinyl-3-cyclopropylprotoporphyrin IX dimethyl ester (11). Prepared from 3-devinyl-3-[3′(*R*,*S*)-(1′-pyrazolinyl)-protoporphyrin IX dimethyl ester (**8**) (21 mg). Yield: 18 mg (92%). Dark-reddish crystals (from dichloromethane/methanol). Mp 214–216°C. UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 404 (13.9), 503 (1.28), 536 (1.13), 572 (0.89), 626 (0.38); ^{1}H NMR δ 10.32 (s, 1H, 10-H), 10.16, 10.04, 9.98 (each s, 3H, 5-H, 15-H, 20-H), 8.28 (dd, 1H, J=17.6, 12.4 Hz, 8^1-H), 6.38 (dd, 1H, J=17.6, 1.3 Hz, 8^2_a-H), 6.21 (dd, 1H, J=12.4, 1.3 Hz, 8^2_b-H), 4.43 (m, 4H, 13^1-CH_2, 17^1-CH_2), 3.67 (s, 6H, CO_2CH_3), 3.63 (s, 3H, 7-CH_3), 3.59 (s, 3H, 18-CH_3), 3.57 (s, 3H, 12-CH_3), 3.54 (s, 3H, 2-CH_3), 3.28 (m, 4H, 13^2-CH_2, 17^2-CH_2), 2.98 (t, 1H, 3^1-H), 1.71 (m, 2H, 3^2_a-H, 3^3_a-H), 1.48 (m, 2H, 3^2_b-H, 3^3_b-H), −0.32 (br s, 2H, 21-NH, 23-NH); HRFABMS $C_{37}H_{40}N_4O_4$ $[MH]^+$ calcd 605.3127, obsd 605.3115. Anal. calcd for $C_{37}H_{40}N_4O_4$: C, 73.49; H, 6.67; N, 9.26. Found: C, 73.11; H, 6.32; N, 9.29.

1.2.10. 8-Devinyl-8-cyclopropylprotoporphyrin IX dimethyl ester (12). Prepared from 8-devinyl-8-[3′(*R*,*S*)-(1′-pyrazolinyl)-protoporphyrin IX dimethyl ester (**9**) (20 mg). Yield: 18 mg (91%). Red-purple crystals (from dichloromethane/methanol). Mp 212–215°C. UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 404 (13.7), 502 (1.26), 537 (1.18), 571 (0.87), 625 (0.35); ^{1}H NMR δ 10.34 (s, 1H, 5-H), 10.19, 10.04, 9.96 (each s, 3H, 10-H, 5-H, 20-H), 8.27 (dd, 1H, J=17.7, 12.6 Hz, 3^1-H), 6.37 (dd, 1H, J=17.7, 1.2 Hz, 3^2_a-H), 6.20 (dd, 1H, J=12.6, 1.2 Hz, 3^2_b-H), 4.45 (m, 4H, 13^1-CH_2, 17^1-CH_2), 3.66 (s, 6H, CO_2CH_3), 3.63 (s, 3H, 7-CH_3), 3.58 (s, 3H, 18-CH_3), 3.57 (s, 3H, 12-CH_3), 3.52 (s, 3H, 2-CH_3), 3.29 (m, 4H, 13^2-CH_2, 17^2-CH_2), 2.99 (t, 1H, 8^1-H), 1.71 (m, 2H, 8^2_a-H, 8^3_a-H), 1.48 (m, 2H, 8^2_b-H, 8^3_b-H), −0.30 (br s, 2H, 21-NH, 23-NH); HRFABMS $C_{37}H_{40}N_4O_4$ $[MH]^+$ calcd 605.3127, obsd 605.3121. Anal. calcd for $C_{37}H_{40}N_4O_4$: C, 73.49; H, 6.67; N, 9.26. Found: C, 73.67; H, 6.41; N, 9.38.

1.2.11. 3,8-Dicyclopropyldeuteroporphyrin IX dimethyl ester (13). Prepared from 3,8-di-[3′(*R*,*S*)-(1′-pyrazolinyl)-deuteroporphyrin IX dimethyl ester (**10**) (40 mg). Yield: 35 mg (90%). Red-purple powder (from dichloromethane/methanol). Mp 206–209°C. UV–Vis λ_{max} (CH_2Cl_2) nm ($\varepsilon\times10^4$) 402 (14.9), 499 (1.36), 533 (1.03), 568 (0.78), 622 (0.35); ^{1}H NMR δ 10.46 (s, 1H, 5-H), 10.42 (s, 1H, 10-H), 10.12, 10.09 (each s, 2H, 15-H, 20-H), 4.46 (m, 4H, 13^1-CH_2, 17^1-CH_2), 3.69 (s, 6H, CO_2CH_3), 3.63 (s, 3H, 7-CH_3), 3.59 (s, 3H, 18-CH_3), 3.57 (s, 3H, 12-CH_3), 3.52 (s, 3H, 2-CH_3), 3.29 (m, 4H, 13^2-CH_2, 17^2-CH_2), 3.05 (m, 2H, 3^1-H, 8^1-H), 1.71 (m, 4H, 3^2_a-H, 3^3_a-H, 8^2_a-H, 8^3_a-H), 1.48 (m, 4H, 3^2_b-H, 3^3_b-H, 8^2_b-H, 8^3_b-H), −0.35 (br s, 2H, 21-NH, 23-NH); HRFABMS $C_{38}H_{42}N_4O_4$ $[MH]^+$ calcd 619.3284, obsd 619.3290. Anal. calcd for $C_{38}H_{42}N_4O_4$: C, 73.76; H, 6.84; N, 9.05. Found: C, 73.45; H, 6.58; N, 9.01.

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