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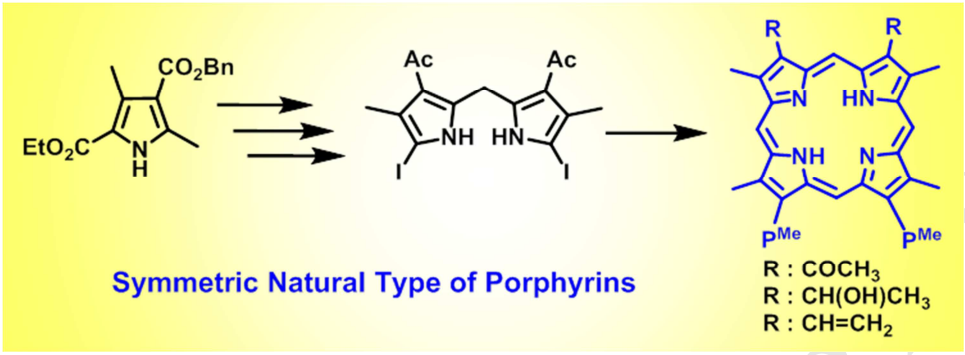

Synthesis of Type III Isomers of Diacetyldeutero-, Hemato-, and Protoporphyrins with the Use of Knorr's Pyrrole

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ABSTRACT

Derivation of the Knorr's pyrrole with 2-ethyl and 4-benzyl mixed-ester groups into 3,3'-diacetyl-5,5'-diiodo-4,4'-dimethyl-2,2'-dipyrromethane was developed. Coupling of the dipyrromethane with 5,5'-diformyl-3,3'-bis(2-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrro-methane afforded in a reasonable yield diacetyldeuteroporphyin III with C_{2v} symmetry. The porphyrin was further converted to protoporphyrin III through hematoporphyrin III. Utilization of readily available Knorr's pyrrole as the starting material much facilitates the access to symmetric iron porphyrins which are free from the orientational disorder in hemoprotein pocket.

Keywords:

Knorr's pyrrole, natural type porphyrin, symmetrical porphyrins, synthetic design

1. Introduction

Many hemoproteins such as hemoglobin, myoglobin, and cytochrome P450 contain protoheme as their prosthetic groups. Protoporphyrin IX (**1**) bearing two vinyl side-chains at the peripheral 2,4-position is asymmetric about the α,γ *meso*-carbon axis as illustrated in Fig. 1. La Mar and coworkers revealed in 1983 that the asymmetric heme exists in two orientations within the globin pocket of myoglobin.[1] Interpretation of the physicochemical properties of hemoproteins is frequently complicated due to the heme orientational disorder.[2-4]

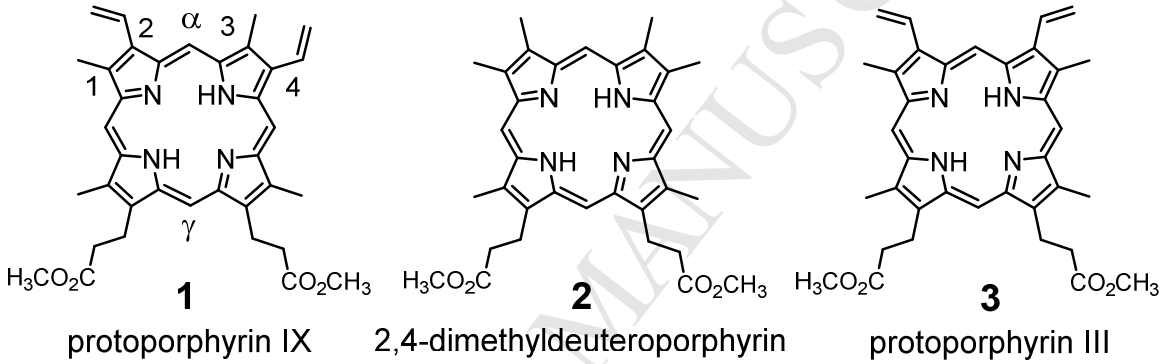


Fig. 1. Structures of the dimethyl esters of natural porphyrin **1** and type III porphyrins **2** and **3**.

2,4-Dimethyldeuteroporphyrin (**2**) has two methyl groups at the 2,4-postions (Fig. 1). Porphyrin **2**, symmetric about the α,γ *meso*-carbon axis, is free from the disorder in globin pocket. Although the hydrolysed iron complex of **2** has been employed for the rigorous structural characterization of hemoproteins,[5-7] methyl and vinyl groups are yet different from each other in their molecular bulk and electronic property. Protoporphyrin III (**3**) is another symmetric porphyrin with two vinyl groups at the 2,3-position (Fig. 1). Since porphyrin **3** is a closer analogue of **1** than porphyrin **2**, it is more suitable for biological analyses. The synthesis of porphyrin **3** has been long known.[8-13] The vinyl groups in **3** have been constructed from the 2-chloroethyl substituents in the precursory porphyrin by eliminating hydrogen chloride.[8,11-13] The chloroethyl pyrrole, the base material for the

chloroethyl porphyrin, is derived from benzyl 4-(methoxycarbonylmethyl)-3,5-dimethylpyrrole-2-carboxylate through several reaction steps.

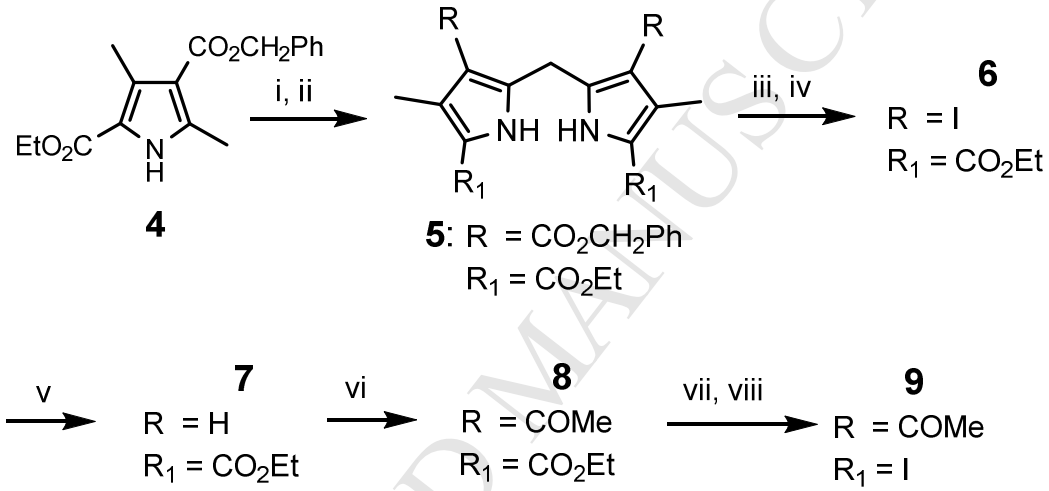
Another route to divinyl-substituted porphyrin is the initial introduction of acetyl groups to the vacant pyrrole β-sites of deuteroporphyrin.[15-17] The acetyl groups attached to porphyrin periphery, is reduced to 1-hydroxyethyl groups, and then dehydrated into vinyl substituents to afford protoporphyrin.[15-17] Second route of the deuteroporphyrin modification suggests that symmetric protoporphyrin may be derived if symmetric diacetyldeuteroporphyin is directly prepared. Based on this fundamental idea, we have devised a new and practical synthesis of protoporphyrin III after the direct synthesis of diacetyldeuteroporphyin III with the use of Knorr's pyrrole as the starting material.

2. Results and discussion

2.1. Dipyrromethanes

Scheme 1 outlines the route to dipyrromethane derivatives for diacetyldeuteroporphyin. The starting compound (**4**), the Knorr's pyrrole with 2-ethyl and 4-benzyl ester groups, was prepared by the established method.[18] Introduction of **4** with the mixed-ester groups is essential to de-esterify independently the two sites with hydrogen gas or aqueous sodium hydroxide. Pyrrole **4** was initially self-coupled into the symmetric dipyrromethane (**5**). Higher temperature and longer reaction time, in comparison with those imposed on ordinary Knorr's pyrrole with 2,4-diethoxycarbonyl groups,[19] were necessary for the coupling due to the bulky benzyl substituents in **4**. The 3,3'-dibenzyl groups in **5** were then removed by hydrogenolysis. Resulting free carboxyl residues were removed by iodination. The diiodo compound (**6**) was reduced to (**7**) under hydrogen atmosphere (yield 87%). ~~It is to be noted that King and Brown have reported incidental formation of **7** in an attempted nitration of ethyl 4,5-dimethylpyrrole-2-carboxylate (28% yield).[20] In contrast, we obtained compound **7** in 87% yield from **6** after the rational synthesis.~~ (These sentences and Reference 20 in

the original version were removed according to the comment 2 by Reviewer #1). Treatment of **7** bearing free 3,3'-position with acetyl chloride in the presence of aluminum chloride afforded 3,3'-diacetyldipyrromethane dimethylester (**8**). Compound **8** was (suggested correction 1 by Reviewer #2) then hydrolyzed with aqueous sodium hydroxide into dipyrromethane 5,5'-dicarboxylic acid. The terminal carboxyl residues in **8** were then removed by iodinative decarboxylation to give 5,5'-diiododipyrromethane (**9**). After the total eight-steps in Scheme 1, we obtained **9** (1.62 g) from pyrrole **4** (18.8 g) with the overall yield of 10.2%.

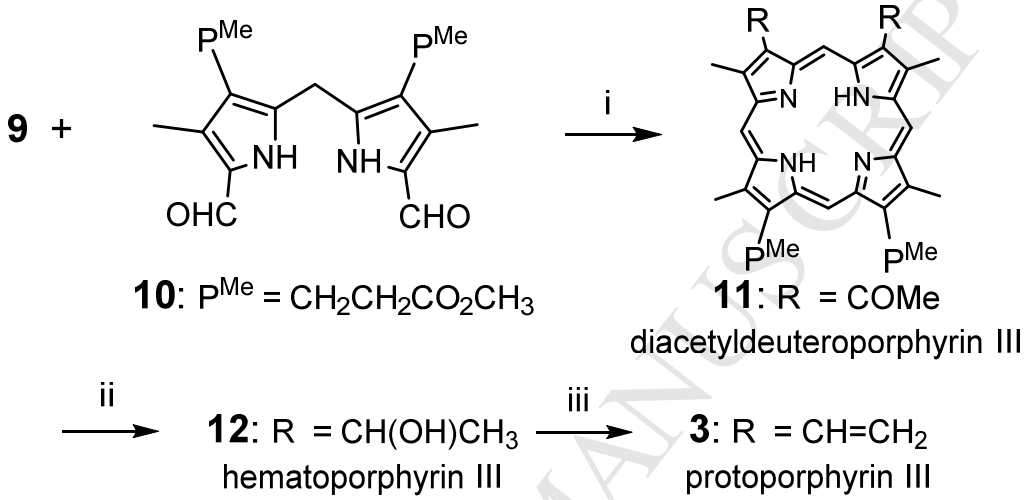


Scheme 1. Synthesis of 5,5'-diiododipyrromethane **9** starting from Knorr pyrrole **4**.

2.2. Porphyrins

Martin et al. recently reported a conceptually new approach to porphyrin.[20] They found that 5,5'-diiododipyrromethane reacts with 5,5'-diformyl dipyrromethane to give porphyrin in an excellent yield. We adopted their "2 + 2" methodology to prepare protoporphyrin III as illustrated in Scheme 2. The coupling of diiodo compound **9** with the diformyl dipyrromethane (**10**)[21] bearing two propionate groups afforded diacetyldeuteroporphyin (**11**) in 31% yield. Reduction of **11** with

sodium borohydride under the reported conditions[16,20] gave hematoporphyrin (**12**) (yield 66%). Subsequent dehydration of **12** mediated by benzoyl chloride[20,22] furnished protoporphyrin **3** (yield 92%).



Scheme 2. Synthesis of type III isomers of diacetyl-, hemato-, and protoporphyrins.

The high-resolution ESI-TOF mass spectra of diacetyldeutero-, hemato-, and protoporphyrins **11**-**13** were consistent with their molecular weights. The ^{1}H-NMR spectra of these porphyrins commonly showed the 1:1:2 intensity patterns for the *meso*-protons as illustrated in Fig. 2. In addition, only the two peaks from the peripheral methyl protons were observed around 3.6 ppm (Figs S6-S8, Supplementary data). These ^{1}H-NMR results are consistent with the type III symmetry of the porphyrins. The ^{13}C-NMR spectra of porphyrins **3**, **11**, and (suggested correction 2 by Reviewer #2) **12** resolved all of the expected signals (Figs. S14-16, Supplementary data). In the ^{13}C-NMR spectra of protoporphyrin **3**, it is notable that the pyrrole C_{α} and C_{β} peaks were significantly broadened out although other side-chain signals were well resolved. The line broadening of the pyrrole carbon signals is likely to arise from the rapid NH tautomerism, as has

been pointed out by Abraham et al.[24] Upon addition of a small amount of trifluoroacetic acid to the porphyrin solution, eight signals from the pyrrole C_α and C_β carbons expectedly appeared (Fig. S16, Supplementary data). The electronic absorption spectra of the type III diacetyldeuteroporphyin **11**, hematoporphyrin **12**, and protoporphyrin **3** (Figs. S17-S19, Supplementary data) were closely similar to those of the corresponding type IX isomers.[23]

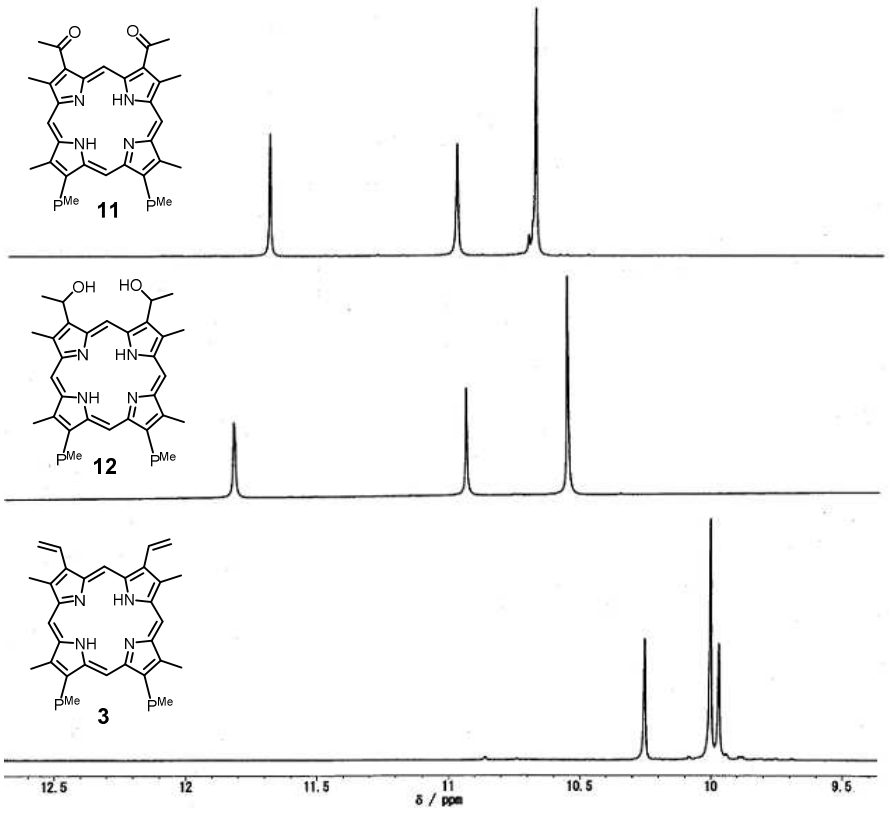


Fig. 2. The 400 MHz ^{1}H-NMR spectra in the *meso*-proton regions of porphyrins. The upper two spectra were recorded in $CDCl_3/CF_3CO_2H$ = 200/1 v/v to improve solubility, and the bottom spectrum was obtained in $CDCl_3$.

3. Conclusions

We have developed a new practical route to the type III isomers of diacetyldeutero-, hemato-, and protoporphyrins with the use of Knorr's pyrrole **4**. In the conventional syntheses,[8,11-13] the starting pyrrole with 4-(methoxycarbonylmetyl) group is synthesized from benzyl acetoacetate and

methyl 3-acetyl-4-oxopentanoate. Unfortunately, the preparation of latter diketone tends to be laborious. Thus, these procedures to protoporphyrin III require much cost and effort. On the other hand, the starting compound **4** is readily accessible with the inexpensive commercial β-diketones,[14] and we can avoid the preparation of methyl 3-acetyl-4-oxopentanoate. Pure dipyrromethane **9** is synthesized with ease to afford symmetric diacetyldeuteroporphyrin **11** in a large quantity (Scheme 1). Subsequent conversions of **11** to porphyrins **12** and **3** (Scheme 2) are conveniently carried out with the established methods.[16,20,22] These results taken together allow us the facile preparation of the type III porphyrins. In addition, the acetyl, 1-hydroxyethyl, and vinyl substituents at the 2,3-position exhibit diferent electron-withdrawing influences to the chelating metals in porphyrin.[25]

In conclusion, Knorr's pyrrole **4**, which has been little employed in natural porphyrin synthesis, is turned out to be a useful building block. The symmetirc iron porphyrins, free from the orientational disorder in globin pocket, are valuable molecular tools in hemoprotein analyses.

4. Experimental section

4.1. General methods

Silica gel and the reagents for pyrrole synthesis were purchased from commercial sources. The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a JEOL spectrometer. Chemical shifts were reported in ppm from internal tetramethylsilane on the δ scale. Electronic absorption spectra were recorded on Shimadzu spectrophotometer. High-resolution mass spectra were measured on a JEOL Accu-TOF using positive mode ESI-TOF method in spectroscopic grade methanol containing reserpine as the internal reference (m/z = 609.2810 $[M + H]^{+}$) spectrometer.

4.2. Compound (5)

Pyrrole **4** (18.8 g), obtained by the literature method with ethyl acetoacetate and benzyl acetoacetate,[18] was dissolved in propionic acid (90 mL) at 50 ^{o}C. To the stirred solution, 5.0 mL of sulfuryl chloride was added over 30 min. The mixture was heated to 60 ^{o}C, and stirred for 5 min at

this temperature. The fine-needles of the 5-chloromethylpyrrole appeared on cooling was filtered off and dried in vacuum (13.4 g, yield 64%). The 5-chloromethylpyrrole was dissolved in propionic acid (30 mL)/water (5 mL) mixture at 100 ^{o}C, and boiled for 2 h. When the solution was cooled on ice bath overnight, the white precipitate of compound **5** appeared. The product was filtered off, rinsed with water, and dried (6.53 g, yield 56%). ^{1}H-NMR ($CDCl_3$): δ 10.11 (br s, 2H, NH), 7.46-7.26 (m, 10H, -C_6H_5), 5.37 (s, 4H, -C$\underline{H}_2$-C_6H_5), 4.48 (s, 2H, *meso* CH_2), 4.29 (q, J = 7.2 Hz, 4H, -C$\underline{H}_2CH_3$), 2.50 (s, 6H, pyrrole CH_3), 1.34 (t, J = 7.0 Hz, 6H, -$CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$): δ 166.3 (-$\underline{C}O_2CH_2C_6H_5$), 161.1 (-$\underline{C}O_2CH_2CH_3$), 139.2 (pyrrole C_α), 136.1 (pyrrole C_α), 129.7/128.7/ 128.23/128.20 (-C_6H_5), 118.8 (pyrrole C_β), 112.9 (pyrrole C_β), 66.1 (-$\underline{C}H_2C_6H_5$), 60.2 (-$\underline{C}H_2CH_3$), 24.6 (*meso* CH_2), 14.4 (-$CH_2\underline{C}H_3$), 12.2 (pyrrole CH_3).

4.3. Compound (6)

Dipyrromethane **5** (10.0 g) was dissolved in tetrahydrofuran (20 mL) and diluted with methanol (100 mL). After addition of 0.3 mL of trimethylamine, the mixture was stirred for 18 h under hydrogen atmosphere in the presence of palladium-activated carbon (Pd 10%, 800 mg) to remove the benzyl groups. Resulting precipitate of dipyrromethane with free acid groups was dissolved with aqueous NaOH (2.0 M, 3 mL), and the solution was filtered to remove the carbon catalyst. The filtrate was diluted with water (50 mL containing 5.0 g of $NaHCO_3$), and heated to 35 ^{o}C. Mixture of I_2 (8.6 g) and KI (12.0 g) in water (80 mL) was added dropwise to the stirred dipyrromethane solution at 35 ^{o}C over 30 min, and the solution was stirred for additional 2 h at the same temperature. The resulting precipitates **6** were collected by filtration, rinsed with water, and dried (7.2 g, yield 85%). ^{1}H-NMR ($CDCl_3$): δ10.51 (br s, 2H, NH), 4.17 (q, J = 7.2 Hz, 4H, -C$\underline{H}_2CH_3$), 4.01 (s, 2H, *meso* CH_2), 2.26 (s, 6H, pyrrole CH_3), 1.31 (t, J = 7.2 Hz, 6H, -$CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$): δ161.6 (-$\underline{C}O_2CH_2CH_3$), 134.0 (pyrrole C_α), 129.8 (pyrrole C_α), 119.4 (pyrrole C_β), 72.9 (pyrrole C_β), 61.2 (-$\underline{C}H_2CH_3$), 28.9 (*meso* CH_2), 14.6 (-$CH_2\underline{C}H_3$), 14.3 (pyrrole CH_3).

4.4. Compound (7)

Dipyrromethane **6** (5.6 g) was dissolved in methanol (100 mL) containing 0.3 mL of trimethylamine. The mixture was stirred over 18 h under hydrogen atmosphere in the presence of palladium-activated carbon (Pd 10%, 600 mg) to remove the iodine substituents before filtration of the catalyst. The filtrate was evaporated to dryness, and the residue was dissolved in hot methanol (30 mL). Water was added to the hot methanol solution until slight turbidity, and the solution was placed on ice bath. The resulting precipitates of compound **7** were collected by filtration, and dried under vacuum (3.1 g, yield 87%). ^{1}H-NMR ($CDCl_3$): δ9.43 (br s, 2H, NH), 5.88 (d, 2H, pyrrole H), 4.27 (q, J = 7.2 Hz, 4H, -C$\underline{H}_2$CH$_3$), 3.89 (s, 2H, *meso* CH_2), 2.30 (s, 6H, pyrrole CH_3), 1.32 (t, J = 7.2 Hz, 6H, -CH$_2$C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$): δ162.4 (-$\underline{C}O_2CH_2CH_3$), 133.4 (pyrrole C_α), 128.9 (pyrrole C_α), 118.6 (pyrrole C_β), 111.4 (pyrrole C_β), 60.1 (-$\underline{C}H_2CH_3$), 26.4 (*meso* CH_2), 14.4 (-CH$_2\underline{C}H_3$), 13.0 (pyrrole CH_3).

4.5. Compound (8)

Compound **7** (1.0 g) in 1,2-dichloroethane (20 mL) was refluxed for 2 h in the presence of $AlCl_3$ (2.51 g) and CH_3COCl (1.48 g). Chloroform (40 mL) was added to the cooled solution, and the mixture was washed with water (30 mL, 5 times) to remove salts before evaporation to dryness under a reduced pressure. The residue was dissolved in hot methanol, and water (ca. 10% v/v) was added to the solution. After standing on ice bath, white precipitate of product **8** appeared, and it was collected with filtration (1.0 g, yield 80%). ^{1}H-NMR ($CDCl_3$): δ10.52 (br s, 2H, NH), 4.32 (q, J = 7.2 Hz, 4H, -C$\underline{H}_2$CH$_3$), 4.29 (s, 2H, *meso* CH_2), 2.58 (s, 6H, -COCH$_3$), 2.53 (s, 6H, pyrrole CH_3), 1.37 (t, J = 7.2 Hz, 6H, -CH$_2$C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$): δ 197.6 (-$\underline{C}OCH_3$), 160.9 (-$\underline{C}O_2CH_2CH_3$), 138.3 (pyrrole C_α), 127.8 (pyrrole C_α), 123.4 (pyrrole C_β), 118.6 (pyrrole C_β), 60.3 (-$\underline{C}H_2CH_3$), 31.2 (-CO$\underline{C}H_3$), 24.9 (*meso* CH_2), 14.5 (-CH$_2\underline{C}H_3$), 12.6 (pyrrole CH_3).

4.6. Compound (9)

To compound **8** (1.0 g) dissolved in methanol (30 mL) at 90 ^{o}C, NaOH (0.6 g) in water (20 mL) was added. The solution was stirred for 3 h at this temperature, and diluted with water (40 mL)

containing $NaHCO_3$ (0.6 g). To this solution, I_2 (1.3 g) and KI (1.7 g) dissolved in water (40 mL) was added dropwise over 30 min at 45 °C. The mixture was stirred for 3 h at the same temperature. The precipitated solid **9** was filtered off, washed with water, and dried under vacuum (0.95 g, yield 76%). ^{1}H-NMR ($CDCl_3$): δ 9.85 (br s, 2H, NH), 4.25 (s, 2H, *meso* CH_2), 2.49 (s, 6H, -$COCH_3$), 2.22 (s, 6H, pyrrole CH_3). ^{13}C-NMR ($CDCl_3$): δ 196.6 (-$\underline{C}OCH_3$), 140.5 (pyrrole C_α), 123.9 (pyrrole C_α), 121.7 (pyrrole C_β), 67.7 (pyrrole C_β), 30.7 (-CO$\underline{C}H_3$), 25.1 (*meso* CH_2), 15.8 (pyrrole CH_3).

4.7. 2,3-Diacetyldeuteroporphyrin (11)

Diiododipyrromethane **9** (2.16 g) and 5,5'-diformyldipyrromethane **10** (1.71 g)[22] were dissolved in acetic acid (260 mL)/acetic anhydride (40 mL), and stirred under dark in the presence of CF_3SO_3H (0.75 mL) for 3 h at room temperature. After quenching the reaction with CH_3CO_2Na (2.0 g), chloroform (500 mL) was added to the solution, and washed with water (300 mL × 5). The organic layer was evaporated to dryness. The residue was purified on silica-gel column with chloroform/pyridine (98/2 v/v) as eluent. The fractions containing porphyrin **11** were collected, and evaporated to dryness (752 mg, yield 29%). ^{1}H-NMR ($CDCl_3$/CF_3CO_2H = 200/1 v/v): δ 11.68 (s, 1H, *meso* H), 10.96 (s, 1H, *meso* H), 10.66 (s, 2H, *meso* H), 4.43 (t J = 7.6 Hz,, 4H, -C$\underline{H}_2CH_2CO_2CH_3$), 3.91 (s, 6H, ring CH_3), 3.65 (s, 6H, ring CH_3), 3.57(s, 6H, -CO_2CH_3), 3.38 (s, 6H, -$COCH_3$), 3.15 (t, J = 7.2 Hz, 4H, -$CH_2C\underline{H}_2CO_2CH_3$), -2.52 (br s, 2H, NH). ^{13}C-NMR ($CDCl_3$/CF_3CO_2H = 200/1 v/v): δ 198.1 (-$\underline{C}OCH_3$), 173.7 (-$\underline{C}O_2CH_3$), 143.5/142.7/141.8/141.1/141.0/140.9/139.8/136.2 (pyrrole C_α and C_β), 105.5/100.4/100.2 (*meso* C), 52.3 (-$CO_2\underline{C}H_3$), 35.3 (-$CH_2\underline{C}H_2CO_2CH_3$), 33.1 (-CO$\underline{C}H_3$), 21.5 (-$\underline{C}H_2CH_2CO_2CH_3$), 14.4/12.0 (ring CH_3). UV-vis. (CH_2Cl_2) λ_{max} nm (ε, $mM^{-1}cm^{-1}$): 420 (137), 513 (10.2), 551 (6.9), 586 (4.9), 640(3.6). HRMS (ESI) *m/z* Calcld for $C_{36}H_{39}N_4O_6^+$ $[M + H]^+$ 623.2870, found 623.2877.

4.8. Hematoporphyrin III (12)

Diacetylporphyrin **11** (100 mg, 0.165 mmol) was dissolved in chloroform (40 mL)/methanol (5 mL) mixture. Nitrogen was bubbled to the solution for 10 min, and $NaBH_4$ (32 mg) was added before

the container was closed with a glass stopper. The solution was stirred in the dark at room temperature for 80 min; the UV-visible spectrum in chloroform showed a Soret band at 401 nm. The solution was washed with 1% hydrochloric acid (40 mL), and then with 2% aqueous NaOH (40 mL). The organic layer was evaporated to dryness. The residue was chromatographed on silica-gel with chloroform/pyridine (100/2 v/v). After washing out impurities, the solvent was changed to chloroform/methanol (4/1 v/v) mixture. The major fraction was collected and evaporated to leave porphyrin **12** (mixture of diasteromers) as purple solid (66 mg, yield 65%). ^{1}H-NMR ($CDCl_3/CF_3CO_2H$ = 200/1 v/v): δ 11.82 (s, 1H, *meso* H), 10.94 (s, 1H, *meso* H), 10.55 (s, 2H, *meso* H), 6.51 (m, *J* = 6.8 Hz, 2H, -C<u>H</u>(OH)CH_3), 4.46 (t, *J* = 7.2 Hz, 4H, -C<u>H</u>$_2$$CH_2CO_2CH_3$), 3.66 (s, 6H, ring CH_3), 3.63 (s, 6H, ring CH_3), 3.54 (s, 6H, -CO_2CH_3), 3.17 (t, *J* = 7.2 Hz, 4H, -CH_2C<u>H</u>$_2$$CO_2CH_3$), 2.12 (m, *J* = 6.8 Hz, 6H, -CH(OH)C<u>H</u>$_3$), -3.06 (br s, 1H, NH), -3.19 (br s, 1H, NH). ^{13}C-NMR ($CDCl_3/CF_3CO_2H$ = 200/1 v/v): δ 173.7 (-<u>C</u>O_2CH_3), 143.1/142.0/141.8/141.7/140.32/ 140.28/138.7/136.9 (pyrrole C_α and C_β), 102.9/99.3/98.7 (*meso* C), 66.0 (-<u>C</u>H(OH)CH_3), 52.1 (-CO_2<u>C</u>H_3), 35.4 (-CH_2<u>C</u>$H_2CO_2CH_3$), 25.2 (-CH(OH)<u>C</u>H_3), 21.7 (-<u>C</u>$H_2CH_2CO_2CH_3$), 12.0/11.9 (ring CH_3). UV-vis. (CH_2Cl_2) λ_{max} nm (ε, $mM^{-1}cm^{-1}$): 401 (165), 497 (13.9), 532 (8.1), 567 (5.9), 595 (1.1), 621 (3.7). HRMS (ESI) *m/z* Calcld for $C_{36}H_{42}N_4O_6^+$ $[M + H]^+$ 627.3183, found 627.3198.

4.9. Protoporphyrin III (3)

Porphyrin **12** (100 mg) was dissolved in *N*,*N*-dimethylformamide (4.2 mL) containing C_6H_5COCl (0.47 mL), and the solution was stirred under nitrogen at 100 ^{o}C for 60 min; the reaction was complete when the Soret band shifted to 407 nm in chloroform/triethylamine. At room temperature, chloroform (50 mL) and trimethylamine (2 mL) were added to the solution, and the mixture was washed with water (50 mL, 4 times) to remove *N*,*N*-dimethylformamide. The organic layer was evaporated to dryness under reduced pressure. The residue was applied to a silica-gel column equilibrated with chloroform/methanol (100/2 v/v). The major band was collected, and the solvent was removed under reduced pressure to leave a residue. It was recrystallized from

chloroform/methanol (1/2 v/v) to afford protoporphyrin **3** (91 mg, yield 97%). ^{1}H-NMR ($CDCl_3$): δ 10.25 (s, 1H, *meso* H), 10.00 (s, 2H, *meso* H), 9.97 (s, 1H, *meso* H), 8.23 (dd, *J* =17.6, 11.2 Hz, 2H, -C<u>H</u>=CH_2), 6.36 (d, *J* = 18.0 Hz, 2H, -CH=C<u>H</u>$_2$), 6.17 (d, *J* = 11.0 Hz, 2H, -CH=C<u>H</u>$_2$), 4.38 (t, *J* = 7.6 Hz, 4H, -C<u>H</u>$_2$$CH_2$CO), 3.67 (s, 6H, ring CH_3), 3.66 (s, 6H, ring CH_3), 3.60 (s, 6H, -CO_2CH_3), 3.26 (t, *J* = 8.0 Hz, 4H, -CH_2C<u>H</u>$_2$CO), -3.85 (br s, 2H, NH). ^{13}C-NMR ($CDCl_3$): δ 173.6 (-<u>C</u>O_2CH_3), 142.1/142.0/141.6/141.0/140.2/138.7/138.0/137.5 (pyrrole C_α and C_β: observable in $CDCl_3$/CF_3CO_2H = 200/1 v/v), 130.3 (-<u>C</u>H=CH_2), 120.8 (-CH=<u>C</u>H$_2$), 98.3/96.9/96.1 (*meso* C), 51.8 (-CO_2<u>C</u>H_3), 36.9 (-CH_2<u>C</u>H_2CO), 21.8 (-<u>C</u>H_2CH_2CO), 12.7/11.7 (ring CH_3). UV-vis. (CH_2Cl_2) λ_{max} nm (ε, $mM^{-1}cm^{-1}$): 407 (171), 506 (14.7), 541 (11.6), 575 (7.1), 629 (5.4). HRMS (ESI) *m/z* Calcld for $C_{36}H_{38}N_4O_4^+$ $[M + H]^+$ 591.2971, found 591.2998.

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Supplementary data

The ^{1}H- (Figs. S1-S8) and ^{13}C-NMR (Figs. S9-S16) spectra of the compounds and the UV-visible (Figs. S17-S19) spectra of the porphyrins.