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Synthesis of New Derivatives of Protoporphyrin IX and Chlorophyll *a**

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Abstract—The vinyl groups in protoporphyrin IX and chlorophyll *a* derivatives were selectively transformed into hydroxymethyl and acetoxymethyl substituents. The reactivities of β-hydroxymethyl and β-acetoxymethyl groups in porphyrins and chlorins toward nucleophilic reagents were compared for the first time using the reaction with acetylacetone as an example. Peripheral acetylacetone moieties in porphyrins and chlorins were shown to be promising as building blocks for generation of exo heterocyclic structures.

Development of new methods for regioselective modification of peripheral substituents in protoporphyrin IX and chlorophyll *a* is crucial in the design and synthesis of novel physiologically active tetrapyrrole derivatives, as well as in fundamental studies on the reactivity of porphyrin-like macrocyclic compounds [2–7]. Structural specificity of the porphyrin macroring makes it possible to effect selective modifications both at the *meso* positions and of β-substituents. In 1976, Arnold *et al*. [8] found that heating of nickel *meso*-(hydroxymethyl)octaethylporphyrin (**I**) with H_2SO_4 in DMF leads to formation of dimer **II** in a good yield (Scheme 1). In 1977, the corresponding *meso*-ethoxymethyl derivative **IV** was formed in quantitative yield upon chromatographic purification of copper *meso*-(hydroxymethyl)etioporphyrin I (**III**) on silica gel (using chloroform stabilized with ethanol as eluent) [9]. At the same time, *meso*-methoxymethyl derivative **VI** was obtained in high yield by recrystallization of zinc(II) *meso*-(acetoxymethyl)octaethylporphyrin (**V**) from methanol [10]. In 1980, Smith *et al*. [11] made an attempt to demetalate copper *meso*-(hydroxymethyl)octaethylchlorin (**VII**) by treatment with 10% sulfuric acid in trifluoromethanesulfonic acid but isolated dimeric chlorin **VIII**. The authors also noted a high reactivity of *meso*-acetoxymethylchlorophyll *a* copper complex **IX** toward nucleophiles. Summarizing the above data on facile reactions of nucleophiles at *meso*-hydroxymethyl and *meso*-acetoxymethyl groups in various porphyrin substrates, it was reasonable to presume that β-(hydroxymethyl)- and β-(acetoxymethyl)tetrapyrroles should also behave as active electrophiles.

In order to unify methods for selective modification of peripheral substituents in pharmacophoric tetrapyrrole structures, we were the first to perform a comparative study of the reactivity of β-hydroxymethyl and β-acetoxymethyl groups in protoporphyrin IX and chlorophyll *a* derivatives toward nucleophiles. As model nucleophile we used acetylacetone which is a 1,3-dicarbonyl compound with pronounced nucleophilic properties and a valuable building block for design of heterocyclic pharmacophores [12].

β-Hydroxymethyl and β-acetoxymethyl derivatives of protoporphyrin IX and chlorophyll *a*. The starting compound for the synthesis of protoporphyrin IX derivatives is protohemin IX (**X**) which is readily isolated from defibrinated bovine blood. Protohemin IX (**X**) was converted into protoporphyrin IX dimethyl ester (**XI**) [13], and the latter was transformed into formylporphyrins **XII** and **XIII** [14] (Scheme 2).

* For preliminary communication, see [1].

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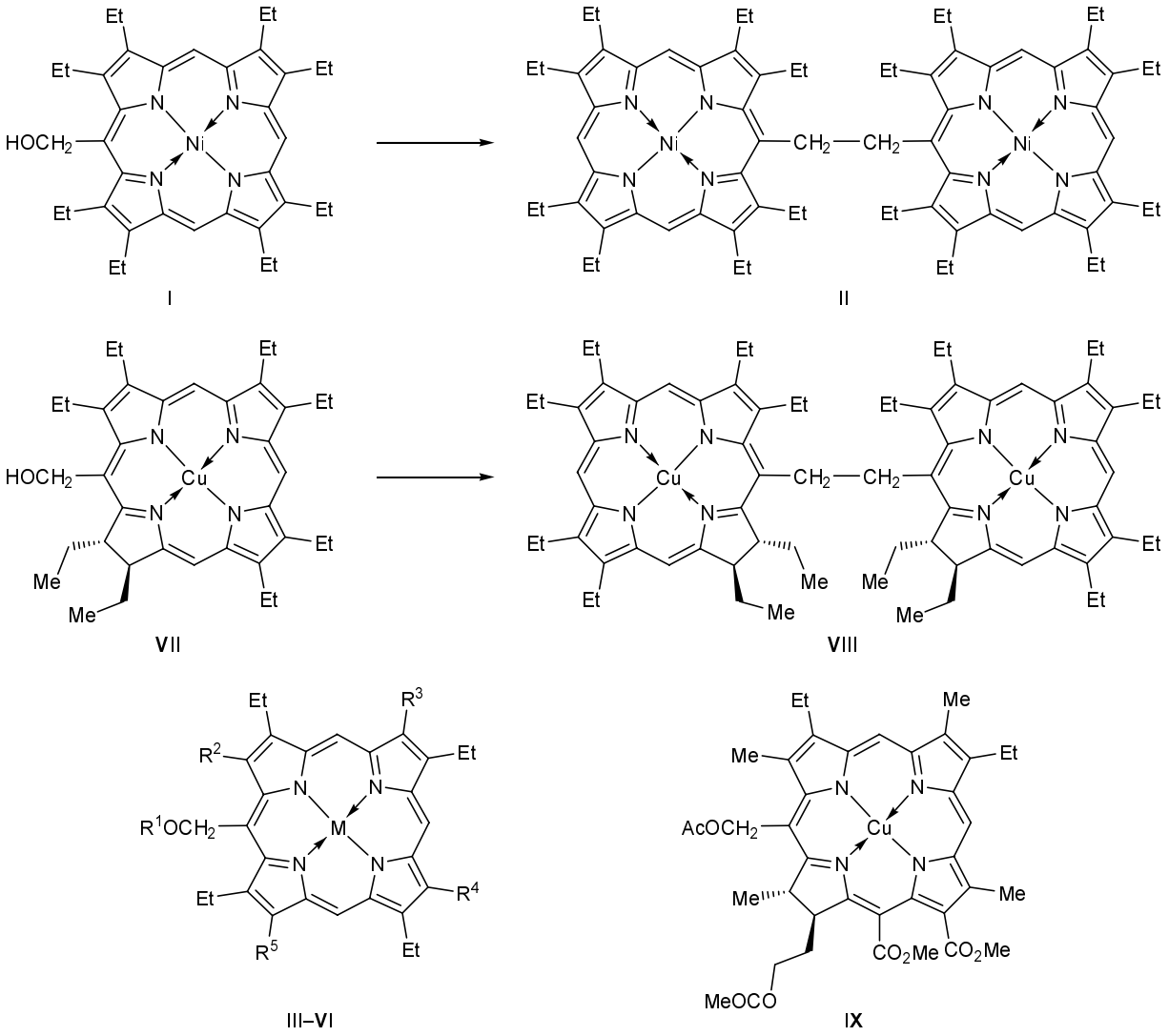
Scheme 1.

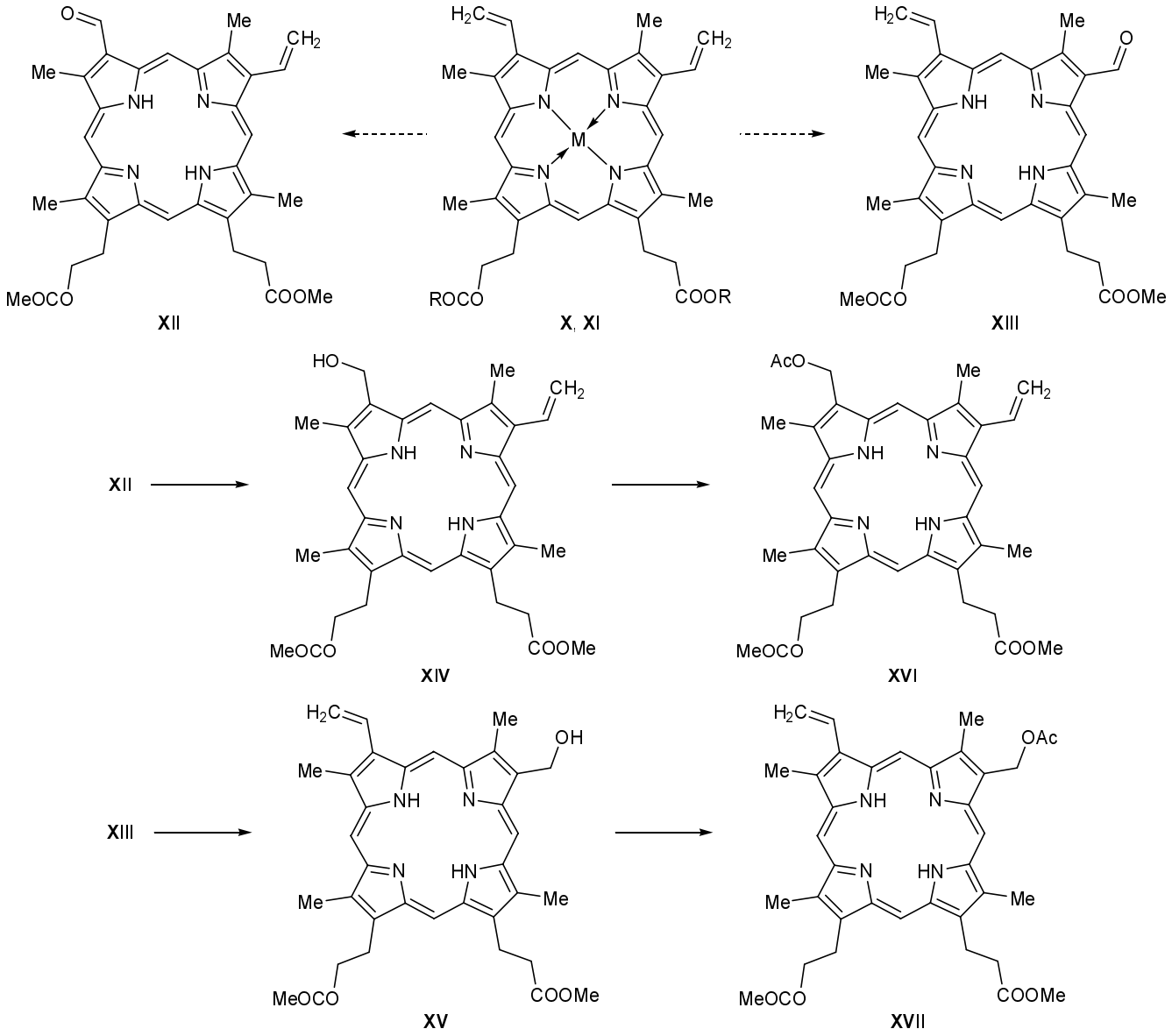


III, M = Cu(II), R^1 = H, $R^2 = R^3 = R^4 = R^5$ = Me; **IV**, M = Cu(II), R^1 = Et, $R^2 = R^3 = R^4 = R^5$ = Me; **V**, M = Zn(II), R^1 = Ac, $R^2 = R^3 = R^4 = R^5$ = Et; **VI**, M = Zn(II), R^1 = Me, $R^2 = R^3 = R^4 = R^5$ = Et.

According to [15], the reduction of *meso*-formyl group in porphyrins to hydroxymethyl requires prolonged (15 h) treatment with $NaBH_4$ in CH_2Cl_2/MeOH. Under analogous conditions, the reduction of β-formylporphyrins **XII** and **XIII** into hydroxymethyl derivatives **XIV** and **XV** was complete in a much shorter time (20 min). Considerable acceleration of the reaction at β-substituents in porphyrins, as compared to the corresponding *meso*-substituents, was also observed in the synthesis of acetates. In keeping with the data of [15], acetylation of *meso*-hydroxymethyl group in porphyrins with acetic anhydride in pyridine takes 1 h at 80°C and is characterized by a high yield. We have found that β-hydroxymethyl derivatives **XIV** and **XV** are quantitatively converted into acetates **XVI** and **XVII** by the action of the same reagent in 10 min at 40°C. Presumably, the reaction at β-substituents in porphyrins is facilitated due to much greater spatial accessibility of the β-positions as compared to *meso*.

Chlorophyll *a* (**XVIII**) was isolated by extraction from lyophilized *Spirulina Platensis* and was transformed into pheophorbide *a* methyl ester (**XIX**) [16] (Scheme 3). Compound **XIX** was treated with sodium methoxide in THF–MeOH under nitrogen to obtain chlorin e_6 trimethyl ester (**XX**) [11] in high yield. The vinyl group in **XX** was selectively oxidized to aldehyde **XXI** with OsO_4–$NaIO_4$ [17] (yield 62%). Hydroxymethylchlorin **XXII** and acetoxy derivative

Scheme 2.



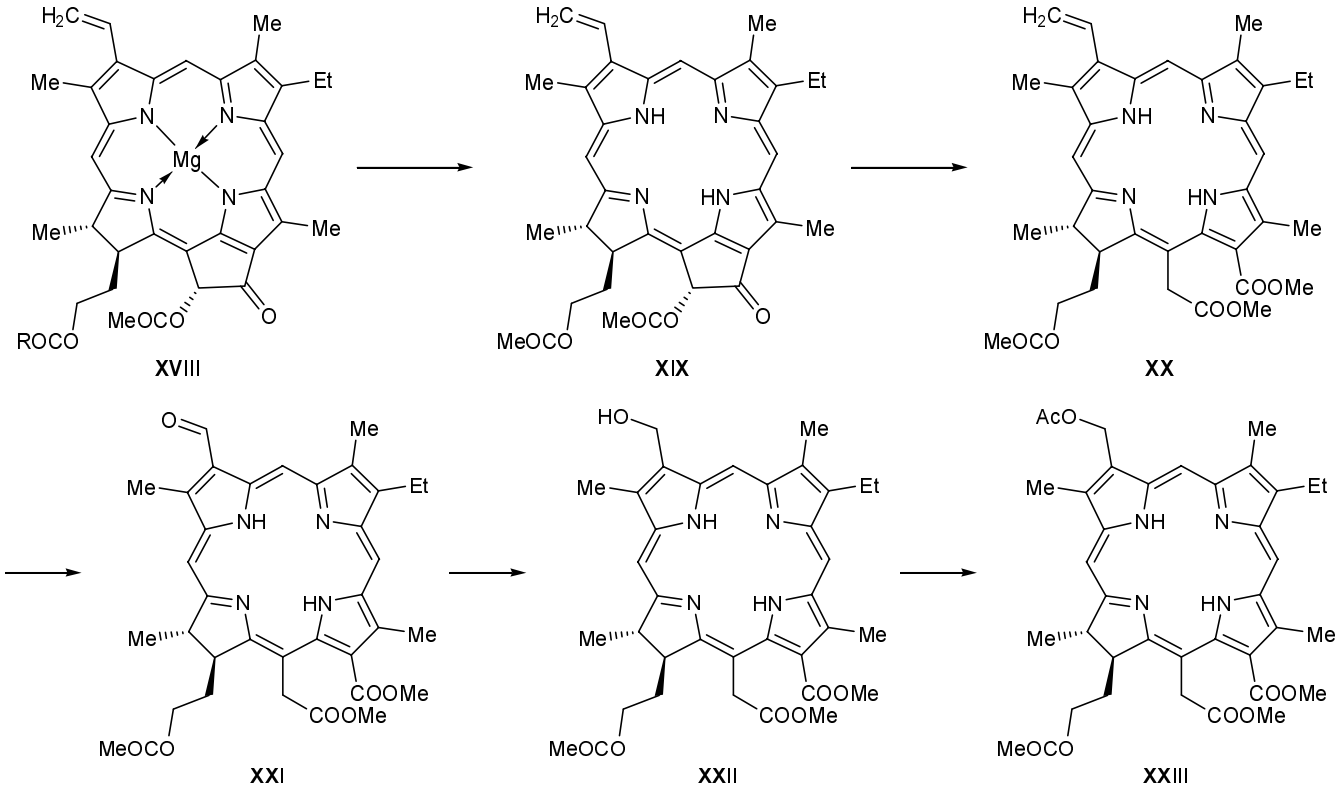
X, R = H, M = Fe(III)Cl; **XI**, R = Me, M = 2H.

XXIII were successively synthesized in quantitative yield by the procedure developed by us for the preparation of acetates **XVI** and **XVII** (Scheme 3).

In the ^{1}H NMR spectra of hydroxymethyl derivatives **XIV**, **XV**, and **XXII**, signals from methylene protons of the CH_2OH group appeared as singlets at δ 5.96–5.91 ppm, i.e., in the region typical of benzylic protons in conventional aromatic systems. The corresponding signal (C**H**$_2$OAc) in the spectra of acetates **XVI**, **XVII**, and **XXIII** was observed in a weaker field (δ 6.55–6.40 ppm). The acetyl protons gave singlets typical of common acetates (δ 2.22–2.18 ppm); in the spectrum of chlorophyll *a* derivative **XXIII**, that signal was overlapped by multiplet belonging to the 17-$CH_2CH_2CO_2CH_3$ substituent.

Protoporphyrin IX and chlorophyll *a* derivatives containing an acetylacetone residue and transformation of the latter into pyrazole ring. There are almost no published data on the reactivity of β-hydroxymethyl and β-acetoxymethyl groups in derivatives of protoporphyrin IX and chlorophyll *a*, although the chemistry of their closest structural analogs, *meso*-hydroxymethyl- and *meso*-acetoxymethyltetrapyrroles have been documented in sufficient detail (see [18] and references therein). Analysis of published data shows that thermolysis and chromatography in the presence

Scheme 3.



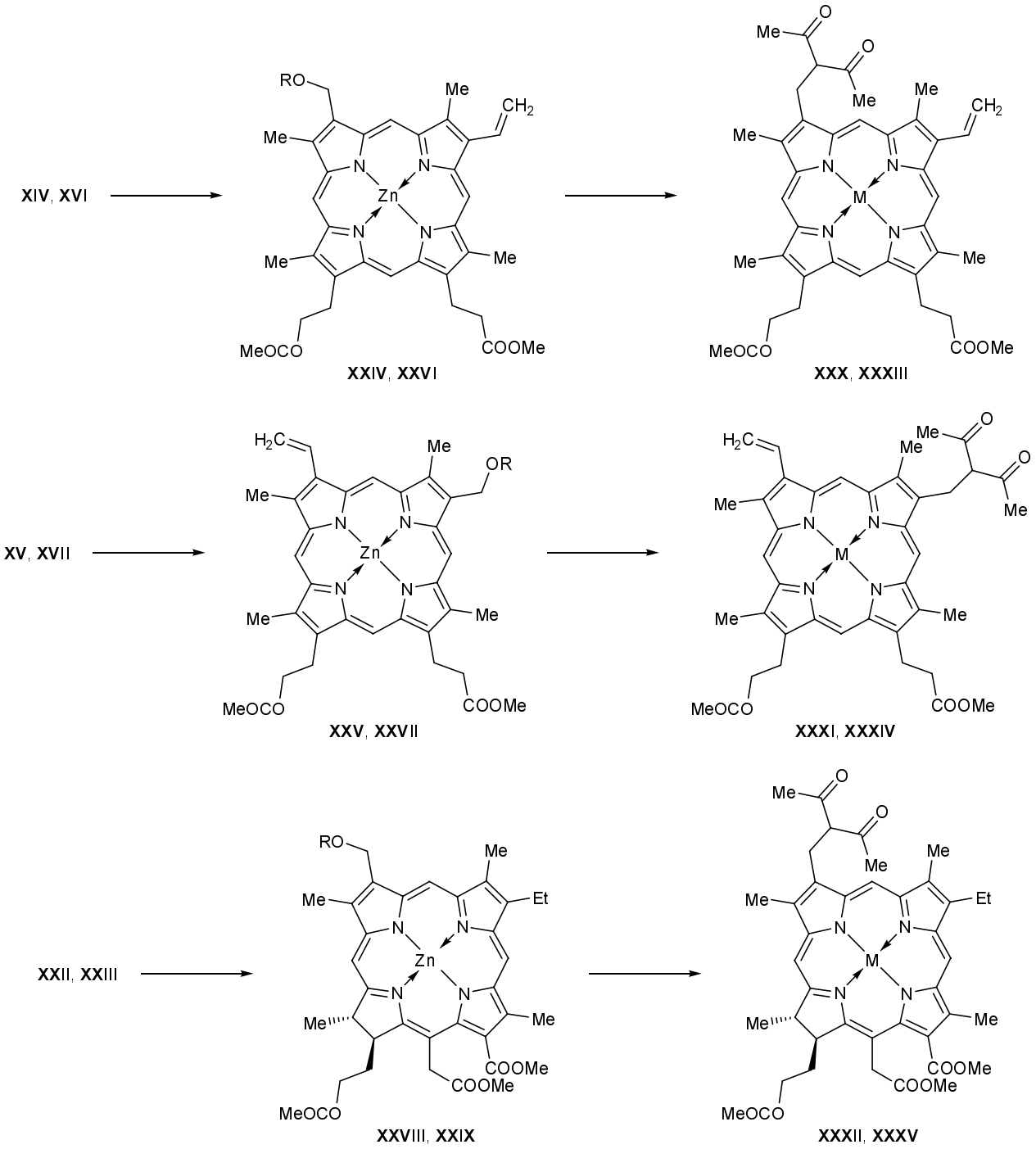
XVIII, R = phytyl.

of nucleophiles are efficient methods for the activation of *meso*-hydroxymethyl [9, 19] and *meso*-acetoxymethyl substituents [10, 11, 15, 20] in porphyrin-like structures to nucleophilic replacement. An important factor influencing the reactivity of *meso*-hydroxymethyl and *meso*-acetoxymethyl groups is the presence of coordinated metal ion [9, 10, 19]. In the present study we selected zinc as such a metal, taking into account that it readily forms complexes with tetrapyrroles and can readily be removed therefrom in quantitative yield. By heating free bases **XIV**–**XVII**, **XXII**, and **XXIII** with excess $Zn(OAc)_2 \cdot 2H_2O$ in CH_2Cl_2–MeOH [13] for a short time we obtained the corresponding zinc complexes **XXIV**–**XXIX** (yield 100%; Scheme 4).

The data reflecting the efficiency of activation of β-hydroxymethyl and β-acetoxymethyl substituents to nucleophilic replacement in the reaction with acetylacetone are collected in table. Thermolysis of neither free bases **XIV**–**XVII**, **XXII**, and **XXIII** nor their zinc complexes **XXIV**–**XXIX** with acetylacetone in solvents of various polarities afforded expected substitution products **XXX**–**XXXV** (Scheme 4). By contrast, chromatography of both free bases **XIV**–**XVII**, **XXII**, and **XXIII** and zinc complexes **XXIV**–**XXIX** on silica gel plates in the presence of 1% of acetylacetone gave the corresponding products **XXX**–**XXXV** in poor yields (3–26%) but with high regioselectivity. In all cases, acetoxy derivatives reacted more effectively than hydroxy compounds, and the metal complexes were more active than the corresponding free ligands (see table).

According to published data, β-methoxymethylporphyrins having no peripheral vinyl group readily and efficiently react with acetylacetone and other nucleophiles in the presence of excess $Zn(OAc)_2 \cdot 2H_2O$ which acts here as a soft Lewis acid [21]. Therefore, we anticipated that β-hydroxymethyl- and β-acetoxymethylporphyrins should also react with acetylacetone. When zinc complexes of β-(hydroxymethyl)porphyrins **XXIV** and **XXV** were heated with acetylacetone in the presence of $Zn(OAc)_2 \cdot 2H_2O$, their transformation into the desired derivatives **XXXIII** and **XXXIV** was characterized by a poor yield (no more than 20%; Scheme 5). Under analogous conditions, only traces of **XXXIII** and **XXXIV** (<2%) were formed from zinc β-acetoxymethylporphyrins **XXVI** and **XXVII**. In all cases, the transformations were not selective, and the

Scheme 4.



XXIV, **XXV**, **XXVIII**, R = H; **XXVI**, **XXVII**, **XXIX**, R = Ac; **XXX**–**XXXII**, M = 2H; **XXXIII**–**XXXV**, M = Zn(II).

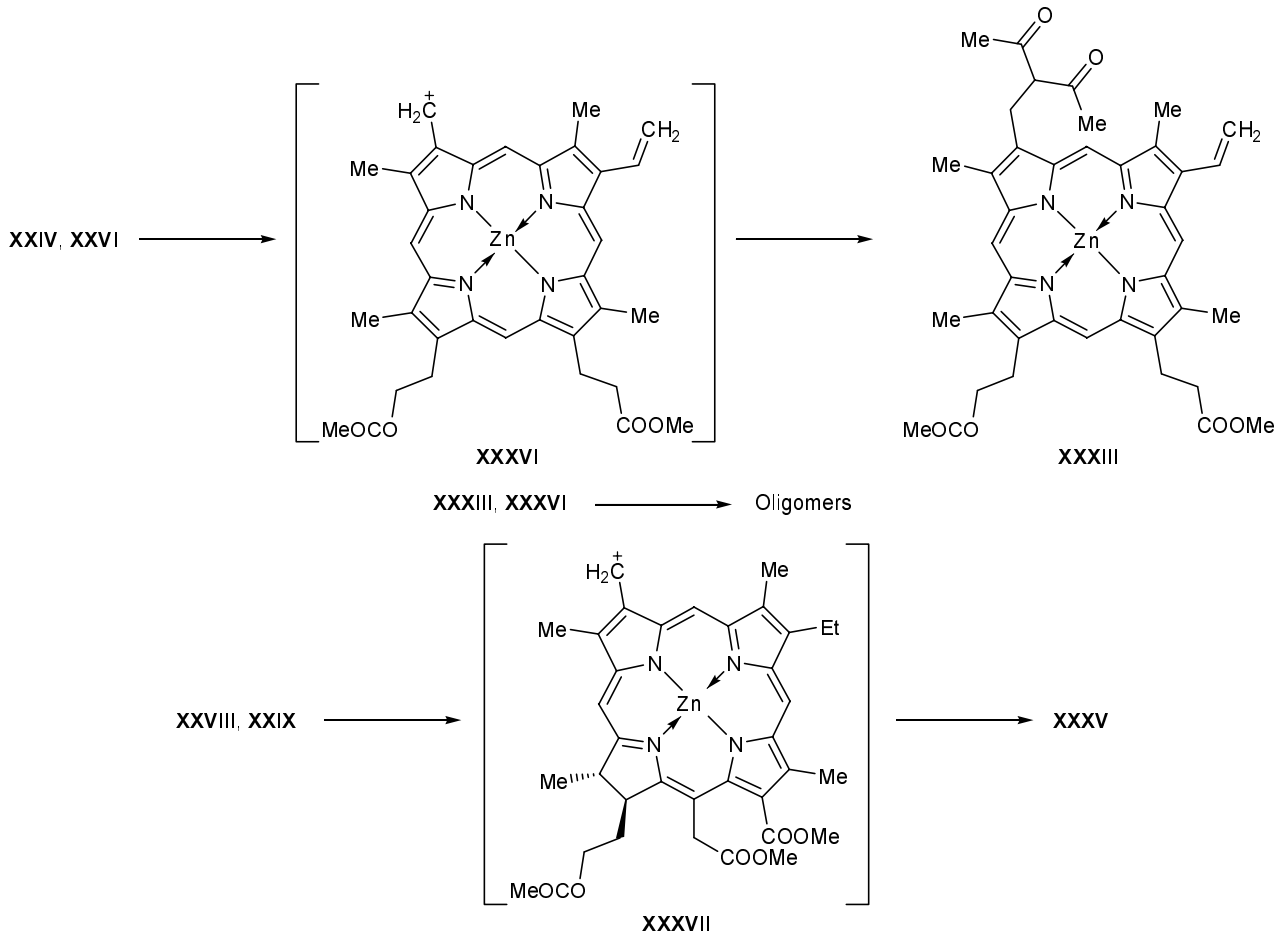
main reaction pathway was oligomerization. Presumably, the reaction begins with elimination of the hydroxy or acetoxy group to produce highly reactive pseudobenzylic carbocation **XXXVI** which then reacts with acetylacetone to give compound **XXXIII**. An alternative transformation pathway of cation **XXXVI** involves nonspecific interaction with peripheral vinyl groups thus initiating abundant oligomerization (Scheme 5). Naturally, the possibility for cross reaction of cation **XXXVI** with any peripheral vinyl group makes the situation even more complex. A strong evidence in support of the above mechanism is provided

Condensation of β-hydroxymethyl- and β-acetoxymethyltetrapyrroles with acetylacetone upon chromatography and thermolysis in the presence of $Zn(OAc)_2 \cdot 2H_2O$

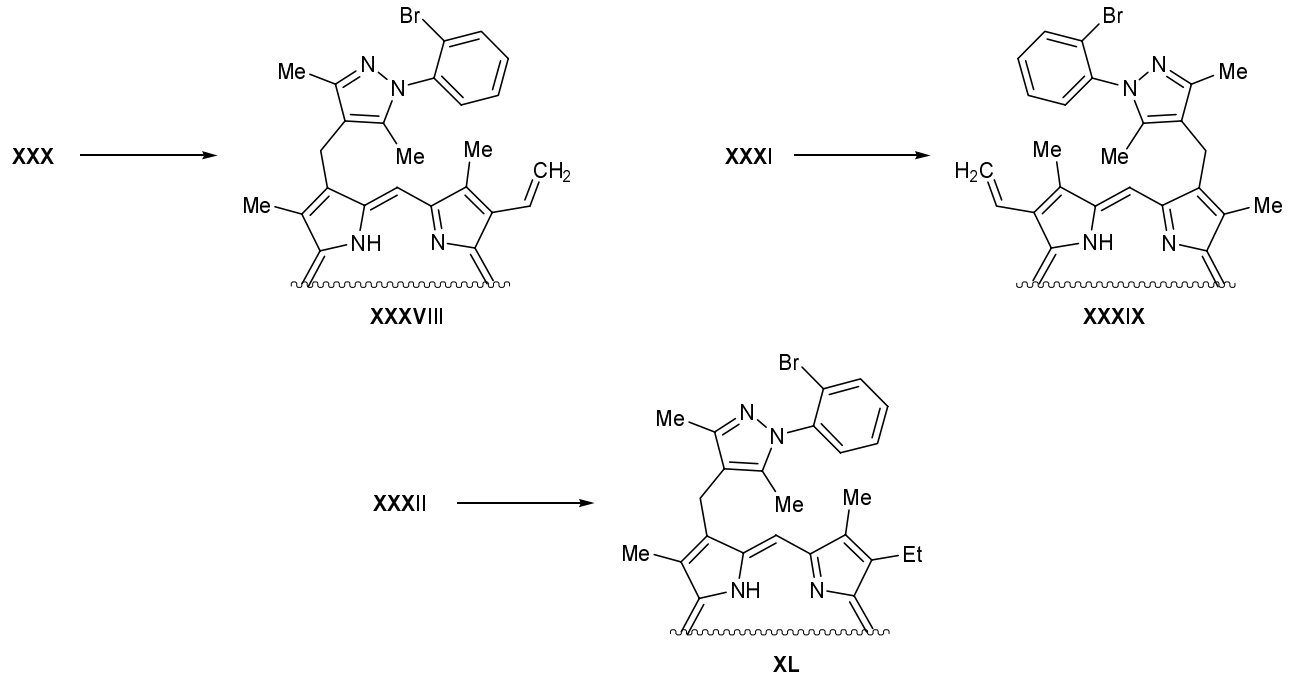
Initial tetrapyrrole no.	Product no.	Chromatography, $CH_2Cl_2/AcCH_2Ac$		$Zn(OAc)_2 \cdot 2H_2O/AcCH_2Ac$, 110°C	
		reaction time, min	yield, %	reaction time, min	yield, %
XIV	**XXX**	200	4	–	–
XV	**XXXI**	200	3	–	–
XVI	**XXX**	200	8	–	–
XVII	**XXXI**	200	10	–	–
XXII	**XXXII**	200	5	–	–
XXIII	**XXXII**	200	11	–	–
XXIV	**XXX**[a] **(XXXIII)**	200	16	40	18
XXV	**XXXI**[a] **(XXXIV)**	200	14	40	20
XXVI	**XXX**[a] **(XXXIII)**	200	20	40	<2
XXVII	**XXXI**[a] **(XXXIV)**	200	23	40	<2
XXVIII	**XXXII**[a] **(XXXV)**	200	13	40	85
XXIX	**XXXII**[a] **(XXXV)**	200	26	40	87

[a] After quantitative demetalation of the corresponding Zn(II) complexes with 6 N hydrochloric acid.

Scheme 5.



Scheme 6.



by published data on the lability of vinyl groups in tetrapyrroles in the presence of pseudobenzylic cations derived from porphyrin-like compounds [22, 23].

Unlike tetrapyrroles having a peripheral vinyl group, chlorophyll *a* derivatives **XXVIII** and **XXIX** containing no side vinyl group reacted with acetylacetone on heating in the presence of a large excess of $Zn(OAc)_2 \cdot 2H_2O$ to give compound **XXXV** in a high yield (85–87%). Presumably, considerable increase in the yield, as compared to β-vinylporphyrins, results from the absence of pathways alternative to the reaction of pseudobenzylic carbocation **XXXVII** with acetylacetone.

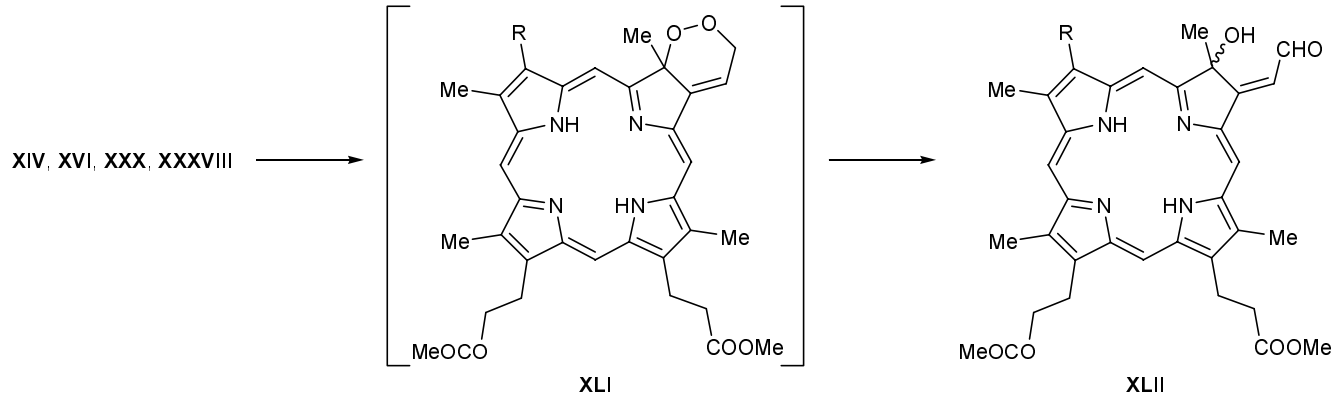
In the ^{1}H NMR spectra, the acetylacetone fragment CH_2CHAc_2 in compounds **XXX**–**XXXII** gives rise to a triplet from the CH proton at δ 4.72–4.63 ppm, a doublet from the methylene protons at δ 4.51–4.36 ppm (in the spectrum of chlorophyll *a* derivative **XXXII**, this doublet is overlapped by multiplet signal from 17-H and 18-H), and a singlet from the acetyl protons at 2.13–2.06 ppm (in the spectrum of **XXXII**, the acetyl proton signal is overlapped by multiplet from the methylene protons in the 17-$CH_2C\mathbf{H}_2CO_2CH_3$ substituent).

The final step of our study implied demonstration of the possibility of using the acetylacetone moiety in tetrapyrroles **XXX**–**XXXII** as a convenient building block for appending heterocyclic exo substituents. As the other heteroring-forming component we used commercially available *o*-bromophenylhydrazine (*o*-$BrC_6H_4NHNH_2$). The main factor determining the efficiency of condensation of 2-acetyl-3-oxobutyl substituents with *o*-$BrC_6H_4NHNH_2$ to produce a pyrazole ring was the solvent nature. The best results were obtained with the use of pyridine which was simultaneously an acceptable solvent and selectively acting base. By heating tetrapyrroles **XXX**–**XXXII** with *o*-bromophenylhydrazine in boiling pyridine for 1 h we succeeded in synthesizing the corresponding tetrapyrrole–pyrazole systems **XXXVIII**–**XL** in more than 70% yield (Scheme 6). It should be noted the formation of compounds **XXXVIII**–**XL** under these conditions is favored by the activating effect of the tetrapyrrole macroring. For comparison, the condensation of *o*-bromophenylhydrazine with 3-ethylpentane-2,4-dione under analogous conditions is characterized by a poor yield.

The 1-(*o*-bromophenyl)-3,5-dimethylpyrazole fragment in molecules **XXXVIII**–**XL** gave rise to multiplet signals at δ 7.67–7.17 ppm from the aromatic protons and singlets at δ 2.35–2.34 and 1.85–1.82 ppm from the methyl protons. Protons of the methylene bridge between the tetrapyrrole and pyrazole heterorings appeared as a singlet at δ 5.16–5.01 ppm.

Some typical chemical and spectral properties of the prepared protoporphyrin IX and chlorophyll *a* derivatives. While performing this study, we found that a solution of any monovinyl protoporphyrin IX

Scheme 7.



derivative (**XIV**–**XVI**, **XXX**, **XXXI**, **XXXVIII**, or **XXXIX**) gradually turned greenish on storage on exposure to light. According to the TLC data, apart from the red monovinyl derivative, the solution contained a green polar substance whose concentration increased proportionally to the time of exposure to daylight. The electron absorption spectra revealed a strong maximum in the long-wave region (λ 659–661 nm). The red shift is so large (by more than 30 nm) that it might be caused only by transformation of the porphyrin system into a new macroring. In keeping with published data [24], we believe that the observed transformation involves photochemical reaction of singlet oxygen with the diene fragment of monovinylporphyrins **XIV**, **XVI**, **XXX**, and **XXXVIII** with intermediate formation of endoperoxides **XLI** which undergo instantaneous rearrangement into stable "photoprotoporphyrin" products like **XLII** (Scheme 7). Analogous transformations are typical of isomeric porphyrins **XV**, **XVII**, **XXXI**, and **XXXIX** and were reported previously for other monovinyl-substituted porphyrins [25–29].

The electron spectra of compounds **XIV**–**XVII**, **XXII**, **XXIII**, **XXX**–**XXII**, and **XXXVIII**–**XL** showed a weak dependence of the shape and position of absorption maxima on the nature of peripheral substituent. Protoporphyrin IX derivatives **XIV**–**XVII**, **XXX**, **XXXI**, **XXXVIII**, **XXXIX** are characterized by etioporphyrin-like spectra with the long-wave absorption maximum located at λ 627–628 nm. The electron absorption spectra of chlorophyll *a* derivatives **XXII**, **XXIII**, **XXXII**, and **XI** resemble that of chlorin: the long-wave maximum is located at λ 656–661 nm. Electron spectroscopy clearly detects the presence of a pyrazole chromophore in conjugates **XXXVIII**–**XL**. Their electron absorption spectra are superpositions of the spectra of the tetrapyrrole and phenylpyrazole fragments, indicating the lack of appreciable interaction between the chromophores in the ground state.

EXPERIMENTAL

Protohemin IX from Sigma (USA) and lyophilized *Spirulina Platensis* (China) were used. Pyridine was distilled over sodium hydroxide, and chloroform and methylene chloride were distilled over P_2O_5 and were stored over 4-Å molecular sieves. Acetylacetone, tetrahydrofuran, dioxane, and diethyl ether were distilled just before use. Analytical thin-layer chromatography was performed on Kieselgel 60 F_{254} plates (Merck). Silica gel 0.040–0.063 mm (Merck) and neutral aluminum oxide 0.040–0.230 mm were used for preparative chromatography. The mass spectra were recorded on a Finnigan MAT LCQ instrument (electrospray ionization). The ^{1}H NMR spectra were measured on a Bruker AMX-III spectrometer (400 MHz) from solutions in chloroform-*d*. The electron absorption spectra were obtained on a Hewlett–Packard 8453 spectrophotometer from solutions in chloroform.

3-Hydroxymethyl-8-vinyldeuteroporphyrin IX dimethyl ester (XIV). Formylporphyrin **XII**, 530 mg (0.894 mmol), was dissolved in a mixture of 300 ml of methylene chloride and 20 ml of methanol, and 530 mg (14.009 mmol) of thoroughly powdered $NaBH_4$ in 10 ml of ice-cool methanol was added under vigorous stirring. After 15 min, the mixture was diluted with 100 ml of water, stirred for 20 min, and neutralized with 50 ml of 20% aqueous acetic acid. The organic phase was washed in succession with a 5% aqueous solution of sodium carbonate and 5×200 ml of water, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on 200 g of aluminum oxide using chloroform as eluent. A dark red fraction was collected, filtered through a cotton wool, and evaporated to dryness, and the residue was recrystallized from $CHCl_3$–MeOH. Yield 468 mg (88%), black powder. Electron absorption spectrum, λ_{max}, nm

(ε): 406 (172400), 503 (16100), 538 (10500), 573 (7200), 627 (3300). ^{1}H NMR spectrum, δ, ppm: 10.12 s, 10.12 s, 9.99 s, and 9.97 s (4H, *meso*-H); 8.30–8.22 d.d (1H, 8-C**H**=CH_2, J_{trans} = 17.7, J_{cis} = 11.5 Hz); 6.39–6.34 d (1H, *trans*-8-CH=C**H**$_2$, ^2J = 0.8 Hz); 6.20–6.17 d (1H, *cis*-8-CH=C**H**$_2$); 5.96 s (2H, 3-C**H**$_2$OH); 4.37–4.32 m (two overlapping broadened triplets, 4H, C**H**$_2$$CH_2CO_2CH_3$); 3.66 s, 3.66 s, 3.65 s, 3.61 s, 3.59 s, and 3.57 s (18H, $CH_2CH_2CO_2C$**H**$_3$, CH_3); 3.26–3.23 m (two overlapping triplets, 4H, CH_2C**H**$_2CO_2CH_3$); –3.86 br.s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 595.4 (100) [*M* + H]$^+$. Found, %: C 70.61; H 6.48; N 9.36. $C_{35}H_{38}N_4O_5$. Calculated, %: C 70.68; H 6.44; N 9.41.

8-Hydroxymethyl-3-vinyldeuteroporphyrin IX dimethyl ester (XV) was synthesized in a similar way from 474 mg (0.800 mmol) of formylporphyrin **XIII**. Yield 428 mg (90%). Electron absorption spectrum, λ_{max}, nm (ε): 406 (164000), 502 (14600), 538 (9100), 572 (6500), 628 (3100). ^{1}H NMR spectrum, δ, ppm: 10.08 s, 10.03 s, 9.99 s, and 9.94 s (4H, *meso*-H); 8.27–8.19 d.d (1H, 3-C**H**=CH_2, J_{trans} = 17.7, J_{cis} = 11.5 Hz); 6.37–6.33 d (1H, *trans*-3-CH=C**H**$_2$, ^2J = 1.6 Hz); 6.19–6.16 d (1H, *cis*-3-CH=C**H**$_2$); 5.92 s (2H, 8-C**H**$_2$OH), 4.36–4.31 m (two broadened triplets, 4H, C**H**$_2$$CH_2CO_2CH_3$); 3.67 s, 3.66 s, 3.66 s, 3.65 s, 3.56 s, and 3.56 s (18H, $CH_2CH_2CO_2C$**H**$_3$, CH_3); 3.26–3.22 m (two overlapping triplets, 4H, CH_2C**H**$_2CO_2CH_3$); –3.91 br.s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 595.4 (100) [*M* + H]$^+$. Found, %: C 70.73; H 6.41; N 9.49. $C_{35}H_{38}N_4O_5$. Calculated, %: C 70.68; H 6.44; N 9.41.

3-Acetoxymethyl-8-vinyldeuteroporphyrin IX dimethyl ester (XVI). Hydroxy derivative **XIV**, 300 mg (0.500 mmol), was dissolved in a mixture of 25 ml of pyridine and 6 ml of acetic anhydride. The mixture was heated for 10 min at 40°C in a tightly capped flask. The solvent was removed under reduced pressure (water-jet pump), and the residue was dissolved in 50 ml of chloroform. Water, 200 ml, was added to the solution, the mixture was vigorously shaken, and the organic phase was separated, dried over Na_2SO_4, and evaporated to dryness. Yield 310 mg (97%). Electron absorption spectrum, λ_{max}, nm (ε): 406 (162200), 503 (17300), 539 (10900), 572 (6900), 627 (2900). ^{1}H NMR spectrum, δ, ppm: 10.18 s, 10.17 s, 10.07 s, and 10.04 s (4H, *meso*-H); 8.33–8.25 d.d (1H, 8-C**H**=CH_2, J_{trans} = 17.4, J_{cis} = 11.2 Hz); 6.55 s (2H, 3-C**H**$_2$OAc); 6.41–6.37 d (1H, *trans*-8-CH=C**H**$_2$, ^2J = 0.9 Hz); 6.22–6.19 d (1H, *cis*-8-CH=C**H**$_2$); 4.43–4.36 m (two overlapping broadened triplets, 4H, C**H**$_2$$CH_2CO_2CH_3$); 3.73 s, 3.70 s, 3.66 s, 3.65 s, 3.63 s, and 3.60 s (18H, $CH_2CH_2CO_2C$**H**$_3$, CH_3); 3.29–3.25 m (two overlapping triplets, 4H, CH_2C**H**$_2CO_2CH_3$); 2.22 s (3H, 3-CH_2OCOC**H**$_3$); –3.73 br.s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 637.5 (100) [*M* + H]$^+$. Found, %: C 69.84; H 6.40; N 8.77. $C_{37}H_{40}N_4O_6$. Calculated, %: C 69.79; H 6.33; N 8.79.

8-Acetoxymethyl-3-vinyldeuteroporphyrin IX dimethyl ester (XVII) was synthesized in a similar way from 240 mg (0.403 mmol) of hydroxymethyl derivative **XV**. Yield 256 mg (100%), red film. Electron absorption spectrum, λ_{max}, nm (ε): 406 (172000), 501 (15100), 538 (9300), 574 (6900), 628 (2600). ^{1}H NMR spectrum, δ, ppm: 10.11 s, 10.06 s, 10.01 s, and 9.99 s (4H, *meso*-H); 8.26–8.19 d.d (1H, 3-C**H**=CH_2, J_{trans} = 18.0, J_{cis} = 11.5 Hz); 6.49 s (2H, 8-C**H**$_2$OAc); 6.38–6.33 d (1H, *trans*-3-C**H**=CH_2, ^2J = 1.3 Hz); 6.20–6.17 d (1H, *cis*-3-CH=C**H**$_2$); 4.42–4.34 m (two overlapping broadened triplets, 4H, C**H**$_2$$CH_2CO_2CH_3$); 3.67 s, 3.66 s, 3.65 s, 3.63 s, 3.62 s, and 3.58 s (18H, $CH_2CH_2CO_2C$**H**$_3$, CH_3); 3.29–3.25 m (two overlapping triplets, 4H, CH_2C**H**$_2CO_2CH_3$); 2.21 s (3H, 8-CH_2OCOC**H**$_3$); –3.86 br.s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 637.5 (100) [*M* + H]$^+$. Found, %: C 69.73; H 6.30; N 8.77. $C_{37}H_{40}N_4O_6$. Calculated, %: C 69.79; H 6.33; N 8.79.

3-Hydroxymethylchlorine e_6 trimethyl ester (XXII). Aldehyde **XXI**, 250 mg (0.390 mmol), was dissolved in 100 ml of a 1:1 (v/v) CH_2Cl_2–MeOH mixture, and 150 mg (3.964 mmol) of finely powdered $NaBH_4$ was added over a period of 2 min under vigorous stirring. The originally brown mixture turned emerald green. The mixture was treated dropwise with 20 ml of 1% aqueous acetic acid, stirred for 20 min, and poured into 250 ml of water. The organic phase was separated, diluted with 200 ml of chloroform, washed with water (3 × 500 ml), dried over Na_2SO_4, and evaporated to dryness. Yield 250 mg, green glassy material. Electron absorption spectrum, λ_{max}, nm (ε): 399 (163000), 499 (14800), 526 (4300), 604 (4600), 660 (46100). ^{1}H NMR spectrum, δ, ppm: 9.69 s, 9.56 s, and 8.74 s (3H, *meso*-H); 5.91 s (2H, 3-C**H**$_2$OH); 5.37–5.21 q (2H, 15-C**H**$_2$$CO_2CH_3$, *J* = 18.6, 29.5 Hz); 4.46–4.39 m (2H, 17-H, 18-H); 4.25 s (3H, 13-CO_2CH_3); 3.80–3.75 m (5H, 8-C**H**$_2$$CH_3$, CH_3); 3.61 s, 3.56 s, 3.45 s, and 3.29 s (12H, CH_3, 15-CH_2CO_2C**H**$_3$, 17-$CH_2CH_2CO_2C$**H**$_3$); 2.59–2.50 m and 2.23–2.03 m (4H, 17-C**H**$_2$C**H**$_2$$CO_2CH_3$); 1.75–1.68 m (6H, 18-$CH_3$, 8-$CH_2C$**H**$_3$); –1.38 br.s and –1.54 br.s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 643.4 (100) [*M* + H]$^+$. Found, %: C 67.33; H 6.62;

N 8.64. $C_{36}H_{42}N_4O_7$. Calculated, %: C 67.27; H 6.58; N 8.71.

3-Acetoxymethylchlorin e_6 trimethyl ester (XXIII) was synthesized from 50 mg (0.077 mmol) of compound **XXII**, following the procedure described above for acetoxy derivative **XVI**. Yield quantitative. Electron absorption spectrum, λ_{max}, nm (ε): 400 (137200), 499 (14100), 527 (4500), 606 (4800), 661 (49000). ^{1}H NMR spectrum, δ, ppm: 9.70 s, 9.56 s, and 8.76 s (3H, *meso*-H); 6.40 s (2H, 3-C**H**$_2$OAc); 5.38–5.21 q (2H, 15-C**H**$_2$CO$_2$CH$_3$, J = 19.0, 30.5 Hz); 4.46–4.40 m (2H, 17-H, 18-H); 4.25 s (3H, 13-CO$_2$CH$_3$); 3.81–3.75 m (5H, 8-C**H**$_2$CH$_3$, CH$_3$); 3.61 s, 3.57 s, 3.48 s, and 3.31 s (12H, CH$_3$, 15-CH$_2$CO$_2$C**H**$_3$, 17-CH$_2$CH$_2$CO$_2$C**H**$_3$); 2.58–2.50 m (2H, 17-C**H**$_2$CH$_2$CO$_2$CH$_3$); 2.27–2.16 m (5H, 17-CH$_2$-C**H**$_2$CO$_2$CH$_3$, 3-CH$_2$OCOC**H**$_3$); 1.74–1.69 m (6H, 18-CH$_3$, 8-CH$_2$C**H**$_3$); –1.41 br.s and –1.66 br.s (2H, NH). Mass spectrum, m/z (I_{rel}, %): 685.3 (100) [M + H]$^+$. Found, %: C 66.57; H 6.41; N 8.22. $C_{38}H_{44}N_4O_8$. Calculated, %: C 66.65; H 6.47; N 8.18.

Condensation of β-hydroxymethyl- and β-acetoxymethyltetrapyrroles with acetylacetone (*general procedure*). Tetrapyrrole **XIV**–**XVII**, **XXII**, or **XXIII**, 0.050 mol, was dissolved in 30 ml of freshly distilled acetylacetone containing 350 mg of Zn(OAc)$_2\cdot$2H$_2$O, and the mixture was heated for 40 min at 110°C. Excess acetylacetone was removed under reduced pressure (oil pump), the residue was dissolved in 50 ml of chloroform, and the solution was treated with 50 ml of 10% aqueous acetic acid. The organic phase was separated, 50 ml of 6 N hydrochloric acid was added, the mixture was vigorously shaken over a period of 2 min, 500 ml of water was quickly added, and the aqueous phase was discarded. The organic phase was washed with 100 ml of a 5% aqueous solution of sodium carbonate and with water (4×100 ml), dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated to dryness. The residue was dissolved in a minimal amount of chloroform, the solution was applied to a silica gel plate, and the plate was placed into a chromatographic chamber protected from light and charged with chloroform–diethyl ether–pyridine (100:10:1). After 4 h, the plate was withdrawn and dried at room temperature in the dark over a period of 5 min. The major zone was separated with a scalpel and transferred into a flask charged with 25 ml of a 1:1 CHCl$_3$–MeOH mixture. The solution was filtered from silica gel and evaporated to dryness, the residue was dissolved in CHCl$_3$, and the product was precipitated by gradually adding petroleum ether.

3-(2-Acetyl-3-oxobutyl)-8-vinyldeuteroporphyrin dimethyl ester (XXX). Electron absorption spectrum, λ_{max}, nm (ε): 406 (169300), 501 (15800), 539 (10900), 573 (7600), 627 (3200). ^{1}H NMR spectrum, δ, ppm: 10.18 s, 10.05 s, 10.00 s, and 9.95 s (4H, *meso*-H); 8.31–8.24 d.d (1H, 8-C**H**=CH$_2$, J_{trans} = 17.7, J_{cis} = 11.5 Hz); 6.39–6.35 d (1H, *trans*-8-CH=C**H**$_2$, ^2J = 1.1 Hz); 6.20–6.17 d (1H, *cis*-8-CH=C**H**$_2$); 4.72–4.69 t (1H, 3-CH$_2$C**H**Ac$_2$, J = 7.1 Hz); 4.51–4.49 d (2H, 3-C**H**$_2$CHAc$_2$); 4.41–4.37 m (two overlapping broadened triplets, 4H, C**H**$_2$CH$_2$CO$_2$CH$_3$); 3.71 s, 3.64 s, 3.64 s, 3.62 s, 3.61 s, and 3.55 s (18H, CH$_2$CH$_2$CO$_2$C**H**$_3$, CH$_3$); 3.28–3.25 m (two overlapping triplets, 4H, CH$_2$C**H**$_2$CO$_2$CH$_3$); 2.06 s (6H, 3-CH$_2$CH**Ac**$_2$); –3.78 br.s (2H, NH). Mass spectrum, m/z (I_{rel}, %): 677.4 (100) [M + H]$^+$.

8-(2-Acetyl-3-oxobutyl)-3-vinyldeuteroporphyrin dimethyl ester (XXXI). Electron absorption spectrum, λ_{max}, nm (ε): 406 (174100), 502 (15800), 538 (9700), 573 (7100), 628 (2900). ^{1}H NMR spectrum, δ, ppm: 10.06 s, 10.03 s, 10.00 s, and 9.84 s (4H, *meso*-H); 8.27–8.20 d.d (1H, 3-C**H**=CH$_2$, J_{trans} = 18.0, J_{cis} = 11.8 Hz); 6.37–6.33 d (1H, *trans*-3-CH=C**H**$_2$, ^2J = 0.8 Hz); 6.19–6.16 d (1H, *cis*-3-CH=C**H**$_2$); 4.70–4.67 t (1H, 8-CH$_2$C**H**Ac$_2$, J = 7.4 Hz); 4.49–4.48 d (2H, 8-C**H**$_2$CHAc$_2$); 4.40–4.37 m (two overlapping broadened triplets, 4H, C**H**$_2$CH$_2$CO$_2$CH$_3$); 3.68 s, 3.66 s, 3.64 s, 3.61 s, 3.52 s, and 3.48 s (18H, CH$_2$CH$_2$CO$_2$-C**H**$_3$, CH$_3$), 3.27–3.24 m (two overlapping triplets, 4H, CH$_2$C**H**$_2$CO$_2$CH$_3$); 2.06 s (6H, 8-CH$_2$CH**Ac**$_2$); –3.98 br.s (2H, NH). Mass spectrum, m/z (I_{rel}, %): 677.4 (100) [M + H]$^+$.

3-(2-Acetyl-3-oxobutyl)chlorin e_6 trimethyl ester (XXXII). Electron absorption spectrum, λ_{max}, nm (ε): 400 (175000), 499 (7500), 526 (3700), 601 (4700), 656 (48300). ^{1}H NMR spectrum, δ, ppm: 9.69 s, 9.34 s, and 8.67 s (3H, *meso*-H); 5.35–5.20 q (2H, 15-C**H**$_2$CO$_2$CH$_3$, J = 19.0, 24.9 Hz); 4.67–4.63 t (1H, 3-CH$_2$C**H**Ac$_2$, J = 7.1 Hz); 4.44–4.36 m (4H, 17-H, 18-H, 3-C**H**$_2$CHAc$_2$); 4.24 s (3H, 13-CO$_2$CH$_3$); 3.80–3.76 m (5H, 8-C**H**$_2$CH$_3$, CH$_3$); 3.63 s, 3.56 s, 3.34 s, and 3.31 s (12H, CH$_3$, 15-CH$_2$CO$_2$C**H**$_3$, 17-CH$_2$CH$_2$-CO$_2$C**H**$_3$); 2.60–2.50 m (2H, 17-C**H**$_2$CH$_2$CO$_2$CH$_3$); 2.22–2.13 m (8H, 17-CH$_2$C**H**$_2$CO$_2$CH$_3$, 3-CH$_2$CH**Ac**$_2$); 1.74–1.69 m (6H, 18-CH$_3$, 8-CH$_2$C**H**$_3$); –1.48 br.s and –1.55 br.s (2H, NH). Mass spectrum, m/z (I_{rel}, %): 725.4 (100) [M + H]$^+$.

Condensation of tetrapyrroles XXX–XXXII with *o*-bromophenylhydrazine (*general procedure*). Tetrapyrrole **XXX**–**XXXII**, 0.015 mmol, was dissolved in 10 ml of pyridine, 0.045 mmol of *o*-bromophenyl-

hydrazine was added, and the solution was heated for 1 h under reflux. The solvent was removed under reduced pressure, the residue was dissolved in 10 ml of methylene chloride, and the solution was washed with water (3×10 ml). The organic phase was dried over anhydrous Na_2SO_4, evaporated to a minimal volume, and applied to a silica gel plate. The plate was placed into a chromatographic chamber protected from light and charged with chloroform–diethyl ether–pyridine (100:10:1). After 2 h, the plate was withdrawn and dried at room temperature in the dark over a period of 5 min. The major zone was separated with a scalpel and transferred into a flask charged with 25 ml of a 1:1 $CHCl_3$–MeOH mixture. The solution was filtered from silica gel and evaporated to dryness, the residue was dissolved in $CHCl_3$, and the product was precipitated by gradually adding petroleum ether.

3-{1-[1-(2-Bromophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]ethyl}-8-vinyldeuteroporphyrin dimethyl ester (XXXVIII). Electron absorption spectrum, λ_{max}, nm (ε): 245 (18700), 285 (15300), 405 (171000), 504 (16100), 539 (10800), 573 (6900), 627 (3000). ^{1}H NMR spectrum, δ, ppm: 10.18 s, 10.06 s, 10.04 s, and 10.00 s (4H, *meso*-H); 8.30–8.22 d.d (1H, 8-C**H**=CH_2, J_{trans} = 18.0, J_{cis} = 11.8 Hz); 7.57–7.55 m, 7.34–7.33 m, and 7.25–7.20 m (4H, H_{arom}); 6.35–6.31 d (1H, *trans*-8-CH=C**H**$_2$); 6.17–6.14 d (1H, *cis*-8-CH=C**H**$_2$); 5.12 s (2H, 3-CH_2); 4.44–4.37 m (two overlapping triplets, 4H, C**H**$_2$$CH_2$COOMe); 3.65 s, 3.64 s, 3.64 s, 3.62 s, 3.58 s, and 3.56 s (18H, $CH_2CH_2CO_2$-C**H**$_3$, CH_3); 3.29–3.25 m (two overlapping triplets, 4H, CH_2C**H**$_2$COOMe); 2.35 s and 1.82 s (6H, CH_3 in pyrazole); –3.73 br.s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 827.5 (100) $[M + H]^+$.

8-{1-[1-(2-Bromophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]ethyl}-3-vinyldeuteroporphyrin dimethyl ester (XXXIX). Electron absorption spectrum, λ_{max}, nm (ε): 245 (19200), 286 (14800), 405 (167000), 504 (15400), 539 (11200), 573 (7300), 627 (3200). ^{1}H NMR spectrum, δ, ppm: 10.16 s, 10.08 s, 10.01 s, and 9.98 s (4H, *meso*-H); 8.31–8.23 d.d (1H, 3-C**H**=CH_2, J_{trans} = 17.9, J_{cis} = 11.6 Hz); 7.58–7.54 m, 7.32–7.31 m, and 7.21–7.17 m (4H, H_{arom}); 6.33–6.29 d (1H, *trans*-3-CH=C**H**$_2$); 6.14–6.11 d (1H, *cis*-3-CH=C**H**$_2$); 5.16 s (2H, 8-CH_2), 4.47–4.39 m (two overlapping triplets, 4H, C**H**$_2$$CH_2$COOMe); 3.67 s, 3.65 s, 3.64 s, 3.62 s, 3.59 s, and 3.55 s (18H, $CH_2CH_2CO_2$-C**H**$_3$, CH_3); 3.26–3.22 m (two overlapping triplets, 4H, CH_2C**H**$_2$COOMe); 2.34 s and 1.83 s (6H, CH_3 in pyrazole); –3.68 br.s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 827.5 (100) $[M + H]^+$.

3-{1-[1-(2-Bromophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]ethyl}chlorin e_6 trimethyl ester (XL). Electron absorption spectrum, λ_{max}, nm (ε): 243 (20000), 286 (16200), 400 (184000), 499 (14100), 525 (4100), 601 (4900), 656 (45700). ^{1}H NMR spectrum, δ, ppm: 9.66 s, 9.38 s, and 8.66 s (3H, *meso*-H); 7.67–7.61 m, 7.38–7.37 m, and 7.28–7.21 m (4H, H_{arom}); 5.34–5.19 q (2H, 15-C**H**$_2$$CO_2CH_3$, J = 19.0, 24.0 Hz); 5.01 s (2H, 3-CH_2); 4.44–4.35 m (2H, 17-H, 18-H); 4.24 s (3H, 13-CO_2CH_3); 3.78–3.72 m (5H, 8-C**H**$_2$$CH_3$, CH_3); 3.63 s, 3.55 s, 3.32 s, and 3.21 s (12H, CH_3, 15-CH_2-CO_2C**H**$_3$, 17-$CH_2CH_2CO_2$C**H**$_3$); 2.57–2.50 m and 2.23–2.12 m (4H, 17-C**H**$_2$C**H**$_2$$CO_2CH_3$); 2.34 s and 1.95 s (6H, CH_3 in pyrazole); 1.74–1.73 d (3H, 18-CH_3, J = 6.8 Hz); 1.70–1.66 t (3H, 8-CH_2C**H**$_3$, J = 7.8 Hz); –1.32 br.s and –1.44 br.s (2H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 875.4 (100) $[M + H]^+$.

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