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**REVIEW**

*Dedicated to 125th Anniversary of outstanding German chemist, Nobel Prize Winner H. Fischer*

# Modern Aspects of the Chemistry of Protoporphyrin IX

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Received February 27, 2006

**Abstract**—Numerous recently published data on the methods for modification of protoporphyrin IX and its derivatives have been summarized and analyzed. Special attention has been given to those transformations which are important from the practical viewpoint for the preparation of compounds possessing valuable medical, biological, and physical properties, as well as to specific transformations inherent to the tetrapyrrole macroring.

**DOI:** 10.1134/S10704280007010010



**Vsevolod Pavlov** was born in 1978 in Moscow. In 2000, he graduated from the Faculty of Chemistry, Moscow State University, and in 2001, from the English Language Department, Higher Courses of Foreign Languages at the Ministry of Foreign Economic Relations of the Russian Federation. Candidate of Chemical Sciences since 2006. V. Pavlov is scientific worker at the Organic Chemistry Department, Faculty of Chemistry, Moscow State University, and at the Faculty of Biotechnology and Organic Synthesis, Lomonosov Moscow State Academy of Fine Chemical Technology.

Fields of scientific interest: organic and medicinal chemistry, synthesis and reactivity of low-molecular heterocyclic compounds, and chemistry and biological activity of derivatives of natural macrocyclic compounds.

## 1. INTRODUCTION

Protoporphyrin IX occupies a specific place among numerous families of tetrapyrroles. It is a parent structure of a large group of natural tetrapyrroles responsible for vital functions of aerobic organisms [1, 2]. In particular, protoporphyrin IX acts as ligand toward prosthetic group of proteins which ensure transport (hemoglobin) and deposition of oxygen (myoglobin) [2–4], as well as toward enzymes responsible for key bioregulatory functions such as detoxication and synthesis of sex hormones and antiinflammatory and antihypertensive compounds (cytochrome P450 family) [5–7]. Strong interest in the chemistry of protoporphyrin IX originates from unique combination of valuable physical, chemical, and biological properties [8] of its purposefully modified derivatives and their synthetic accessibility [9]. Effective catalysts of organic reactions [10–12], components of sensor complexes [13–15], and convenient models for studying photosynthesis [16, 17] and oxygen transport *in vivo* [18] were found among protoporphyrin IX derivatives.

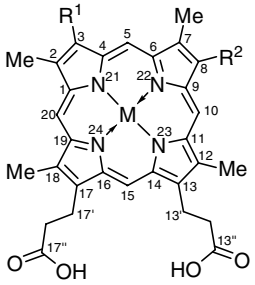
An exceptional combination of profitable photophysical properties, low systemic toxicity, and affinity for hyperproliferating tissues makes protoporphyrin IX derivatives very promising for use in the diagnostics and therapy of cancer and eye diseases, as well as in cardiology, cosmetology, and other fields of medicine [8, 19–28].

The chemistry of protoporphyrin IX has started to extensively develop since mid XXth century due to H. Fischer's studies; since 1934 till 1940 he published a collection of fundamental works on the synthesis and chemical transformations of tetrapyrrole compounds [29–31]. Voluminous data on the chemistry of protoporphyrin IX derivatives were covered by books [32–34] and several reviews [9, 20–22, 35–37], as well as by the 20-volume series *The Porphyrin Handbook* published in 2000–2003 [38, 39].

The present review summarizes and analyzes data published in the past decade on modifications of protoporphyrin IX derivatives with account taken of publications not covered by the above reviews and monographs. The data are discussed with respect to the substitution pattern in protoporphyrin IX and the possibility for modification of the tetrapyrrole macroring.

## 2. NOMENCLATURE AND TRIVIAL NAMES OF BASIC PROTOPORPHYRIN IX DERIVATIVES

The structures of protoporphyrin IX (**1**) and its some most important derivatives **2–13** are given below. Atoms in the porphyrin macroring are numbered according to Fischer or IUPAC recommendations [36]. This review uses the IUPAC atom numbering, except for trivial names proposed by Fischer.




**1–13**

**1**, M = 2H, $R^1 = R^2 = CH_2$=CH (protoporphyrin IX); **2**, M = 2H, $R^1$ = CHO, $R^2 = CH_2$=CH (chlorocruoroporphyrin); **3**, M = 2H, $R^1 = R^2$ = H (deuteroporphyrin); **4**, M = 2H, $R^1 = R^2 = HOCOCH_2CH_2$ (coproporphyrin III); **5**, M = 2H, $R^1 = CH_2$=CH, $R^2 = HOCOCH_2CH_2$ (harderoporphyrin); **6**, M = 2H, $R^1$ = CHO, $R^2$ = CH=CH$R^3$ ($R^3 = C_{12}H_{25}$ to $C_{15}H_{31}$) (cryptoporphyrin *a*); **7**, M = 2H, $R^1 = R^2$ = MeCH(OH) (hematoporphyrin IX); **8**, M = 2H, $R^1 = CH_2$=CH, $R^2$ = H (pemtoporphyrin); **9**, M = 2H, $R^1$ = HOCOCH=CH, $R^2 = HOCOCH_2CH_2$ (porphyrin S-411); **10**, M = $Fe^{2+}$, $R^1 = R^2 = CH_2$=CH (heme); **11**, M = $[FeCl]^{2+}$, $R^1$ = CHO, $R^2 = CH_2$=CH (chlorocruorohemin); **12**, M = $[FeCl]^{2+}$, $R^1 = R^2 = CH_2$=CH (protohemin IX); **13**, M = $[FeOH]^{2+}$, $R^1 = R^2 = CH_2$=CH (hematin).

## 3. MODIFICATION OF PERIPHERAL SUBSTITUENTS

Analysis of the structure of protoporphyrin IX (**1**) shows that the main peripheral substituents capable of being involved in various chemical transformations are vinyl, 13- and 17-(2-carboxyethyl), and methyl groups. Data on possible modifications of these substituents are discussed below.

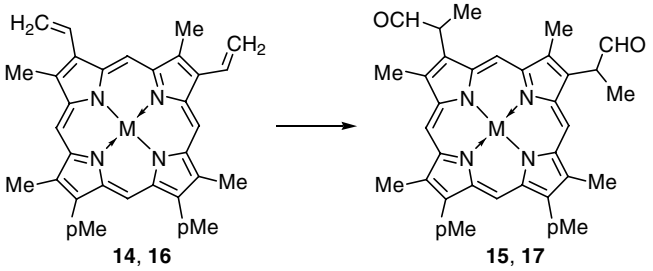
### *3.1. Modification of Vinyl Groups*

A combination of high reactivity of the vinyl groups in protoporphyrin IX derivatives and considerable stability of the porphyrin macroring is responsible for their easy transformations such as reduction, oxidation, addition, substitution, elimination, electrocyclic reactions, and olefin metathesis.

**3.1.1. Reduction.** Specific features of the reduction of peripheral vinyl groups in porphyrins to ethyl substituents were considered in the classical treatise [33]. A detailed discussion of practical large-scale methods for hydrogenation of the vinyl groups in protohemin IX (**12**) was given in patent application [40].

The porphyrin vinyl groups are converted into branched 1-formylethyl substituents by hydroformylation catalyzed by rhodium complexes with organophosphorus ligands [41, 42]. The regioselectivity of the process strongly depends on the central metal ion. Zinc complex **14** gives rise to 100% of aldehyde **15**, while the yield of formylethyl derivative **17** from nickel complex **16** is 75% (Scheme 1) [42].

**Scheme 1.**




**14**, **16** **15**, **17**

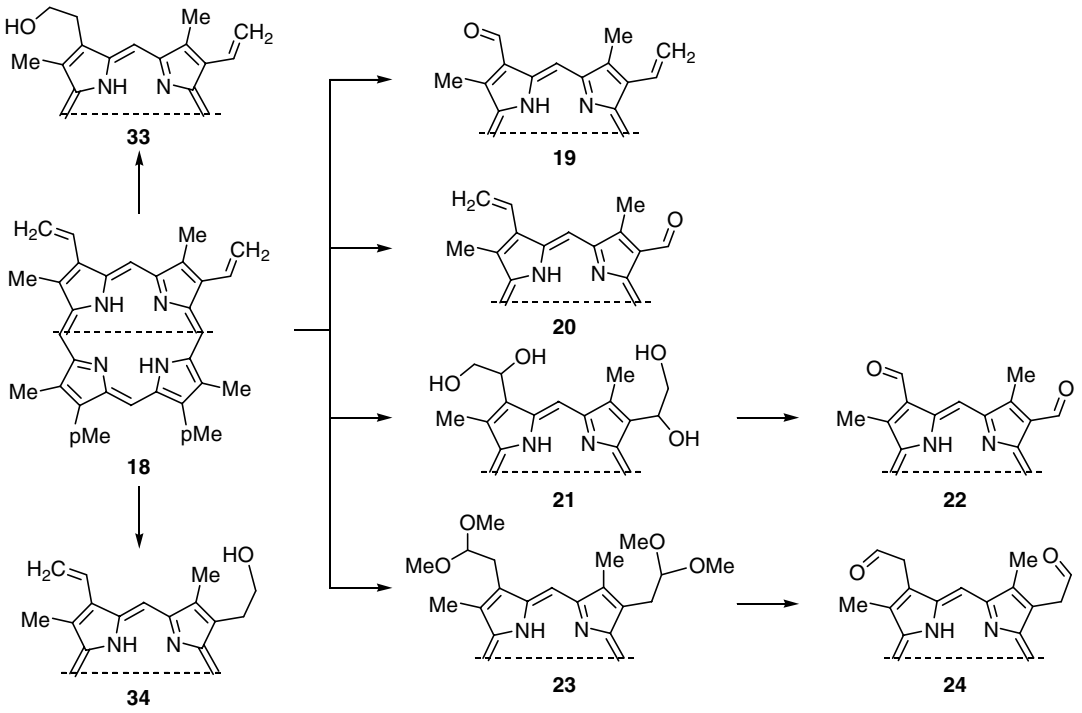
**14**, **15**, M = Zn(II); **16**, **17**, M = Ni(II); hereinafter, "p" stands for $CH_2CH_2CO_2$, i.e., pMe = $CH_2CH_2CO_2Me$.

**3.1.2. Oxidation.** The vinyl groups in divinylporphyrin **18** can be oxidized to formyl substituents with the aid of a large number of reagents [9, 33, 43]. The general disadvantage of direct oxidation methods is that they lead to the formation of mixtures of monoformyl derivatives **19** and **20** which are difficult to separate (Scheme 2). The use of the $OsO_4$–4-methylmorpholine *N*-oxide system ensures complete oxidation of both vinyl groups. In this case, porphyrin **18** is converted into bis-diol **21** in almost quantitative yield, and treatment of the latter with $HIO_4$ gives dialdehyde **22** in a high yield [44]. Compound **21** is the key intermediate product in the synthesis of BOPP, an efficient agent for photodynamic therapy of cancer [44]. Divinylporphyrin **18** is oxidized in high yield to bisacetal **23** by the action of 3 equiv of $Tl(NO_3)_3 \cdot 3H_2O$ in MeOH–$CH_2Cl_2$; acid hydrolysis of **23** gives bisaldehyde **24**, and reduction of the latter with $NaBH_4$ leads to diol **25** which may formally be regarded as the anti-Markownikow vinyl group hydration product [33, 44]. The direct anti-Markownikow hydration (by treatment with $B_2H_6$) of vinyl groups in porphyrins is characterized by a poor yield [9]. Nucleophilic replacement of the hydroxy groups in diol **25** by chlorine atoms may be achieved by treatment with $SOCl_2$ in $CHCl_3$–DMF in the presence of $K_2CO_3$. Dichloro derivative **26** is transformed in a high yield into initial divinylporphyrin **18** by the action of *t*-BuOK over a period of 3 days (Scheme 3) [33]. Under analogous conditions, 5-methylporphyrin **27** is not converted into divinylporphyrin **28**, but closure of six-membered ring occurs to give compound **29** (Scheme 4) [45]. An effective and universal method for regeneration of vinyl group from 2-hydroxyethyl substituent consists of treatment of diols **25** and **30** with the system *o*-$NO_2C_6H_4SeCNO$–$Bu_3P$, followed by oxidation of the corresponding organoselenium porphyrin derivatives **31** and **32** with hydrogen peroxide [45]. This procedure makes it possible to shorten the reaction time to 5 h, avoid undesirable cyclization to compound **29**, and obtain 5-methyl-substituted analog of protoporphyrin IX **28** with high regioselectivity [45]. Transformations of the hydroxyethyl groups in **25** were used in the design of efficient photosensitizers for photodynamic therapy of cancer [22, 46] and in some classical syntheses [9, 33].

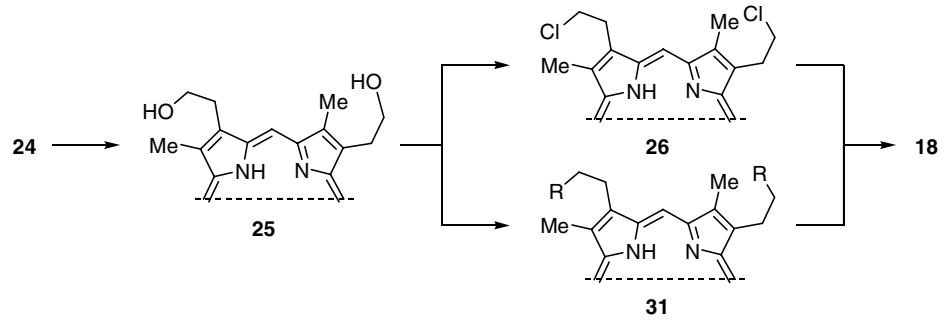
Treatment of divinylporphyrin **18** with 2 equiv of $Tl(NO_3)_3 \cdot 3H_2O$ in MeOH–$CH_2Cl_2$ resulted in oxidation of only one vinyl group; the subsequent hydrolysis, reduction with $NaBH_4$, and chromatographic separation gave individual monohydroxy isomers **33** and **34** that are important intermediate products in a number of classical syntheses of key natural porphyrins [33]. The oxidation of **18** under severe conditions (with a hot solution of $KMnO_4$ in $Me_2CO$) leads to the formation of dicarboxylic acid **35** [33].

**3.1.3. Addition to vinyl groups.** Electrophilic addition of aliphatic amines to the vinyl groups in protoporphyrin IX derivatives occurs on prolonged heating. Heating of porphyrin **18** in boiling ethylenediamine was accompanied by amidation of the ester groups to give compound **36**. Brunner et al. [47] proposed to use the diamine fragments in **36** as bidentate chelating ligands toward Pt(II). The reaction of **36** with $K_2PtCl_4$ gave complex **37** containing a photodynamically active

**Scheme 2.**

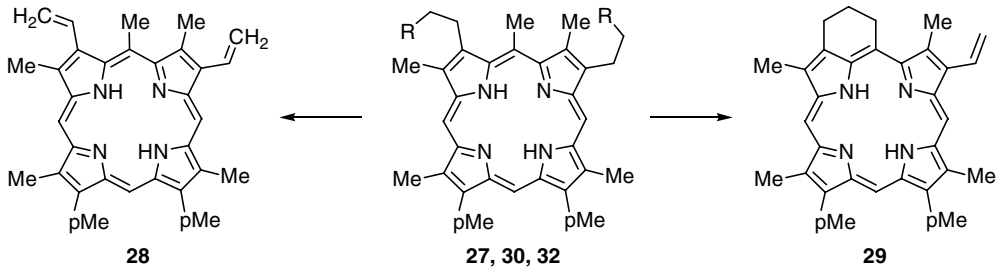


**Scheme 3.**



**31**, R = *o*-$O_2NC_6H_4Se$.

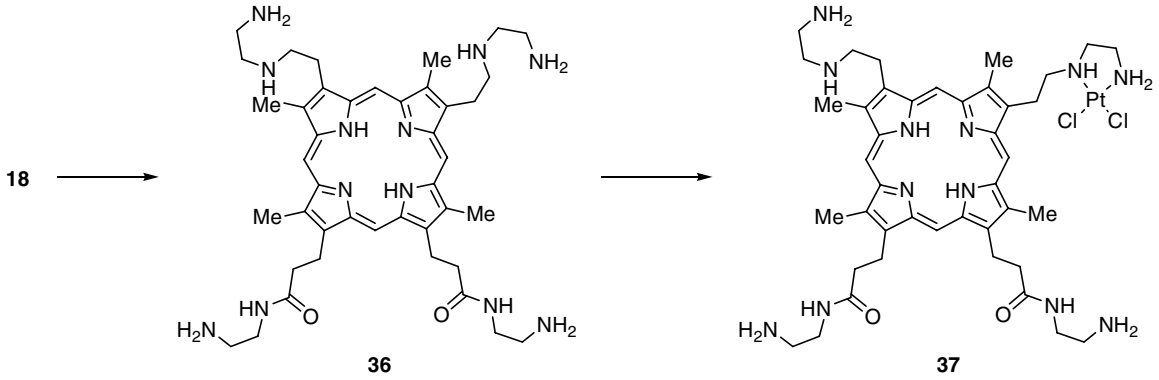
**Scheme 4.**



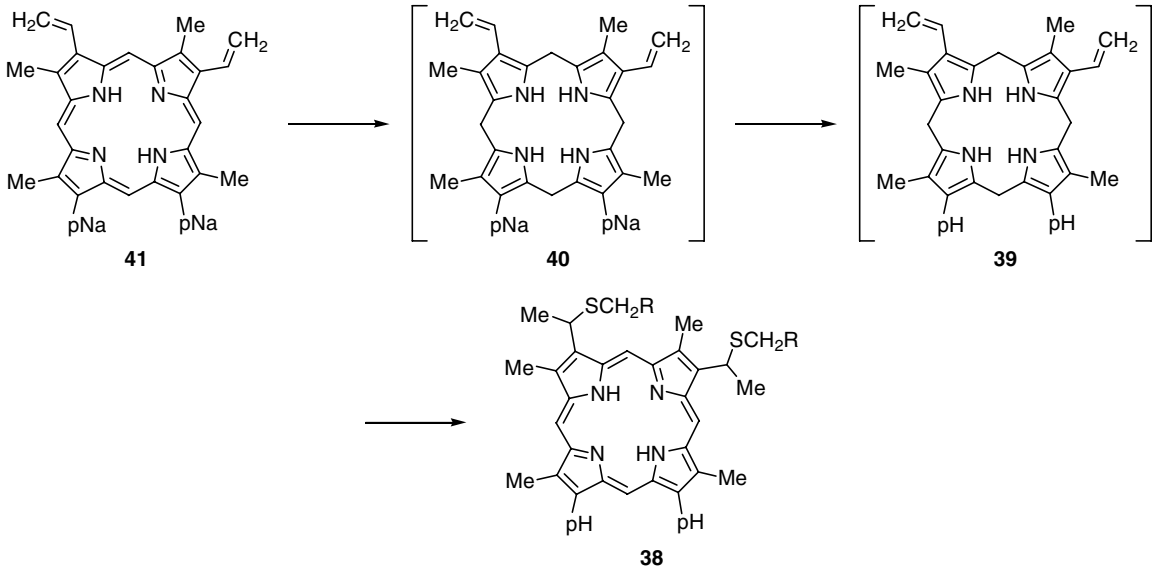
**27**, R = Cl; **30**, R = OH; **31**, **32**, R = *o*-$O_2NC_6H_4Se$.

porphyrin chromophore and a cytotoxic Pt(II) coordination entity (Scheme 5). Pilloud et al. [48, 49] reported on effective addition of thiols immobilized on the surface of a quartz or gold electrode to the porphyrin vinyl groups. Sulfanyl derivatives **38** were obtained via autooxidation of a non-porphyrine macroring to porphyrin, by reaction of cysteine and other S-nucleophiles with protoporphyrinogen **39** under

**Scheme 5.**




**Scheme 6.**




**38**, R = $HOCOCH(NH_2)$ or CH-peptide.

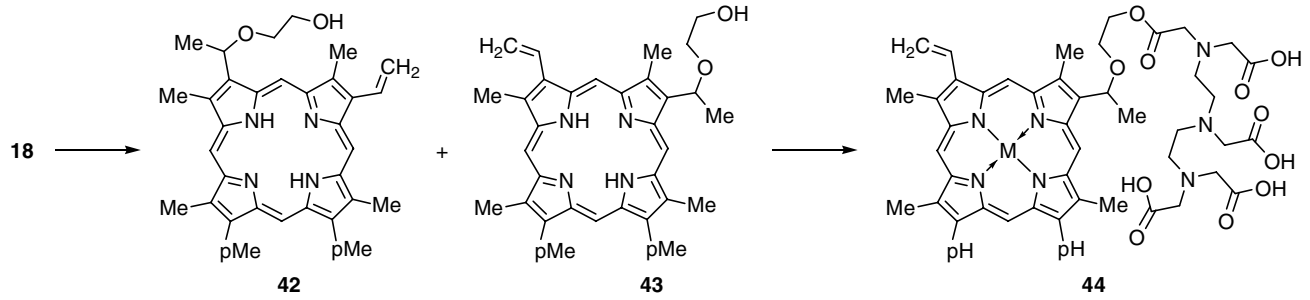
acidic conditions. Compound **39** was synthesized from porphyrinogen **40** disodium salt which was generated from protoporphyrin IX disodium salt (**41**) by the action of Na/Hg under nitrogen (Scheme 6) [50].

A widely used procedure for functionalization of the vinyl groups in protoporphyrin IX is based on hydrobromination with the system HBr–AcOH, followed by replacement of the labile bromine atoms by various nucleophiles [20, 21, 51, 52]. The efficiency of this approach was demonstrated by the synthesis of promising photosensitizers for photodynamic therapy of cancer [20, 21, 53, 54].

Addition of alcohols to the vinyl groups in divinylporphyrin **18** was the initial step in the synthesis of effective diagnostic agents [22, 55]. Successive treatment of **18** with HBr–AcOH and ethylene glycol gave a mixture of isomeric ethers **42** and **43** (Scheme 7). Metalation of **43**, hydrolysis of the ester groups, and esterification of the hydroxy group in the 8-[1-(2-hydroxyethoxy)]ethyl substituent with diethylenetriaminepentaacetic acid led to the formation of compound **44** (ATN-10). Due to the presence in its molecule of a diethylenetriaminepentaacetic acid residue which effectively coordinates various metals, ATN-10 was used to chelate radioactive metal isotopes. Intravenous administration of a solution obtained by mixing ATN-10 with sodium pertechnate (as source of [$^{99}$Tc]) in saline at a dose of 0.1 mg/kg gave a distinct scintigraphic pattern of bone marrow in 5 min after injection [55].

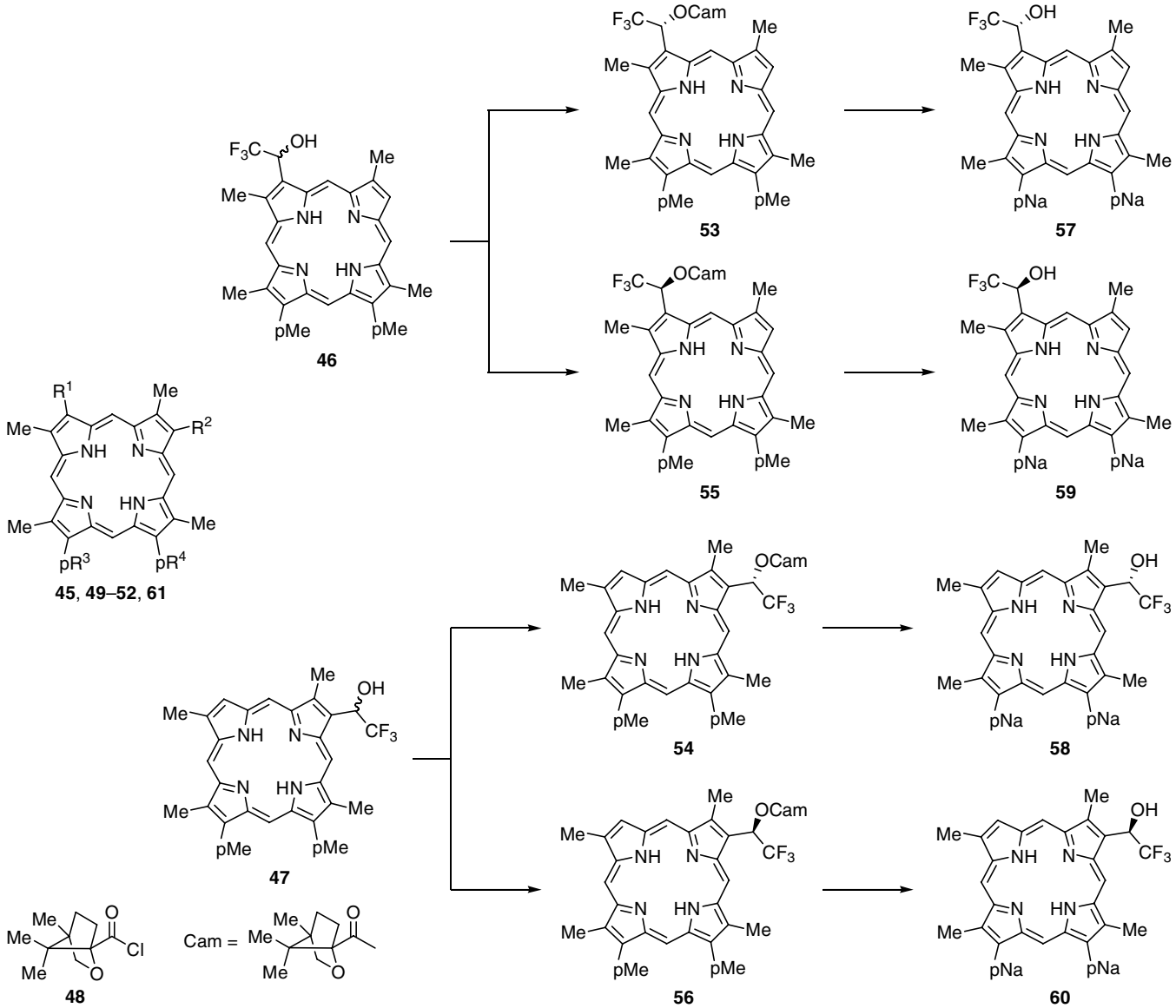
Tian et al. [56] reported on acid hydrolysis of the ether bond in the 3(8)-(1-methoxyethyl) group in porphyrins. The subsequent transformation of the 3(8)-(1-hydroxyethyl) group into vinyl was effected by heating in a mixture of benzoyl chloride with DMF or in

**Scheme 7.**



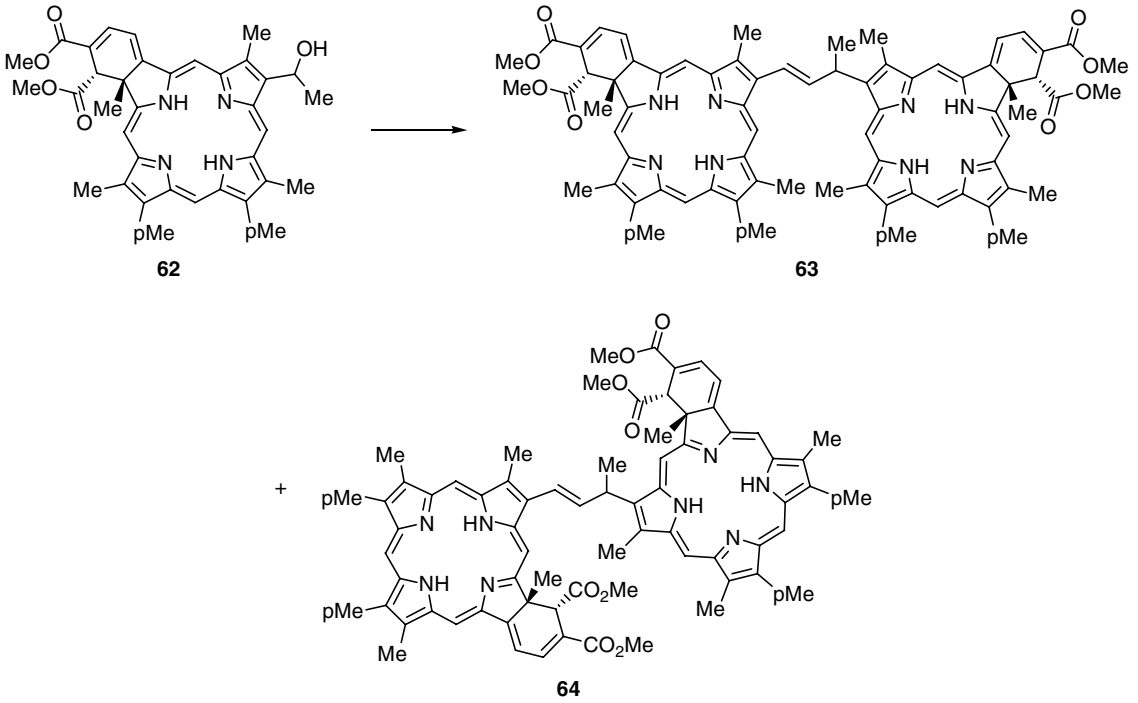

**44**, M = Mn(III).

**Scheme 8.**




**45**, $R^1 = R^2 = (R,S)$-$CF_3CH(OH)$, $R^3 = R^4 = Me$; **49**, $R^1 = (R)$-$CF_3CH(OH)$, $R^2 = (S)$-$CH_3CH(OH)$, $R^3 = R^4 = Me$; **50**, $R^1 = (S)$-$CF_3CH(OH)$, $R^2 = (R)$-$CF_3CH(OH)$, $R^3 = R^4 = Me$; **51**, $R^1 = R^2 = (R)$-$CF_3CH(OH)$, $R^3 = R^4 = Me$; **52**, $R^1 = R^2 = (S)$-$CF_3CH(OH)$, $R^3 = R^4 = Me$; **61**, $R^1 = (S)$-$CF_3CH(OH)$, $R^2 = (R)$-$CF_3CH(OH)$, $R^3 = R^4 = Na$.

**Scheme 9.**



1,2-dichlorobenzene in the presence of *p*-toluenesulfonic acid; protoporphyrin IX dialkyl esters were thus obtained [9, 21, 57].

Hematoporphyrin IX (**7**) possesses two chiral centers and is therefore a mixture of four diastereoisomers [58]. With the goal of elucidating the effect of steric structure on biological activity of porphyrins, Ando et al. [58, 59] tried to perform optical resolution of trifluoromethyl analogs **45**–**47** of hematoporphyrin IX with the aid of (*S*)-camphoroyl chloride (**48**). The authors failed to separate bis(2,2,2-trifluoro-1-hydroxyethyl) derivative **45** into individual stereoisomers **49–52**; the latter were obtained only via total syntheses from chiral monopyrrole compounds [58]. Monosubstituted derivatives **46** and **47** were separated into *R* and *S* isomers **53/54** and **55/56** by column chromatography at the stage of formation of the corresponding esters which were treated with sodium hexamethyldisilazide in MeOH–THF to obtain disodium salts **57–60** (Scheme 8). Experiments on a stomach cancer model *in vitro* showed that (3*S*)-isomer **59** is taken up by tumor cells 15 times more selectively than is (3*R*)-isomer **57** and that the selectivity of (8*R*)-isomer **58** for tumor cells is slightly lower as compared to (8*S*)-isomer **60** [58, 59]. The most active among disubstituted derivatives is (3*S*,8*R*)-isomer **61** [58].

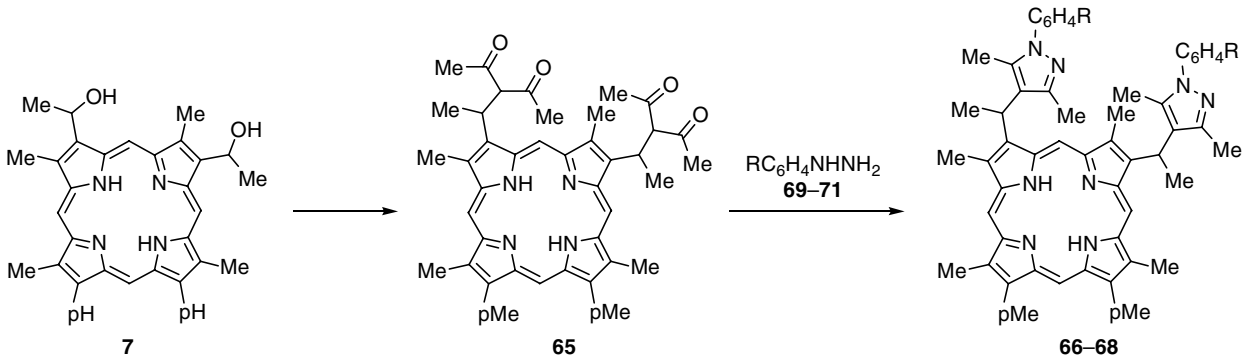
The 3- and 8-[1-hydroxy(alkoxy)ethyl] groups in porphyrins are capable of reacting with various nucleophiles to give the corresponding replacement products due to influence of the tetrapyrrole macroring which activates pseudobenzylic positions in the peripheral substituents. Various products can be obtained, depending on the activation method and nucleophile nature [20, 21, 36, 60–62]. For example, treatment of 8-(1-hydroxyethyl)benzoporphyrin **62** with trifluoromethanesulfonic acid gives a mixture of *cis*- and *trans*-bis-benzoporphyrins **63** and **64** in more than 40% yield [57] (Scheme 9). An alternative method of activation of 3- and 8-(1-hydroxyethyl) groups makes use of a $Zn(OAc)_2 \cdot 2H_2O$–nucleophile system [60, 61, 63]. Bis-acetylacetonate derivative **65** was obtained in a high yield by heating hematoporphyrin IX (**7**) with acetylacetone in the presence of $Zn(OAc)_2 \cdot 2H_2O$, followed by esterification with $H_2SO_4$–MeOH [61]. Further transformations involving the acetylacetone moieties in **65** were described in [60, 63–65]. Condensation of **65** with substituted phenylhydrazines **69–71** gave pyrazole derivatives **66–68** (Scheme 10), thus demonstrating the possibility of using acetylacetonate porphyrin derivatives as synthons [64, 65]. Some products of modification of the acetylacetone moiety showed a high photodynamic activity [66–69].

1-Hydroxyethyl groups in positions *3* and *8* of the porphyrin macroring are readily oxidized to acetyl; depending on the oxidizing system, partial or complete oxidation is achieved. The system $Pr_4NRuO_4$–4-meth-

ylmorpholine *N*-oxide oxidizes both hydroxy groups in porphyrin **72** in a high yield [70]; in reactions with less active $MnO_2$, monoacetyl derivatives **73** and **74** were mainly formed (yield 67%), while the fraction of diacetylporphyrin **75** was insignificant [62] (Scheme 11). By treatment with $NaBH_4$ the acetyl groups can be reduced to hydroxyethyl in a nonstereoselective fashion [9, 57, 62, 71]. Asymmetric reduction of diacetyl derivative **75** with $BH_3 \cdot Me_2S$ in the presence of chiral methyloxazaborolidines ensured enantioselective preparation of hematoporphyrin IX dimethyl ester stereoisomers **72** [72].

Classical nucleophilic addition reactions of acetyl groups in porphyrins were discussed in detail in

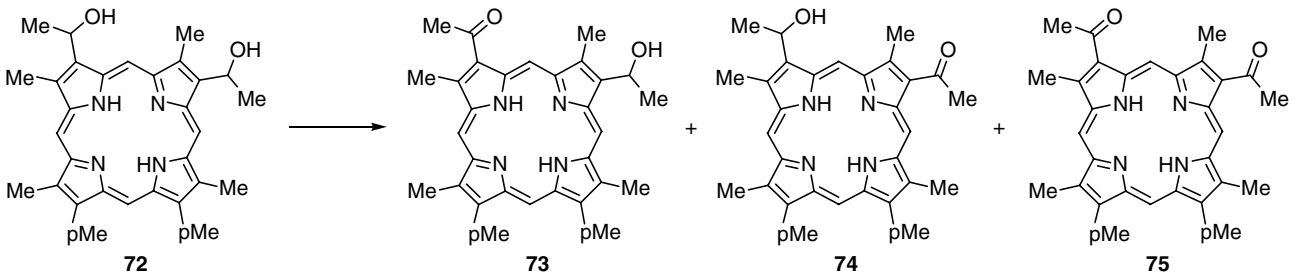
**Scheme 10.**




7 65 66–68

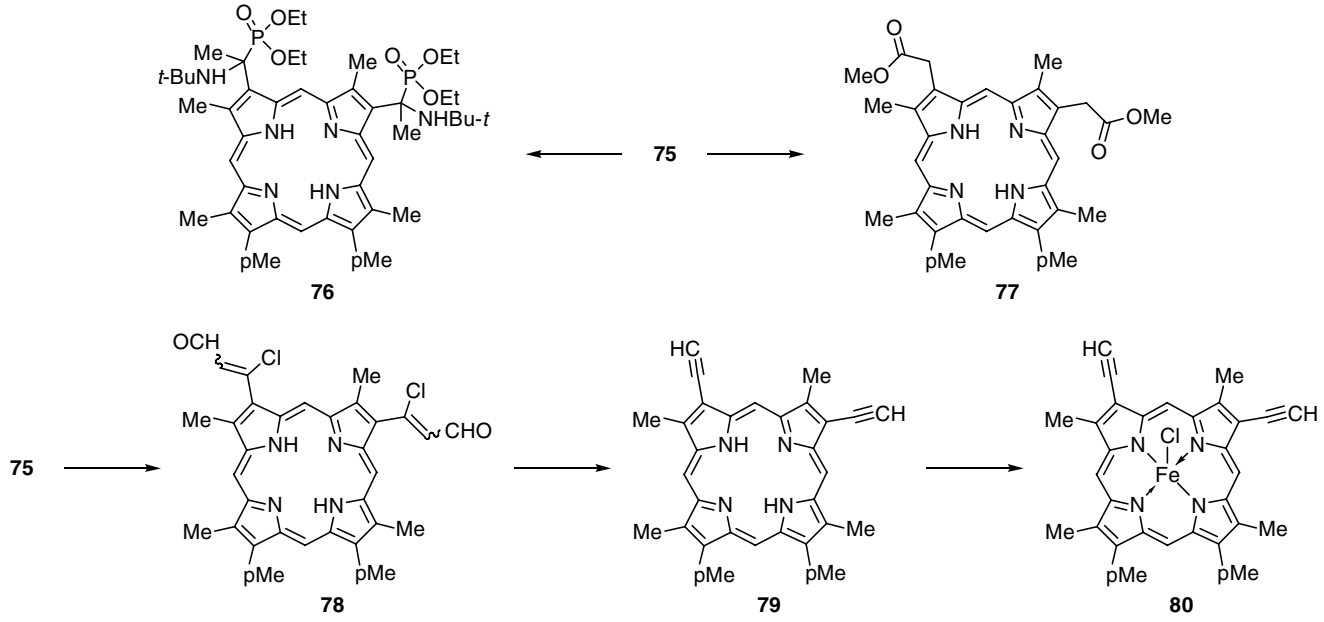
**66**, **69**, R = H; **67**, **70**, R = *p*-Me; **68**, **71**, R = *o*-Br.

**Scheme 11.**



72 73 74 75

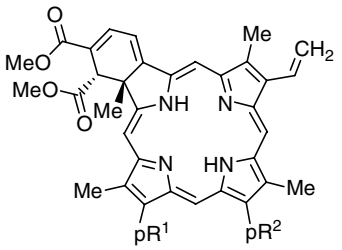
**Scheme 12.**



76 77 78 79 80

reviews [9, 33]. Kabachnik et al. recently reported on the reaction of diacetylporphyrin **75** with $(EtO)_2P(O)H$–*t*-$BuNH_2$ under conditions of microwave activation, which led to the formation of α-aminophosphonate **76** in a high yield [73, 74] (Scheme 12). Treatment of **75** with $Tl(NO_3)_3 \cdot 3H_2O$–MeOH in the presence of concentrated nitric acid involved oxidative rearrangement of the acetyl groups into methoxycarbonyl substituents to give tetraester **77** [75]. Diacetylporphyrin **75** reacted with $POCl_3$–DMF (Vilsmeier reaction), yielding dichloride **78**, and treatment of the latter with KOH in MeOH resulted in the formation of protoporphyrin IX analog **79** containing acetylenic groups instead of vinyl. Compound **79** was converted into hemin (**80**) by the action of $FeCl_2$ [76].

**3.1.4. Electrocyclic reactions involving vinyl groups.** Molecules of some protoporphyrin IX derivatives contain diene fragments formed by peripheral vinyl groups and double bonds in the macroring; such compounds are capable of reacting with C- [9, 57], N- [77], O- [58, 65, 78–83], and other dienophiles to give cycloaddition products. The ability of porphyrin **18** to effectively react with electron-deficient alkenes and alkynes is well known [9, 36, 84]. From the practical viewpoint, the most important is the reaction with dimethyl acetylenedicarboxylate; this reaction is the key step in the synthesis of Visudyne (**81**, **82**) [20, 22–24, 85], an efficient drug for the photodynamic treatment of eye diseases. Compounds **84–87** containing heterocyclic substituents were obtained by reaction of porphyrin **18** with azo compounds **83** as dienophiles



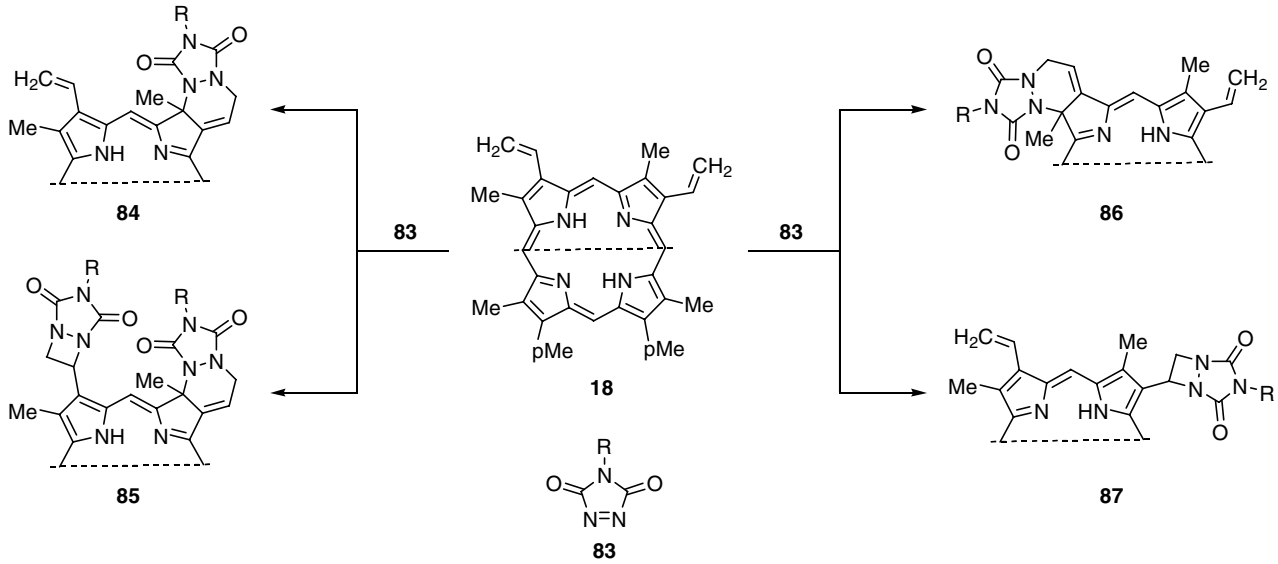
**81**, **82**

**81**, $R^1$ = Me, $R^2$ = H; **82**, $R^1$ = H, $R^2$ = Me.

(Scheme 13). The transformation involves concurrent [4+2]- and [2+2]-cycloaddition processes [77]. The reaction of divinylporphyrin **18** with singlet oxygen is a classical transformation in the chemistry of protoporphyrin IX [9]. Monovinylporphyrins also react with singlet oxygen [65, 78, 79, 81, 83]. Porphyrins **88–91** give rise to photoprotoporphyrins **92–95** [65, 83] (Scheme 14). Presumably, the reaction involves intermediate formation of *endo*-peroxides **96–99** which instantaneously rearrange into stable products **92–95** (the photoprotoporphyrin fragment is shown in Scheme 14 in boldface mode) [65, 83]. Grandadam et al. [78] showed that a chlorin-type photosensitizer is highly effective for the inactivation of human immunodeficiency viruses (HIV-1). Kygova et al. [86] demonstrated high immunosuppressive activity of photooxidation products of protoporphyrin IX dimethyl ester *in vivo*.

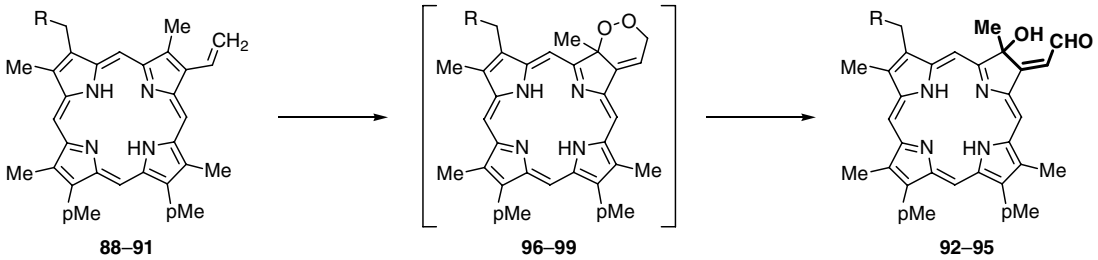
The reaction of divinylporphyrin **18** with diazomethane gives a mixture of pyrazolylporphyrins **100–**

**Scheme 13.**



**83–87**, R = Me, Et, *t*-Bu, Ph, $NH_2$.

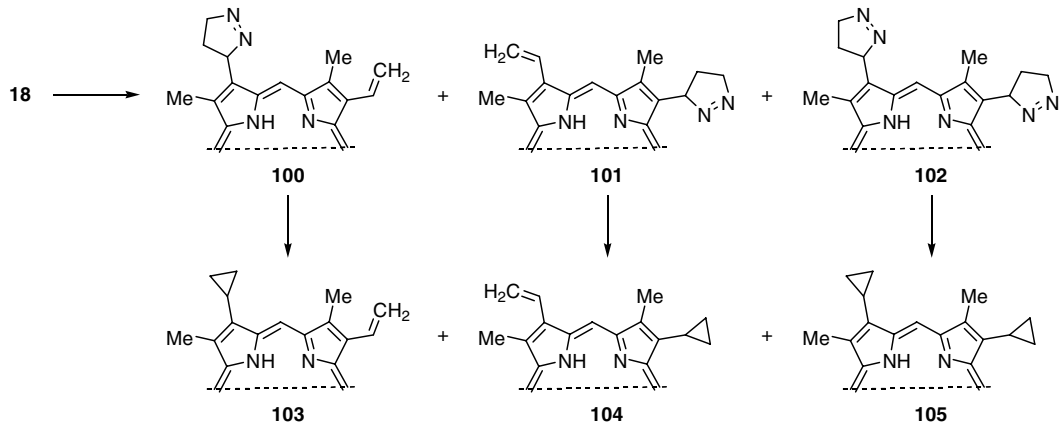
**Scheme 14.**



**88–91** **96–99** **92–95**

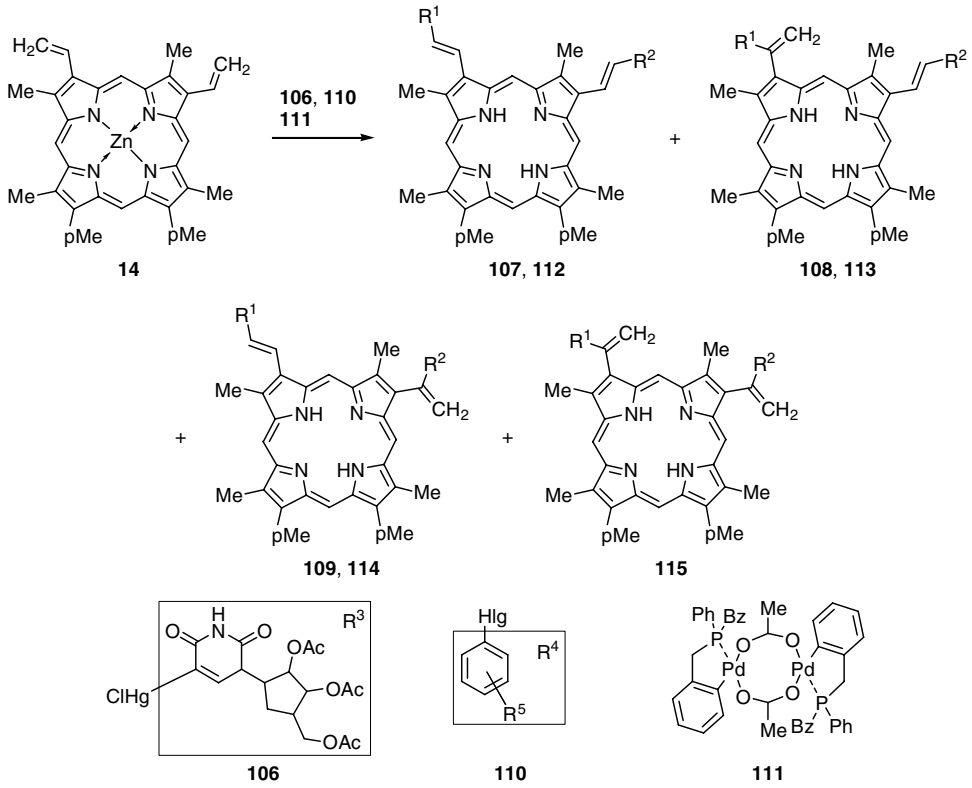
**88**, **92**, **96**, R = OH; **89**, **93**, **97**, R = OAc; **90**, **94**, **98**, R = acac; **91**, **95**, **99**, R = Ht.

**Scheme 15.**



**100** **101** **102** **103** **104** **105**

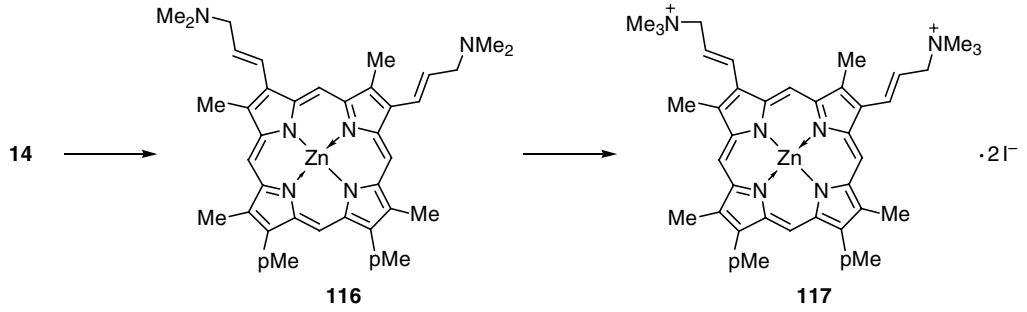
**Scheme 16.**



**14** **107**, **112** **108**, **113** **109**, **114** **115** **106** **110** **111**

**107–109**, $R^1 = R^2 = R^3$; **112–115**, $R^1 = R^2 = R^4$; **110**, Hlg = Br, I, $R^5$ = H, CHO, AlkO.

**Scheme 17.**




**102** in a good overall yield [87, 88], and irradiation of the latter with long-wave (λ 550–650 nm) light leads to cyclopropyl derivatives **103–105** [87] (Scheme 15). The use of pyrazolylporphyrins as photosensitizers for effective binding of substrates in selective photodynamic therapy was covered by patent [89]. The reaction of vinylporphyrins with ethyl diazoacetate to form cyclopropyl derivatives was used by Fischer and Medick [90] to prove the presence of vinyl groups.

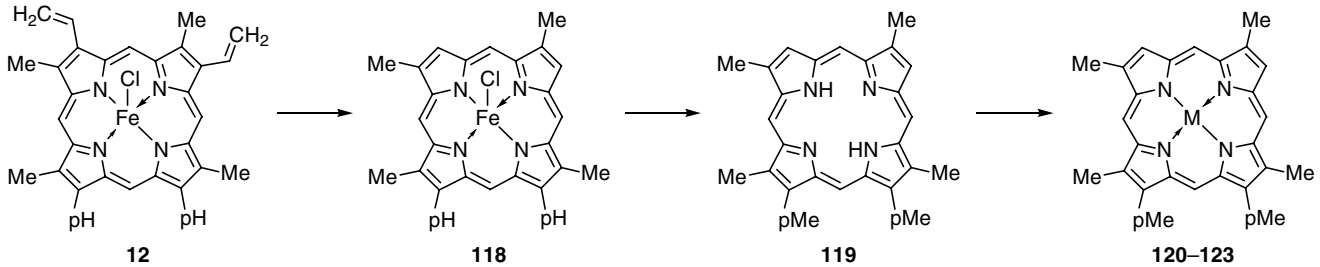
**3.1.5. Substitution at vinyl groups.** Heck reaction of protoporphyrin IX derivatives allows preparation of functionalized olefin derivatives [36, 91–93]. The reaction of zinc complex **14** with modified nucleoside **106** in the presence of $LiPdCl_3$, followed by demetalation, afforded a mixture of bis-*trans*, 3-*gem*-8-*trans*, and 8-*gem*-3-*trans* isomers **107–109** in an acceptable yield, while no bis-*gem* isomers were detected [92] (Scheme 16). Study of the reaction of zinc complex **14** with aryl halides **110** [93] showed that the use of palladium catalyst **111** improves the yield of arylvinylidene derivatives **112–115**; the reaction was nonstereoselective, and isomers **112–115** were difficult to separate. Stereoselective substitution at the vinyl groups of protoporphyrin IX and its metal complexes readily occurs by the action of Eschenmoser's salt ($H_2C{=}NMe_2^+\,I^-$) [94]. Treatment of **14** with $H_2C{=}NMe_2^+\,I^-$ gave bis-*trans*-dimethylaminomethyl derivative **116** with high stereo-selectivity; the subsequent reaction with methyl iodide led to water-soluble ammonium salt **117** in 100% yield (Scheme 17). Cationic porphyrin **117** was shown to effectively bind and cleave DNA in the presence of light [94].

Terminal protons in the vinyl groups of porphyrin metal complexes are replaced by formyl groups under the Vilsmeier reaction conditions ($POCl_3$–DMF) to give acrolein derivatives [9]. Prolonged heating of protoporphyrin IX with *p*-$MeC_6H_4SO_3D$ and $D_2O$ in 1,2-dichlorobenzene resulted in ~90% replacement of the terminal methylene protons by deuterium [9].

**3.1.6. Elimination of vinyl groups.** Vinylporphyrins readily lose vinyl groups on heating in fused resorcinol [9, 33]. Protohemin IX (**12**) is thus converted into deuterohemin IX (**118**) [9, 33]. The mechanism of this transformation was discussed in detail in [9]. Devinylation is an important reaction in the chemistry of protoporphyrin IX, for it makes the 3- and 8-positions in the macroring vacant, thus enabling electrophilic substitution reactions with various reagents [9, 95]. Additional synthetic approaches become possible via transformation of iron(III) complex **118** into the free base (metal-free porphyrin) **119** and then into a series of metal complexes, e.g., **120–123** (Scheme 18).

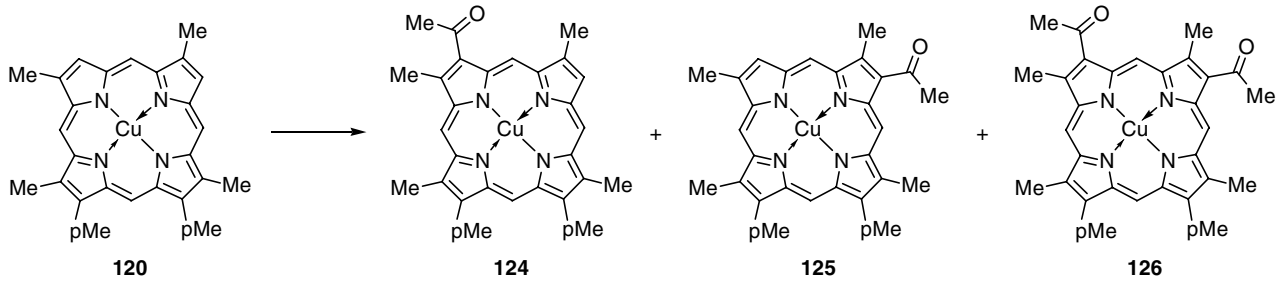
In some cases [9, 96], variation of the reaction conditions ensures controlled preparation of mono- and disubstituted products. For example, treatment of copper complex **120** with acetic anhydride–$SnCl_4$ for

**Scheme 18.**

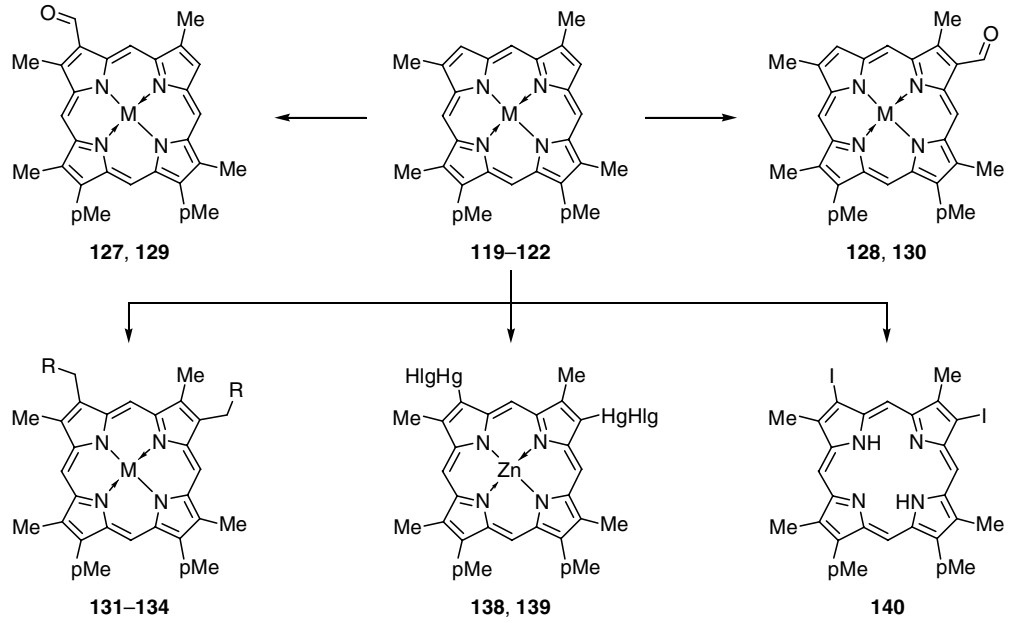



**120**, M = Cu(II); **121**, M = Pt(II); **122**, M = Zn; **123**, M = Ni(II).

**Scheme 19.**

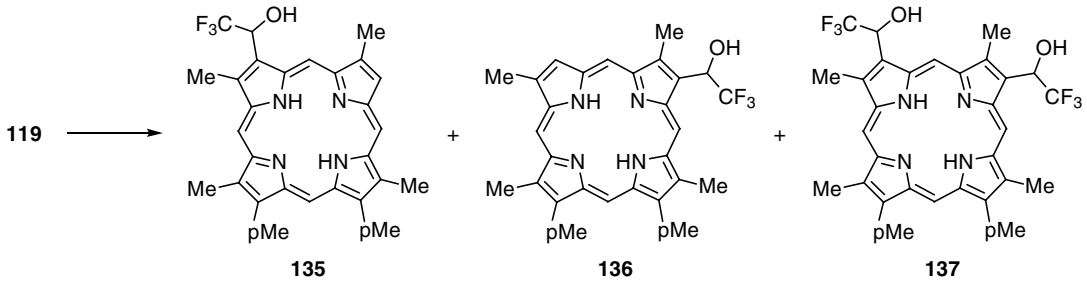



**Scheme 20.**




**119**, **129**, **130**, M = 2H; **120**, M = Cu(II); **121**, M = Pt(II); **122**, M = Zn; **123**, M = Ni(II); **127**, **128**, M = Pt(II); **131**, M = 2H, R = $Me_2N$; **132**, M = Zn, R = $Me_2N$; **133**, M = 2H, R = $Me_3N^+I^-$; **134**, M = Zn, R = $Me_3N^+I^-$; **138**, Hlg = Cl; **139**, Hlg = Br.

**Scheme 21.**




a short time (a few seconds), followed by HPLC separation, gives individual monoacetyl derivatives **124** and **125** in a high yield; considerable extension of the reaction time leads to predominant formation of diacetylporphyrin **126** [9] (Scheme 19). Monoacetylporphyrins **124** and **125** were intermediate products in classical syntheses of some important natural porphyrins [9].

Analysis of the classical data on the formylation of porphyrin metal complexes [97] shows that the reaction occurs at both *meso*- and 3- and/or 8-positions (provided that these positions are vacant). By contrast, Rumyantseva et al. [98] recently reported on the Vilsmeier formylation of Pt(II) complex **121** only at positions *3* and *8* with formation of monoformyl derivatives **127** and **128** (Scheme 20). High regio-

selectivity in the formylation of 3(8)-unsubstituted deuteroporphyrin IX copper complexes with a system $HC(OMe)_3$–Lewis acid was demonstrated in [99, 100]. Thus, copper complex **120** was treated with the system $HC(OMe)_3$–$SnCl_4$, and subsequent demetalation and chromatographic separation gave pure porphyrins **129** and **130** in 46 and 47% yield, respectively [100].

Porphyrin **119** was converted into 3,8-bis-dimethylaminomethyl derivative **131** by reaction with dimethyl(methylidene)ammonium iodide. Analogous reaction with electron-donor Zn complex **122** gave the corresponding dimethylaminomethyl derivative **132** in a higher yield than in the reaction with free base **119**. Quaternization of dimethylaminomethyl derivatives **131** and **132** with methyl iodide leads to ammonium salts **133** and **134** which are capable of effectively binding DNA [94]. Ando and Kumadaki [58] used the system $CF_3CHO$–$AlCl_3$ to introduce $CF_3CH(OH)$ groups into positions *3* and *8* of deuteroporphyrin **119**; as a result, mono- and disubstituted products **135**–**137** were obtained in 27, 23, and 8% yield, respectively (Scheme 21).

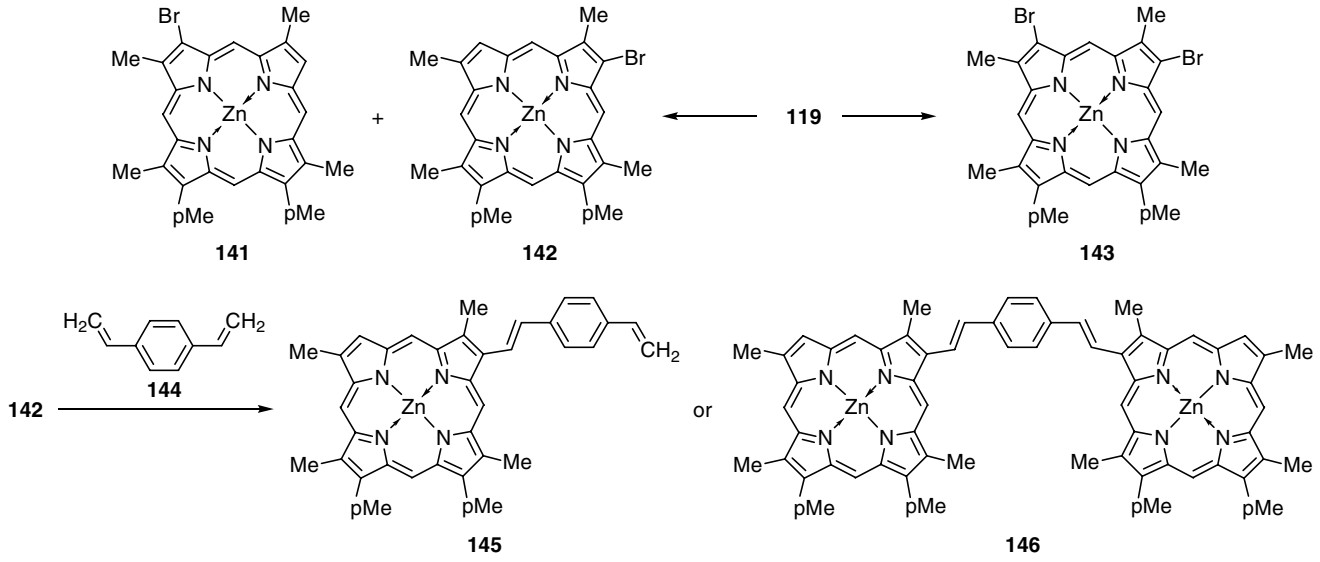
Organomercury deuteroporphyrin IX derivatives **138** and **139** were synthesized in a high yield by heating zinc complex **122** with mercury(II) acetate in MeOH–THF, followed by treatment with a saturated solution of NaCl or NaBr; compounds **138** and **139** are valuable synthons in the Heck reaction [9, 36, 101, 102]. 3,8-Diiodoporphyrin **140** [84, 102, 103] attracts strong interest as substrate for palladium-catalyzed reactions with protoporphyrin IX derivatives; it can be prepared in more than 90% yield from deuteroporphyrin IX (**119**) by iodination with $I_2$ in the presence of $K_2CO_3$ [103]. The formation of mono- and dibromo derivatives in the reaction of deuteroporphyrin IX **119** with *N*-bromosuccinimide in an inert solvent may be controlled by varying the reactant ratio; the products are quantitatively converted into zinc complexes **141**–**143** [96] as substrates for Pd-catalyzed reactions [96, 101, 104] (Scheme 22).

An elegant synthesis of di- and trimeric porphyrins via Heck reaction using the system $Pd(OAc)_2$–LiCl–$K_2CO_3$–$Bu_4NBr$ was proposed in [96]. The reaction of bromoporphyrin **142** with excess 1,4-divinylbenzene **144** gave 67% of *trans*-vinylstyryl derivative **145**, while in the presence of excess porphyrin **142** 73% of dimer **146** and 22% of **145** were formed (Scheme 22). An analogous approach may be used to synthesize trimeric porphyrins. For instance, ensemble **147** consisting of three porphyrin macrorings linked through 1,4-divinylbenzene moieties was obtained in 83% yield with high regioselectivity by reaction of **145** with dibromoporphyrin **143** at a ratio of 2.11. Finally, the reaction of 3 equiv of monobromo derivative **142** with 1,3,5-trivinylbenzene **148** gave 56% of trimer **149** [96] (Scheme 23).

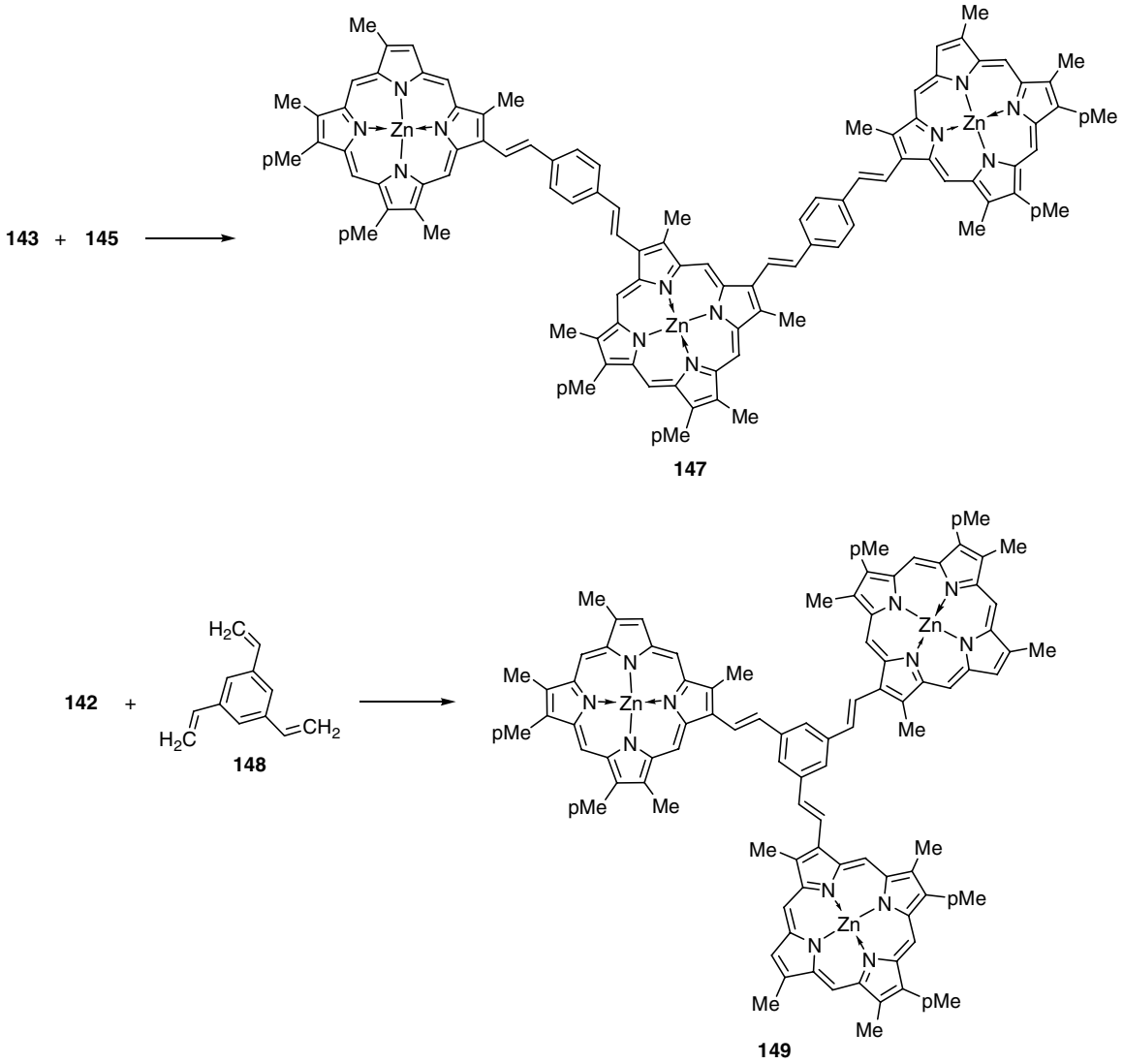
A detailed analysis of prospects in using Pd-catalyzed reactions for functionalization of natural porphyrins was given in [58, 101].

**3.1.7. Olefin metathesis.** In 2004 Liu et al. [105] were the first to demonstrate the possibility of using protoporphyrin IX derivatives in metathesis of olefins

**Scheme 22.**

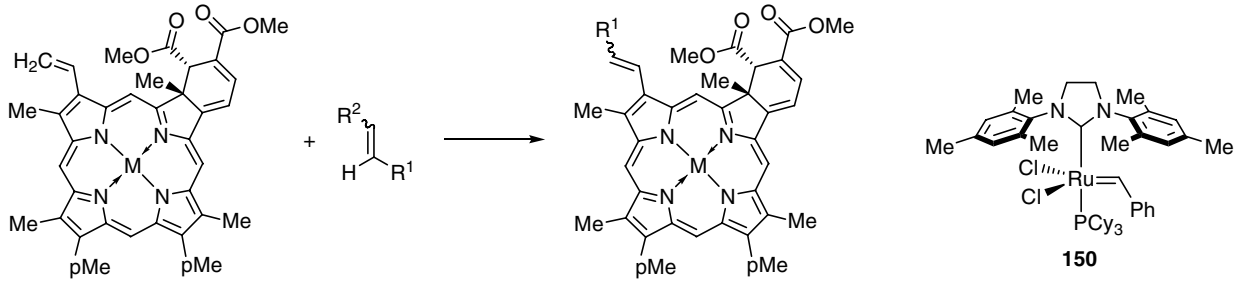


**Scheme 23.**




catalyzed by ruthenium complex **150** [105]. By reactions of benzoporphyrins **151** and **152** with alkenes **153** olefinic derivatives **154** and **155**, respectively, were obtained in high yields (Scheme 24). Electron-donor zinc complex **152** reacted more readily than free base **151**. In all cases, the process was characterized by high *E*-stereoselectivity, presumably due to steric effect of the tetrapyrrole macroring [105].

**Scheme 24.**




**151**, **154**, M = 2H; **152**, **155**, M = Zn; **153**, $R^1$ = Alk, $R^2$ = H or $R^1$ = $R^2$ = Alk; **154**, **155**, $R^1$ = Alk.

### *3.2. Modification of Formyl Groups*

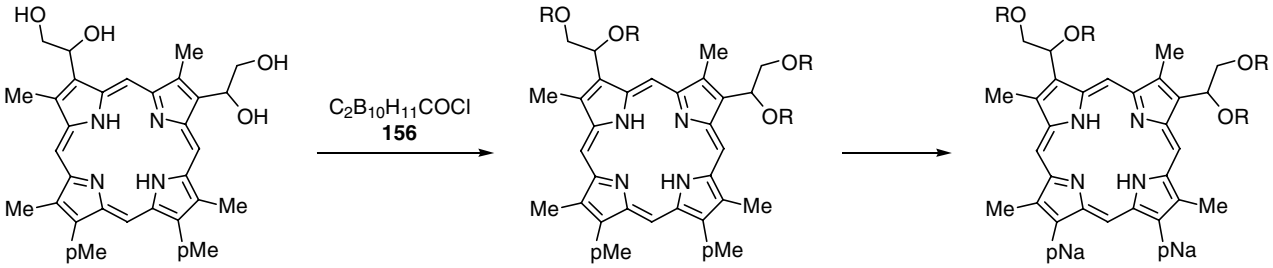
Protoporphyrin IX (**1**) molecule has no formyl group, but such group is present in its closest analogs, e.g., chlorocruoroporphyrin (**2**), cryptoporphyrin *a* (**6**) and different hemes [1]. The data discussed in the preceding section indicate that the vinyl groups in protoporphyrin IX (**1**) can readily be transformed into formyl moieties as characteristic functionalities of fundamental natural porphyrins. Therefore, the present section considers methods for modification of formyl groups in protoporphyrin IX derivatives.

**3.2.1. Reduction.** The formyl groups in protoporphyrin IX derivatives are reduced to hydroxymethyl by the action of $NaBH_4$ [33, 79, 82, 83, 106]; they are converted into methyl substituents under the Wolff–Kishner reaction conditions [9]. Procedures for further modification of hydroxy groups in protoporphyrin IX derivatives were developed [21, 33, 47, 51, 62, 65, 79, 82, 83, 106] (see also Section 3.1.2).

From the practical viewpoint, introduction of carborane moieties (as a source of boron atoms for boron neutron capture therapy) via acylation of hydroxy groups in protoporphyrin IX derivatives with carboranyl chlorides [22, 26, 62, 107] attracted interest. The reaction of bis-diol **21** with chloride **156** in the presence of 4-dimethylaminopyridine gave tetraester **157** containing 4 carborane fragments [22] (Scheme 25). Analogous reaction with bis-*p*-carboranyl acid chloride led to the formation of a porphyrin cluster containing eight carborane cages [107]. Tetraester **157** is a synthetic precursor of effective photosensitizer **158** (BOPP) which used in photodynamic therapy of cancer and is believed to be a potential agent for boron neutron capture therapy of brain tumors [22, 26, 108]. The ability of BOPP to accumulate in tumor cells was demonstrated by experiments *in vivo* (the ratio brain tumor–surrounding intact tissue exceeded 400:1) [26].

In some cases, modification of hydroxy groups leads to unexpected results. Attempts to obtain methanesulfonate derivative **159** by reaction of photoprotoporphyrin **160** with $MeSO_2Cl$ were unsuccessful; the product was 3-(1-chloro-2-oxoethyl)porphyrin **161** [79] (Scheme 26). The reduction of photoprotoporphyrin **163** gave diol **162** whose treatment with $H_5IO_6$ promoted a series of rearrangements leading to formylporphyrin **19** [82].

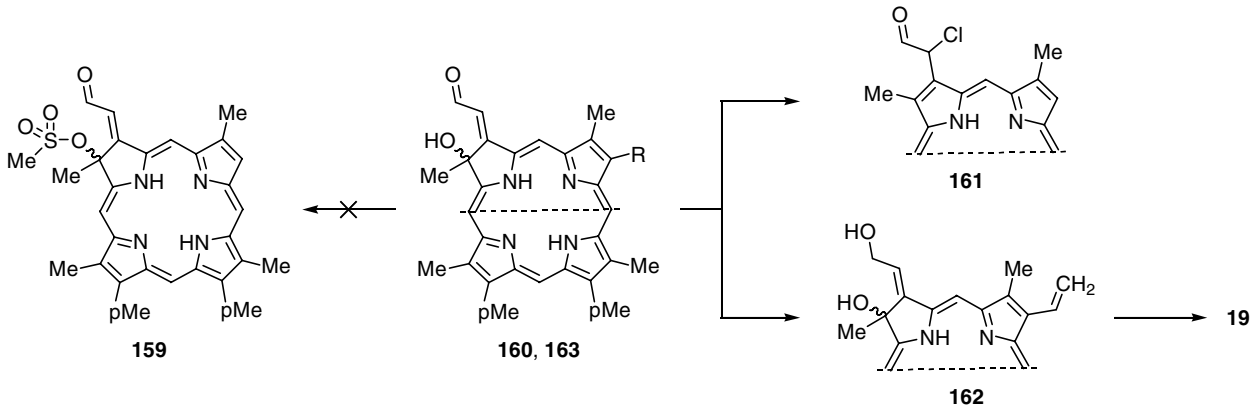
**Scheme 25.**




**21** **157** **158**

R = $C_2B_{10}H_{11}C(O)$.

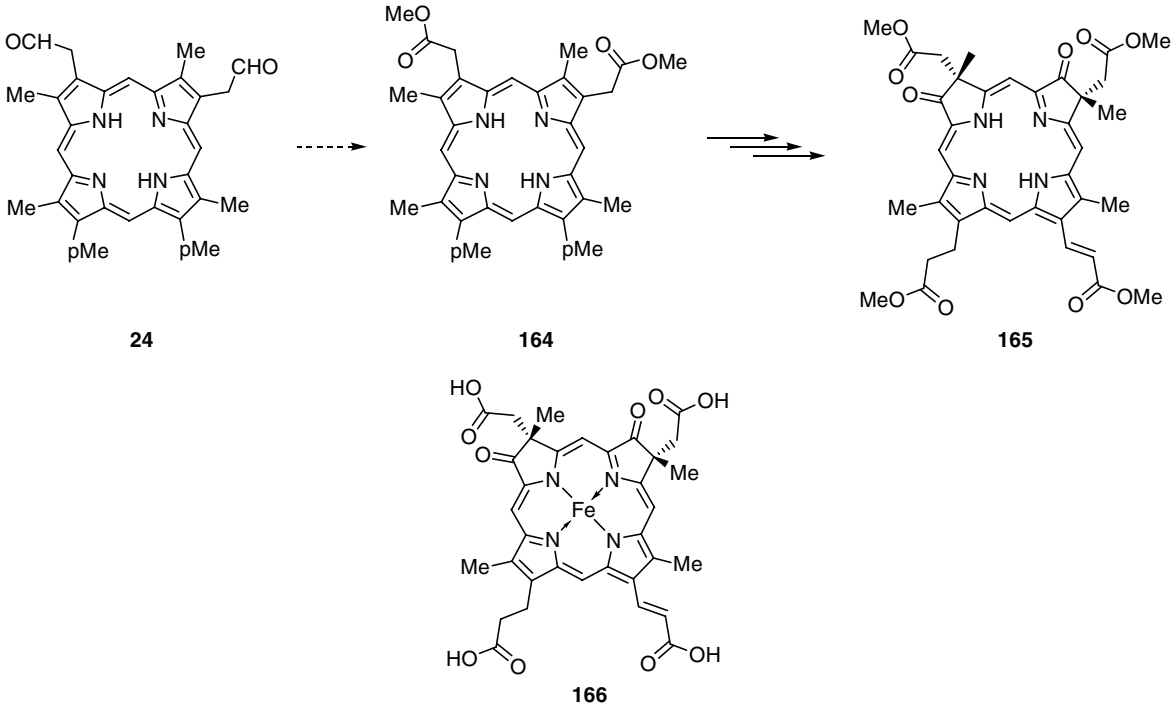
**Scheme 26.**




**159** **160**, **163** **161** **162**

**160**, R = H; **163**, R = $CH_2$=CH.

**Scheme 27.**



**24** **164** **165** **166**

**3.2.2. Oxidation.** The aldehyde moiety in protoporphyrin IX derivatives can be converted into carboxy group via oxidation with $CrO_3$ in $Me_2CO$ [2, 33] or with atmospheric oxygen in the presence of HI [33]. The oxidation of diformylporphyrin **24** according to Jones, followed by esterification, was performed to introduce acetic acid residues into the 3- and 8-positions of protoporphyrin IX. The resulting tetraester **164** is the key intermediate in the synthesis of porphyrin $d_1$ tetramethyl ester (**165**) (Scheme 27). The corresponding tetracarboxylic acid is the ligand in heme $d_1$ (**166**) which plays an important role in the metabolism of sulfur and nitrogen in various organisms [2].

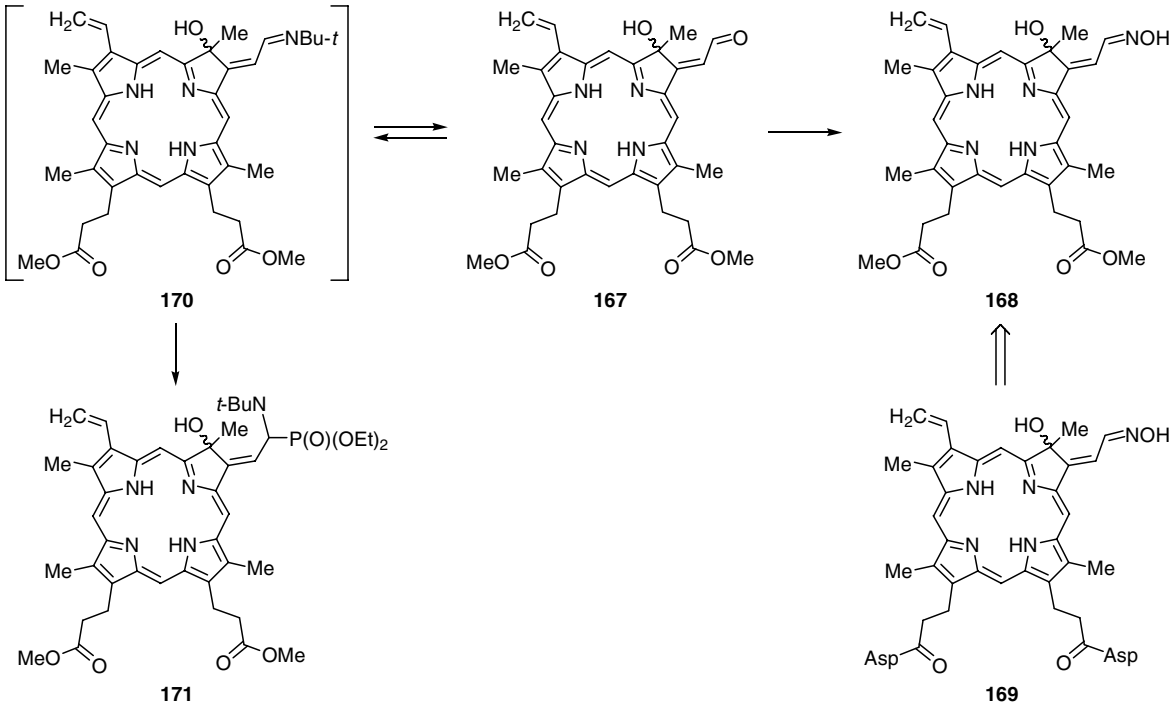
**3.2.3. Nucleophilic addition to formyl groups.** Formyl groups in protoporphyrin IX derivatives readily react with various nucleophiles. In this section, nucleophilic addition reactions leading to formation of multiple bonds and those not involving formation of multiple bonds are considered.

*3.2.3.1. Synthesis of imino derivatives.* Heating of formylporphyrins with hydroxylamine hydrochloride or hydroxylamine ethers give the corresponding oximes in high yields [9, 33, 106, 109, 110]. Isophotoprotoporphyrin **167** is thus converted into oxime **168** [110] which is the key intermediate in the synthesis of ATX-S10 (**169**) used for sonodynamic therapy of cancer [111] (Scheme 28). Formylporphyrins also undergo other transformations typical of common aldehydes [33, 82, 112]. By heating of formyl derivative **167** with *tert*-butylamine unstable Schiff base **170** was obtained [82].

Modification of formyl derivatives of protoporphyrin IX was studied with a view to integrate photodynamic capabilities of tetrapyrroles with pharmacophoric potential of an α-aminophosphonate fragment [74, 82]. Unlike common α-aminophosphonates, syntheses involving natural porphyrins and the model system $(EtO)_2P(O)H$–*t*-$BuNH_2$ may be effected only under conditions of microwave activation, especially in combination with catalysis by $CdI_2$ [82]. Formylporphyrin **167** was thus regioselectively converted into aminophosphonate **171** in 85% yield [82]. This transformation is the first example of microwave-assisted modification of porphyrin structures.

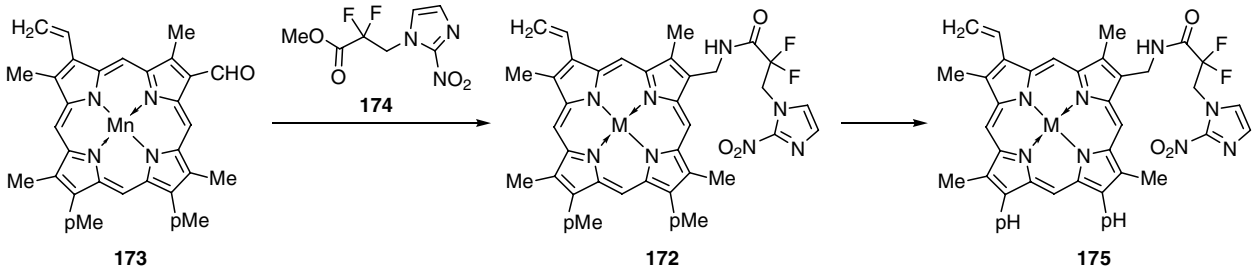
The well known radiosensitizing effect of nitroimidazoles stimulated studies aimed at combining nitroimidazole and porphyrin fragments in a single molecule [109]. Nitroimidazolyl-containing porphyrin manganese(III) complex **172** was successfully synthesized by condensation of oxime **173** with contrast agent **174** in MeOH in the presence of triethylamine [109] (Scheme 29). Dicarboxylic acid **175** was shown by experiments *in vivo* to be promising reagent for cancer diagnostics and therapy [22, 109].

**Scheme 28.**



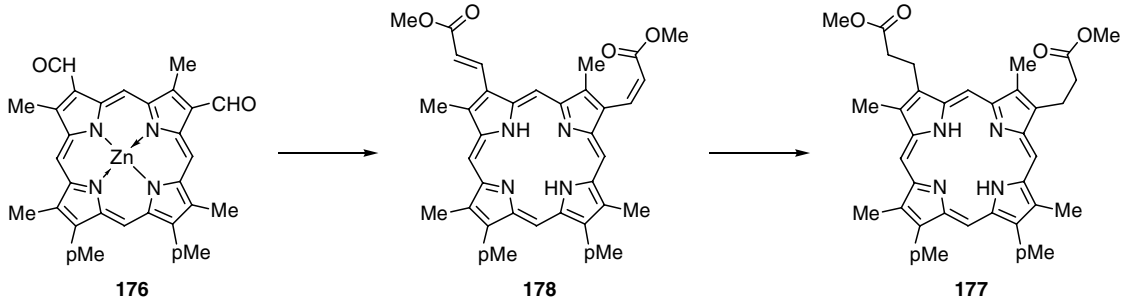

**169**, Asp = $HOCOCH_2CH(COOH)NH$.

**Scheme 29.**




**172**, **175**, M = Mn(III).

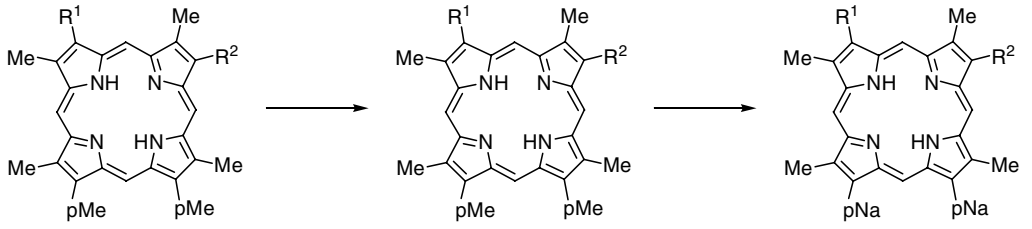
**Scheme 30.**




*3.2.3.2. Synthesis of vinyl derivatives.* The Wittig reaction was used most frequently to convert formyl groups in protoporphyrin IX derivatives into ethylidene moiety [9, 43, 44, 58, 100, 113–115]. Some classical syntheses also involved the Knoevenagel reaction [9, 33]. Protoporphyrins labeled with $^{13}C$ were synthesized by the Wittig reaction with $Ph_3P=^{13}CH_2$ [43, 44]. The condensation of diformylporphyrin **176** with $Ph_3P=CHCO_2CH_3$ was the key stage in a practical synthesis of coproporphyrin III tetramethyl ester (**177**)

[44] (Scheme 30). Acrylate **178** obtained by the Wittig reaction in 96% yield was reduced with hydrogen over Pd/C and then treated with diazomethane; the yield of tetraester **177** was 80% [44]. A convenient procedure for the synthesis of fluoro-substituted protoporphyrin IX derivatives is based on reactions with fluorinated phosphorane generated *in situ* [58, 115, 116]. Fluorine-containing porphyrins **179–181** were synthesized in good yields by heating formylporphyrins **19**, **20**, and **22** with triphenylphosphine and sodium dichlorofluoroacetate in *N*-methylpyrrolidin-2-one [58] (Scheme 31). It was proposed to use porphyrine **181** as starting material in the preparation of difluorovinyl analog of protohemin IX (**12**) [117]. *In vitro* assays of

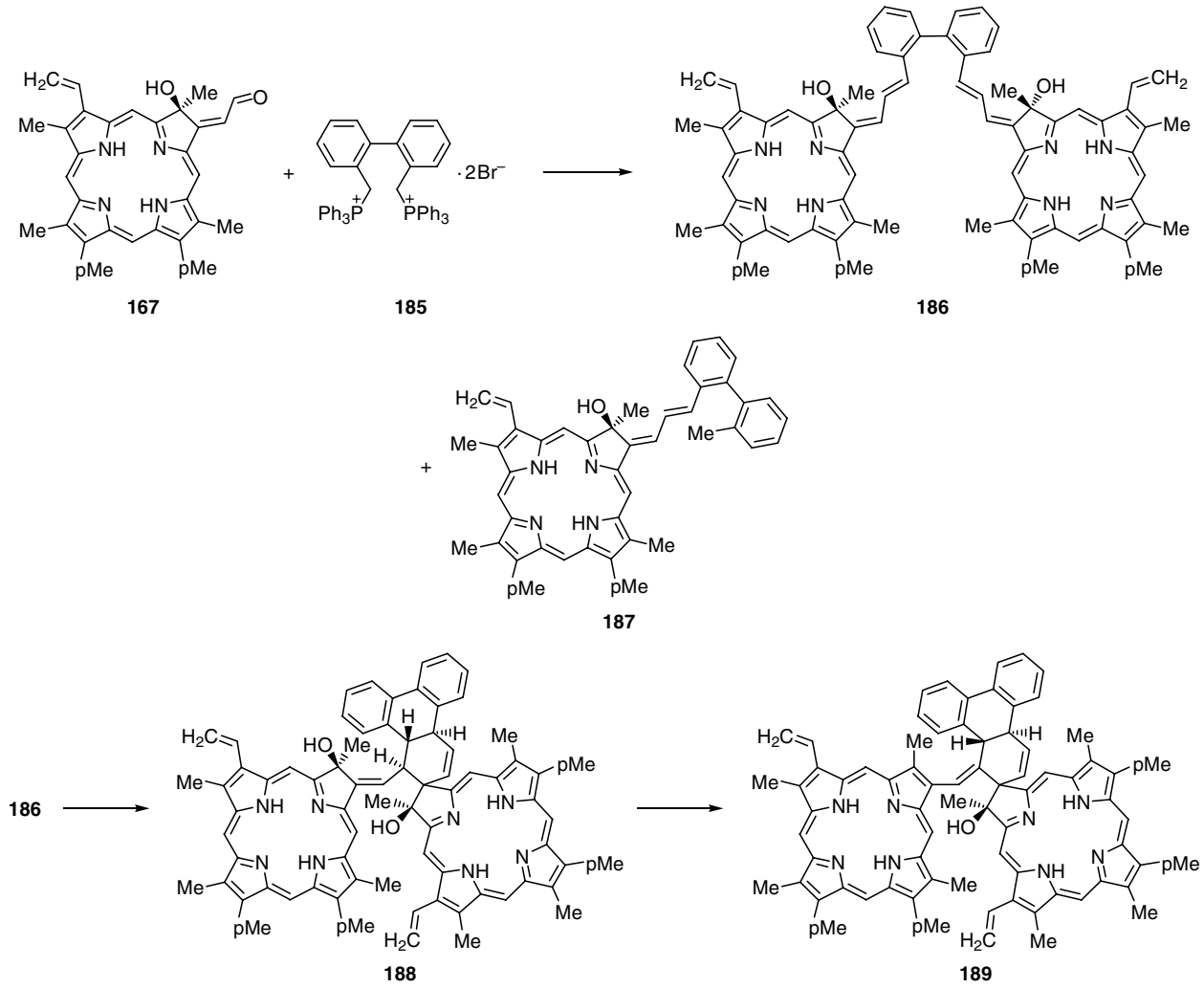
**Scheme 31.**



**19**, **20**, **22** — **179–181** — **182–184**

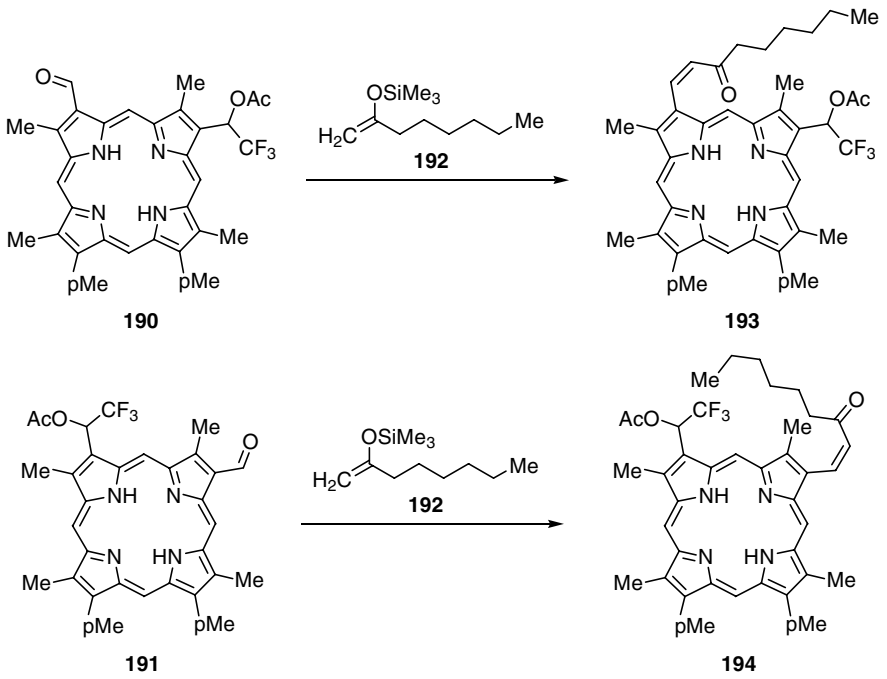
**19**, $R^1$ = CHO, $R^2$ = $CH_2$=CH; **20**, $R^1$ = $CH_2$=CH, $R^2$ = CHO; **22**, $R^1$ = $R^2$ = CHO; **179**, **182**, $R^1$ = $CF_2$=CH, $R^2$ = $CH_2$=CH; **180**, **183**, $R^1$ = $CH_2$=CH, $R^2$ = $CF_2$=CH; **181**, **184**, $R^1$ = $R^2$ = $CF_2$=CH.

**Scheme 32.**



**167** — **185** — **186** — **187** — **188** — **189**

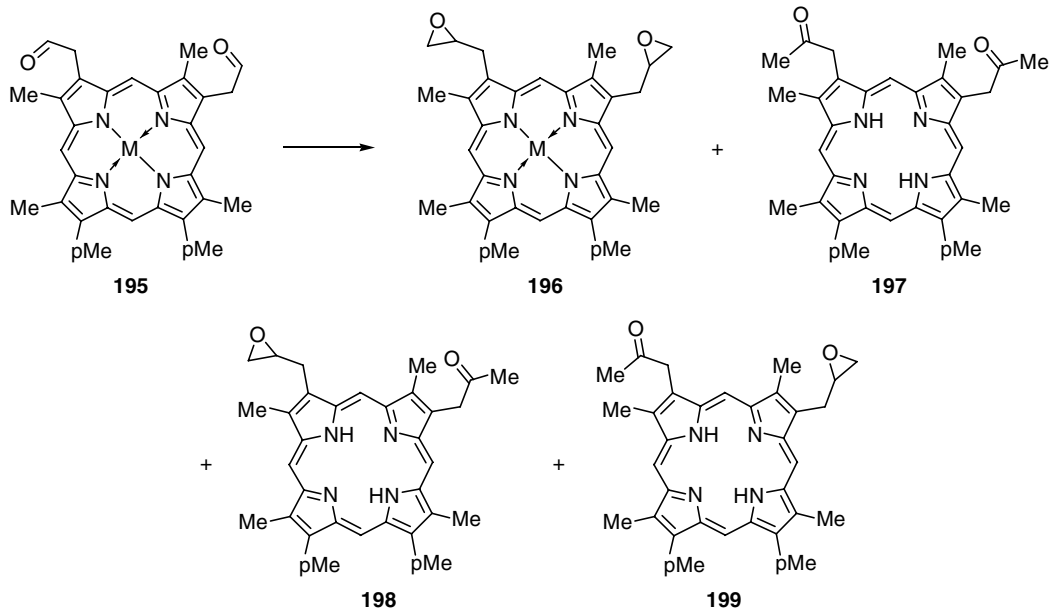
**Scheme 33.**



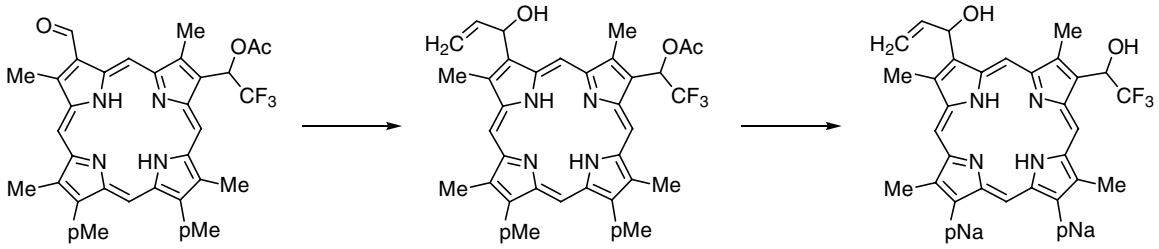

disodium salts **182–184** derived from compounds **179–181** showed that 8-substituted derivative **183** accumulates mainly in stomach tumor cells, and 3,8-disubstituted compound **184**, in hepatoma cells, while 3-substituted analog **182** turned out to be weakly active [58].

A spirochlorin–chlorin dimer as potential model for the "special pair" of the photosynthetic reaction center was obtained via reaction of chlorin **167** with diphosphonium salt **185** [113, 114]. In the presence of DBU, bis- and monochlorin derivatives **186** and **187** were formed in 60 and 20% yield; prolonged reaction (24 h) resulted in the transformation of bis-chlorin **186** into spirochlorin–chlorin dimer **188** (Scheme 32). The mechanism of formation of dimer **188** is likely to include intramolecular Diels–Alder reaction involving the double bond system between the chlorin fragments in initial dimer **186** [114]. Dimer **188** was converted into porphyrin–spirochlorin derivative **189** on storing

**Scheme 34.**



**Scheme 35.**




**190** **200** **201**

in $CDCl_3$ solution [113, 114]. Presumably, the process is promoted by traces of an acid present in $CDCl_3$; protonation of the hydroxy group gives readily departing oxonium moiety whose elimination leads to thermodynamically more stable porphyrin structure.

An alternative method for the synthesis of vinyl derivatives from formylporphyrins is based on the use of silyl enol ethers. Formylporphyrins **190** and **191** reacted with silyl ether **192** in the presence of $TiCl_4$ to give vinyl derivatives **193** and **194**, respectively, in good yields [99] (Scheme 33).

*3.2.3.3. Nucleophilic addition to formyl groups without formation of multiple bonds.* Formylporphyrins are readily converted into the corresponding acetals [33, 41, 42] and sodium hydrogen sulfite derivatives [33]. To introduce a labile epoxy group into protoporphyrin IX derivatives, reactions of various formylporphyrins with sulfur ylides were studied. Only zinc complex **195** gave rise to bis-epoxy derivative **196**, but in a poor yield (9%) [44] (Scheme 34). According to the data of classical study [33], diazomethane is an efficient reagent for introduction of an epoxy group as peripheral substituent. As shown in [44], the product structure can be determined with a sufficient reliability only in the reaction with formylmethyl derivative **195**. The target diepoxide **196** was formed in a small amount, while the major products were diketone **197** and isomeric epoxy ketones **198** and **199** [44].

Formyl derivatives of protoporphyrin IX readily react with Grignard compounds [9, 99]. The reaction of formylporphyrin **190** with vinylmagnesium bromide gives allyl-type alcohol **200** in an acceptable yield [99] (Scheme 35). Alkaline hydrolysis of **200** produced disodium salt **201** which was shown to selectively accumulate in tumor cells [99].

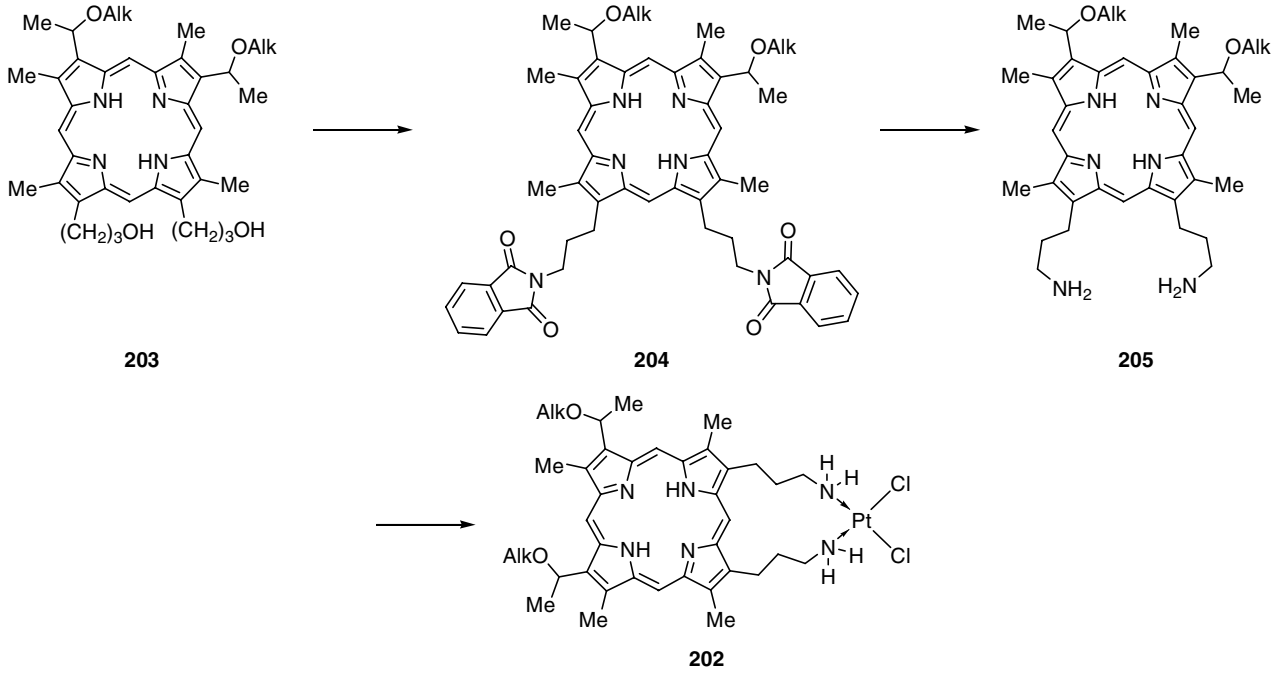
### *3.3. Modification of 13- and 17-(3-Alkoxy-3-oxopropyl) Groups*

**3.3.1. Reduction of ester groups.** The ester substituents in protoporphyrin IX derivatives are readily reduced to 3-hydroxypropyl groups by the action of $LiAlH_4$. Further modifications of the 3-hydroxypropyl groups were used in the synthesis of antitumor agents [118–121], model structures for studying photosynthesis [16, 17], and derivatives capable of effectively modifying electrode surface [122, 123]. Conjugates **202** were synthesized with a view to integrate antitumor effect of platinum(II) coordination compounds with photodynamic activity of porphyrins; the products showed strong cancerostatic and photodynamic activity [120, 121]. The synthetic scheme included treatment of alcohols **203** with the system $Ph_3P$–diethyl azodicarboxylate–phthalimide to obtain bis-phthalimido derivatives **204** which reacted with hydrazine hydrate in the presence of alkali to form diamines **205**. Reaction of **205** with $K_2PtCl_4$ afforded the target coordination compounds **202** [120, 121] (Scheme 36).

Diol **206** was used as starting material in the synthesis of fullerene derivative **207**. Here, the key stage was building up of bis-lactone **209** via reaction of zinc complex **208** with activated malonic acid ester. The final stage was the reaction of fullerene with bis-lactone **209** in the presence of iodine and DBU [16] (Scheme 37). Examination of photophysical properties of conjugate **207** showed that it is a promising model for studying photosynthesis [16, 17].

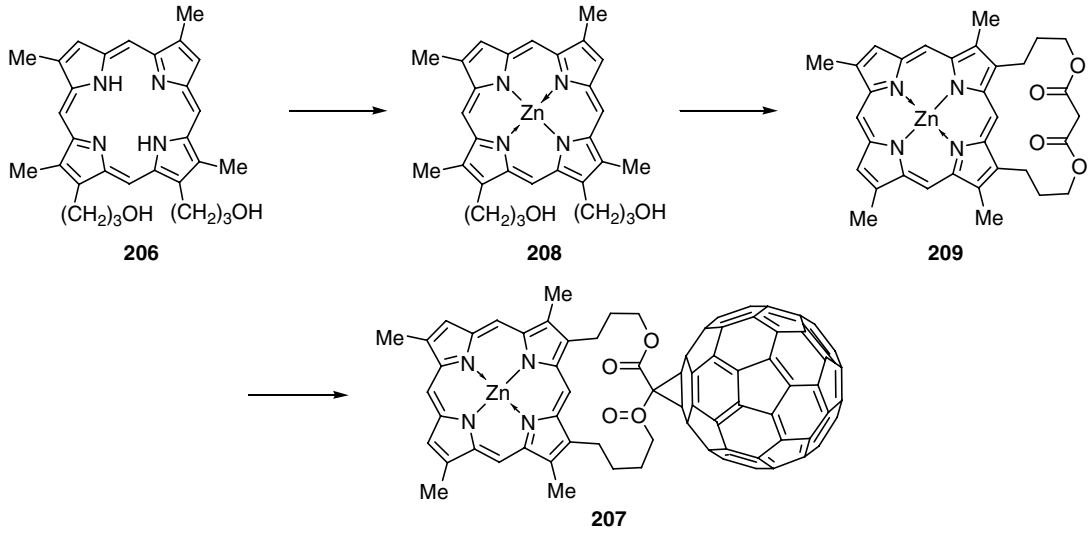
**3.3.2. Hydrolysis of ester groups.** The ester moieties in protoporphyrin IX derivatives can be converted into carboxy groups by acid [33, 47] or alkaline hydrolysis [33, 51, 58, 110]. Obviously, both partial and complete hydrolysis products may be obtained, depending on the conditions. A mixture of isomeric monoesters **81** and **82** is the main component of Visudyne [23, 24]; the synthesis of BOPP (**158**) implies hydrolysis of both methoxycarbonyl groups [22]. Porphyrins **210** react with alkalies and amines to form water-soluble salts **211** which selectively accumulate in tumor cells [21] (Scheme 38). Pessôa and Gushikem [14] succeeded in immobilizing porphyrins on $Nb_2O_5$ grafted to a silica gel surface via formation of

**Scheme 36.**



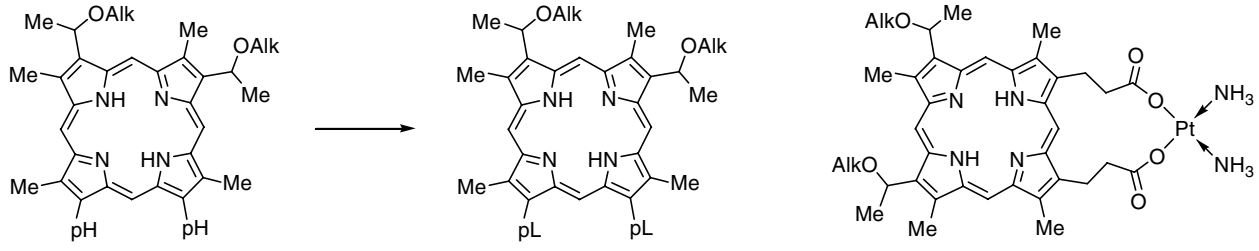
**203** **204** **205** **202**

**Scheme 37.**



**206** **208** **209** **207**

**Scheme 38.**



**210** **211** **212**

**211**, L = $Na^+$, $K^+$; **212**, L = $NH_4^+$.

COO–Nb bonds between the porphyrin and $Nb_2O_5$. Further modification of electrodes by the above system led to creation of an effective sensor for determination of dissolved oxygen [14]. An elegant procedure for modification of carboxy groups in porphyrins was proposed in [51, 84, 124]. Porphyrins **210** reacted with the platinum complex $[Pt(NH_3)_2(H_2O)_2](OH)_2$ in aqueous ethanol to produce coordination compounds **212** (Scheme 38) which showed high cyto- and photocytotoxicity [51].

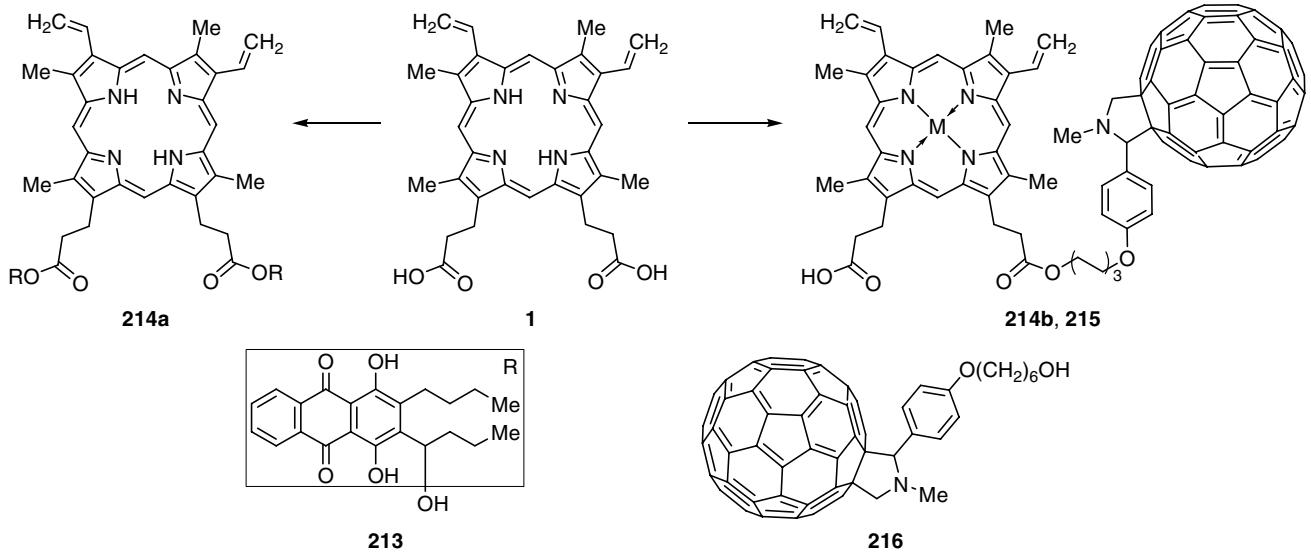
**3.3.3. Different versions of esterification of 13- and 17-(2-carboxyethyl) groups in porphyrins.** Carboxy groups in porphyrins are converted into methoxycarbonyl by treatment with diazomethane or a 5% solution of $H_2SO_4$ in methanol [33]. Methods intrinsic to peptide chemistry are applied to obtain esters containing labile fragments. Variation of the alcohol component allows preparation of derivatives that may be promising for antitumor therapy [125–128], studying photosynthesis [129–131], modification of various proteins [132], and application in technics [13, 15, 123, 133].

Diester **214a** was synthesized in 75% yield by condensation of protoporphyrin IX (**1**) with alcohol **213** in the presence of *N*,*N*′-dicyclohexylcarbodiimide and 4-dimethylaminopyridine [125] with a view to combine anticarcinogenic activity of the anthraquinone derivative and photodynamic properties of tetrapyrroles. Murakami et al. [132] synthesized porphyrin–fullerene diads **214b** and **215** as unique compounds for modification of myoglobins and studied photophysical properties of the modified proteins. The synthesis involved activation of the carboxy groups in protoporphyrin IX (**1**) with oxalyl chloride, condensation with fullerene derivatives **216** in the presence of 4-dimethylaminopyridine, and metalation (Scheme 39).

**3.3.4. Amide derivatives based on 13,17-bis(2-carboxyethyl)porphyrins.** Synthesis of amide derivatives of protoporphyrin IX is important from the viewpoint of design of compounds that may be used in biology [129, 134–142] and medicine [20, 21, 52, 80, 110–112, 126, 128, 130, 131, 135, 143–150]. Effective antitumor agent **216** was synthesized by successive treatment of protoporphyrin IX (**1**) with ethyl chloroformate, ethylenediamine, succinimidopoly(ethylene glycol) (*M* 5000), and zinc(II) acetate [147]. Evstigneeva et al. [135] reported on conjugation of protohemin IX (**12**) with peptides to obtain porphyrin-modified peptides **217** as convenient models for studying heme-containing proteins (Scheme 40).

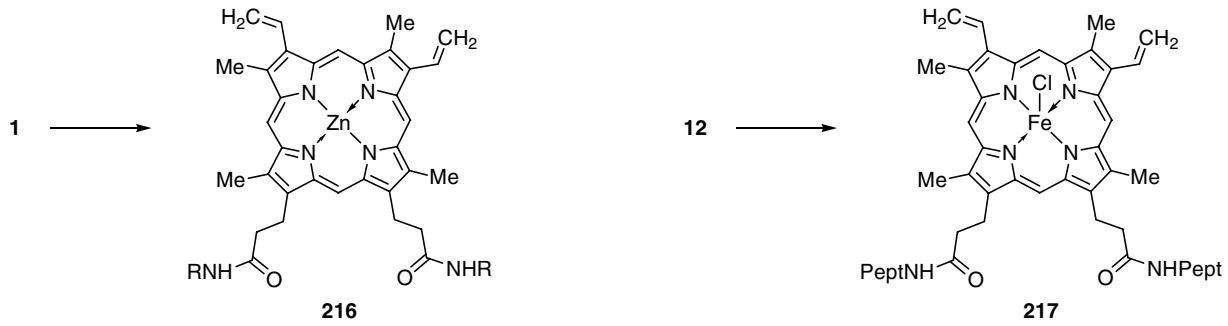
Some amides were prepared from carboxy-containing porphyrins without involving peptide chemistry methods. Rogovina et al. [151] performed solid-phase amidation of carboxy groups in deuteroporphyrin derivatives using chitosan under high pressure (3 GPa). Liang et al. [138] described a successful synthesis of diamide derived from protoporphyrin IX zinc complex by reaction of the corresponding dimethyl ester with aluminum amide. An example of hydrazide modification of carboxy groups in protoporphyrin IX derivatives for conjugation with immunotoxins was also reported [152].

**Scheme 39.**




**214b**, M = Zn; **215**, M = $[FeCl]^{2+}$.

**Scheme 40.**




**216**, R = poly(ethylene glycol)–OC(O)$(CH_2)_2$C(O)NH$(CH_2)_2$.

### *3.4. Modification of Methyl Groups*

Reactions of protoporphyrin IX and its derivatives accompanied by transformations of methyl groups are fairly rare. Electrophilic deuteration of methyl groups by heating protoporphyrin IX dimethyl ester (**18**) in solvents containing MeOD and $MeO^-$ was reported [9]. Mironov et al. [153] performed chlorination of methyl groups by prolonged reaction of porphyrin metal complexes with thionyl chloride.

## 4. MODIFICATION OF MACRORING

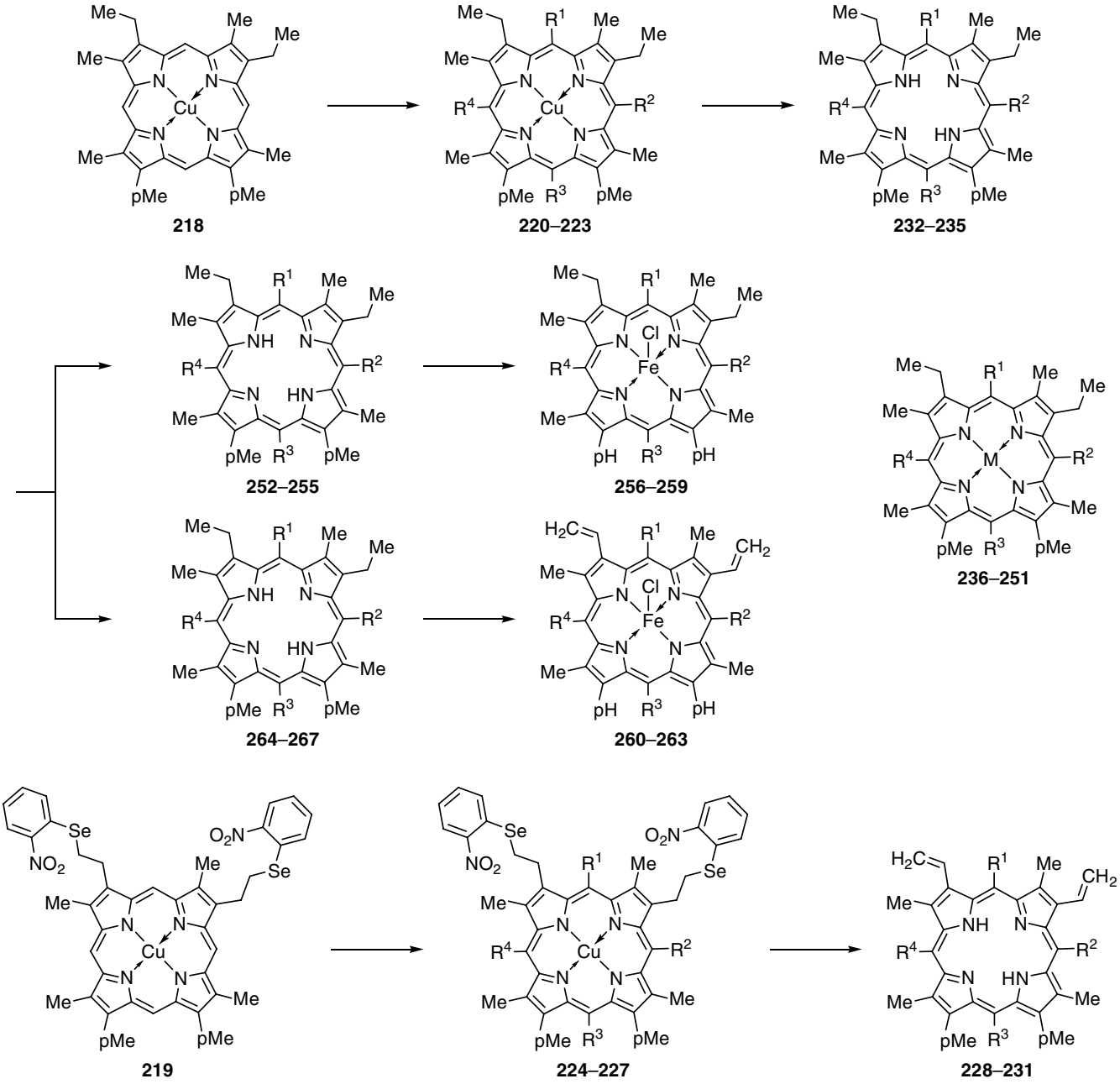
The structure of protoporphyrin IX (**1**) suggests that the macroring therein can be modified at the *meso* positions (*5*, *10*, *15*, *20*), with participation of *2–3*, *7–8*, *12–13*, and *17–18* double bonds, and via coordination with metals. Some examples of macroring identification implied rearrangements involving peripheral substituents. Data on such modifications of the macroring in prophyrins are briefly discussed below.

### *4.1. Modifications at meso Positions*

Transformations involving *meso* positions in the macroring of protoporphyrin IX derivatives are classical reactions in the porphyrin chemistry; they were considered in detail in some reviews [60, 95]. In the recent years, modifications at the *meso* positions were performed to obtain derivatives interesting from the viewpoint of studying metabolism of heme [45, 154–157]. Formylation of copper complexes of mesoporphyrin IX (**218**) [154] and protected protoporphyrin IX (**219**) [45] with $POCl_3$–DMF gave mixtures of the corresponding *meso*-formylporphyrin complexes **220–223** and **224–227** [45, 154] (Scheme 41). The subsequent demetalation of copper complexes **224–227** with 5% $H_2SO_4$ in $CF_3COOH$ and deprotection of vinyl groups with 30% $H_2O_2$ in THF afforded a mixture of *meso*-formyl-substituted protoporphyrin IX analogs **228–231** which were separated by HPLC [45]. Successive treatment of copper complexes **220–223** with $Bu_4NBH_4$ and $H_2SO_4$–$CF_3COOH$ (1:1) resulted in the formation of isomeric *meso*-hydroxymethyl derivatives **232–235** which were separated by column chromatography [154]. The exact position of the *meso*-substituent in individual isomers **228–235** was determined using NOE technique [45, 154]. In early studies, the structure of mesoporphyrin IX formylation products was determined by their transformation into the corresponding *meso*-dimethylaminomethylporphyrins **236–243** and borane complexes **244–251** [60] (in order to simplify interpretation of the $^1$H NMR spectra of **236–251**, the corresponding analogs containing a deuterium label in the 13- and 17-$CH_2CH_2COOC\mathbf{H}_3$ substituents were obtained). Reduction of *meso*-hydroxymethylporphyrins **232–235** gave a set of *meso*-methyl derivatives **252–255**, and the latter were subjected to hydrolysis followed by metalation to obtain four regioisomeric *meso*-methylmesohemins **256–259** [154]. Individual *meso*-formylmesohemins **260–263** were synthesized by oxidation of hydroxymethyl derivatives **232–235** with pyridinium chlorochromate in pyridine, and aldehydes **264–267** thus formed were hydrolyzed and metalated [157].

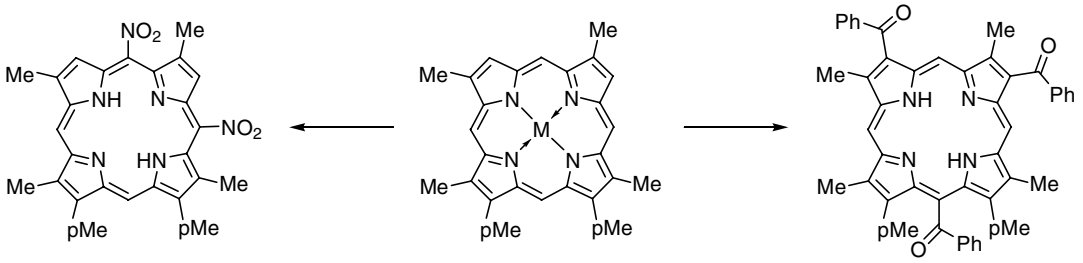
Apart from formylation, successful nitration of deuteroporphyrin IX dimethyl ester (**119**) with a mixture of nitric and sulfuric acids to obtain dinitro derivative **268** [51] and chlorination at the *meso* positions of protoporphyrin IX metal complexes with $SOCl_2$ [153] were reported. Vázquez et al. [158] synthesized tribenzoylporphyrin **269** by acylation of zinc complex **122** with benzoic anhydride in the presence of $SnCl_4$ (Scheme 42). Hemins **273–275** were treated with zinc amalgam to obtain hemes **270–272**, and reactions of the latter with hydrogen peroxide in pyridine in the absence of oxygen were studied to simulate heme

**Scheme 41.**




**218**, $R^1 = R^2 = H$; **220**, **228**, **260**, **264**, $R^1 = CHO$, $R^2 = R^3 = R^4 = H$; **221**, **229**, **261**, **265**, $R^1 = R^3 = R^4 = H$, $R^2 = CHO$; **222**, **230**, **262**, **266**, $R^1 = R^2 = R^4 = H$, $R^3 = CHO$; **223**, **231**, **263**, **267**, $R^1 = R^2 = R^3 = H$, $R^4 = CHO$; **224**, **228**, $R^1 = CHO$, $R^2 = R^3 = R^4 = H$; **225**, **229**, $R^1 = R^3 = R^4 = H$, $R^2 = CHO$; **226**, **230**, $R^1 = R^2 = R^4 = H$, $R^3 = CHO$; **227**, **231**, $R^1 = R^2 = R^3 = H$, $R^4 = CHO$; **232**, $R^1 = HOCH_2$, $R^2 = R^3 = R^4 = H$; **233**, $R^1 = R^3 = R^4 = H$, $R^2 = HOCH_2$; **234**, $R^1 = R^2 = R^4 = H$, $R^3 = HOCH_2$; **235**, $R^1 = R^2 = R^3 = H$, $R^4 = HOCH_2$; **236**, M = Ni(II), $R^1 = CH_2NMe_2$, $R^2 = R^3 = R^4 = H$; **237**, M = Ni(II), $R^1 = R^3 = R^4 = H$, $R^2 = Me_2NCH_2$; **238**, M = Ni(II), $R^1 = R^2 = R^4 = H$, $R^3 = Me_2NCH_2$; **239**, M = Ni(II), $R^1 = R^2 = R^3 = H$, $R^4 = Me_2NCH_2$; **240**, M = 2H, $R^1 = Me_2NCH_2$, $R^2 = R^3 = R^4 = H$; **241**, M = 2H, $R^1 = R^3 = R^4 = H$, $R^2 = Me_2NCH_2$; **242**, M = 2H, $R^1 = R^2 = R^4 = H$, $R^3 = Me_2NCH_2$; **243**, M = 2H, $R^1 = R^2 = R^3 = H$, $R^4 = Me_2NCH_2$; **244**, M = Ni(II), $R^1 = BH_3 \cdot Me_2NCH_2$, $R^2 = R^3 = R^4 = H$; **245**, M = Ni(II), $R^1 = R^3 = R^4 = H$, $R^2 = BH_3 \cdot Me_2NCH_2$; **246**, M = Ni(II), $R^1 = R^2 = R^4 = H$, $R^3 = BH_3 \cdot Me_2NCH_2$; **247**, M = Ni(II), $R^1 = R^2 = R^3 = H$, $R^4 = BH_3 \cdot Me_2NCH_2$; **248**, M = 2H, $R^1 = BH_3 \cdot Me_2NCH_2$, $R^2 = R^3 = R^4 = H$; **249**, M = 2H, $R^1 = R^3 = R^4 = H$, $R^2 = BH_3 \cdot Me_2NCH_2$; **250**, M = 2H, $R^1 = R^2 = R^4 = H$, $R^3 = BH_3 \cdot Me_2NCH_2$; **251**, M = 2H, $R^1 = R^2 = R^3 = H$, $R^4 = BH_3 \cdot Me_2NCH_2$; **252**, **256**, M = Ni(II), $R^1 = Me$, $R^2 = R^3 = R^4 = H$; **253**, **257**, M = Ni(II), $R^1 = R^3 = R^4 = H$, $R^2 = Me$; **254**, **258**, M = Ni(II), $R^1 = R^2 = R^4 = H$, $R^3 = Me$; **255**, **259**, M = Ni(II), $R^1 = R^2 = R^3 = H$, $R^4 = Me$.

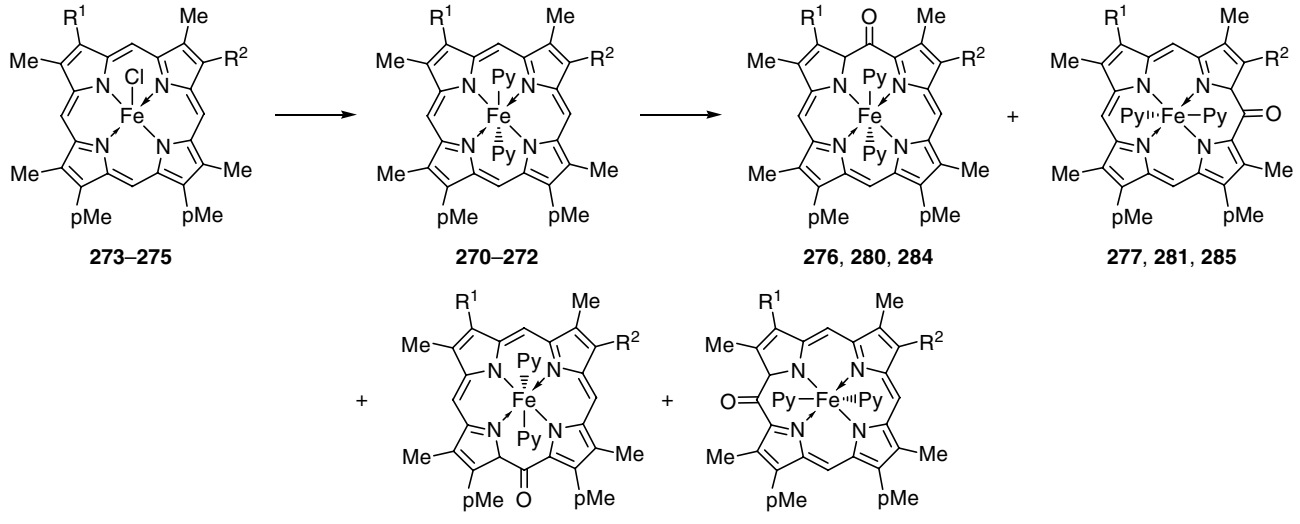
**Scheme 42.**



**268** **119**, **122** **269**

**119**, M = 2H; **122**, M = Zn.

**Scheme 43.**



**273–275** **270–272** **276**, **280**, **284** **277**, **281**, **285**

**278**, **282**, **286** **279**, **283**, **287**

**270**, **273**, **276–279**, $R^1 = R^2 = H$; **271**, **274**, **280–283**, $R^1 = R^2 = CH_2{=}CH$; **272**, **275**, **284–287**, $R^1 = R^2 = Et$.

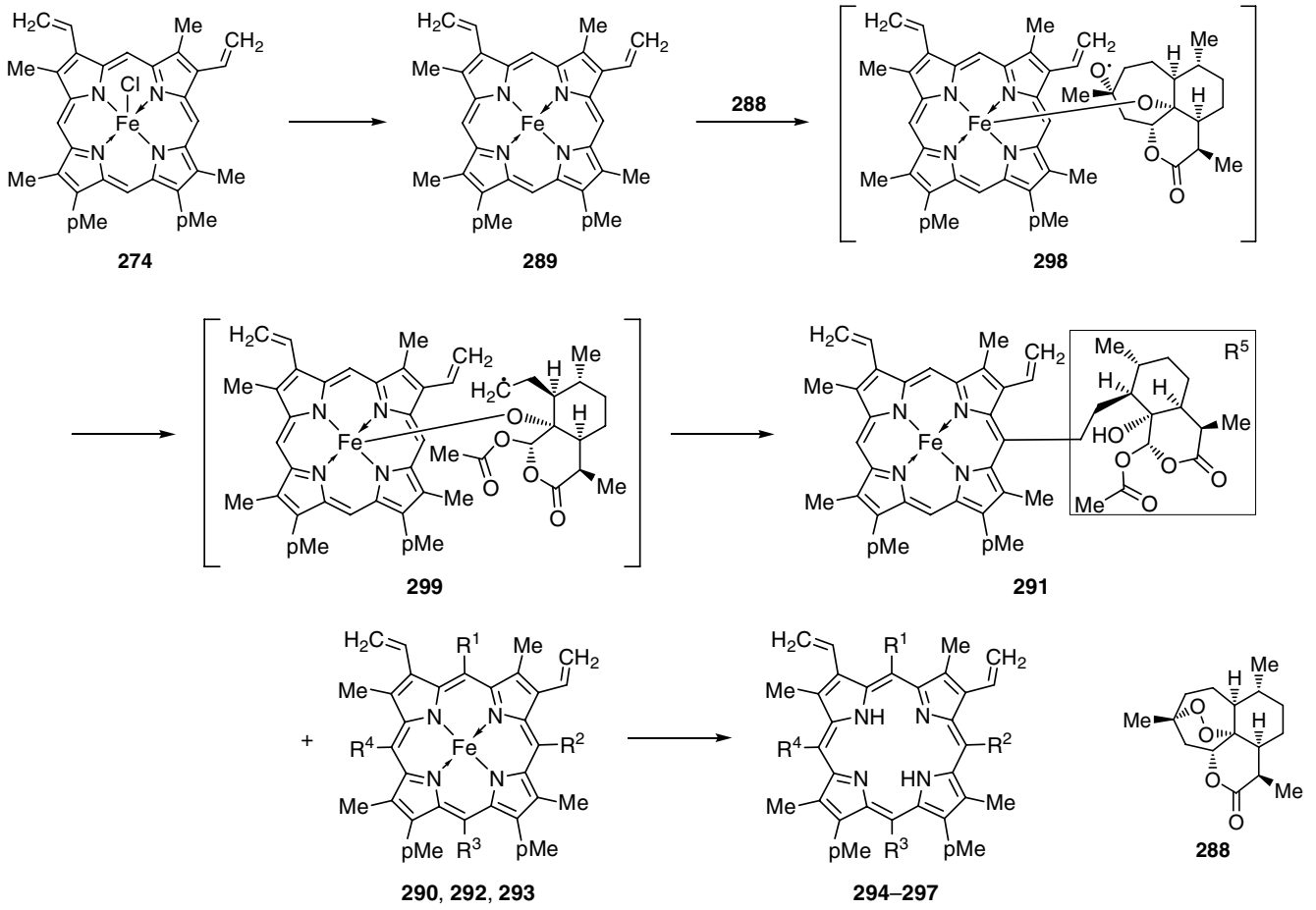
degradation catalyzed by heme oxygenase. As a result, mixtures of all possible isomeric oxophlorin complexes **276–279**, **280–283**, and **284–287** were formed [159] (Scheme 43).

Heme dimethyl ester **289** generated from hemin **271** and 2,3-dimethylhydroquinone was incubated with highly active antimalarial drug Artemisinin (**288**) with a view to determine the structure of products of the reaction of **288** with its biological target, a parasite heme [160]. After standard demetalation of intermediates **290–293**, three possible heme alkylation products **294–296** (at the 5-, 10-, and 20-*meso*-positons) were mainly obtained, while only a small amount of 15-substituted analog **297** was formed (Scheme 44). Presumably, the mechanism of this process includes activation by the iron(II) ion in heme **289** of the peroxide bond in Artemisinin (**288**), its subsequent cleavage with formation of O-centered radical **298**, rearrangement of the latter into carbon-centered radical **299** via homolysis of the C–C bond, and final attack at the *meso* position by the radical center located over the porphyrin macroring plane [160].

In some cases, modification at *meso* positions is accompanied by cleavage of the porphyrin macroring. Oxidative cleavage of 5-phenylprotohemin IX (**300**) in the presence of ascorbic acid, followed by esterification, gave three isomeric biliverdin dimethyl esters **301–303** (Scheme 45). The reaction did not involve the *meso* position occupied by phenyl group: no biliverdin IXα dimethyl ester (**304**) was detected among the products [161].

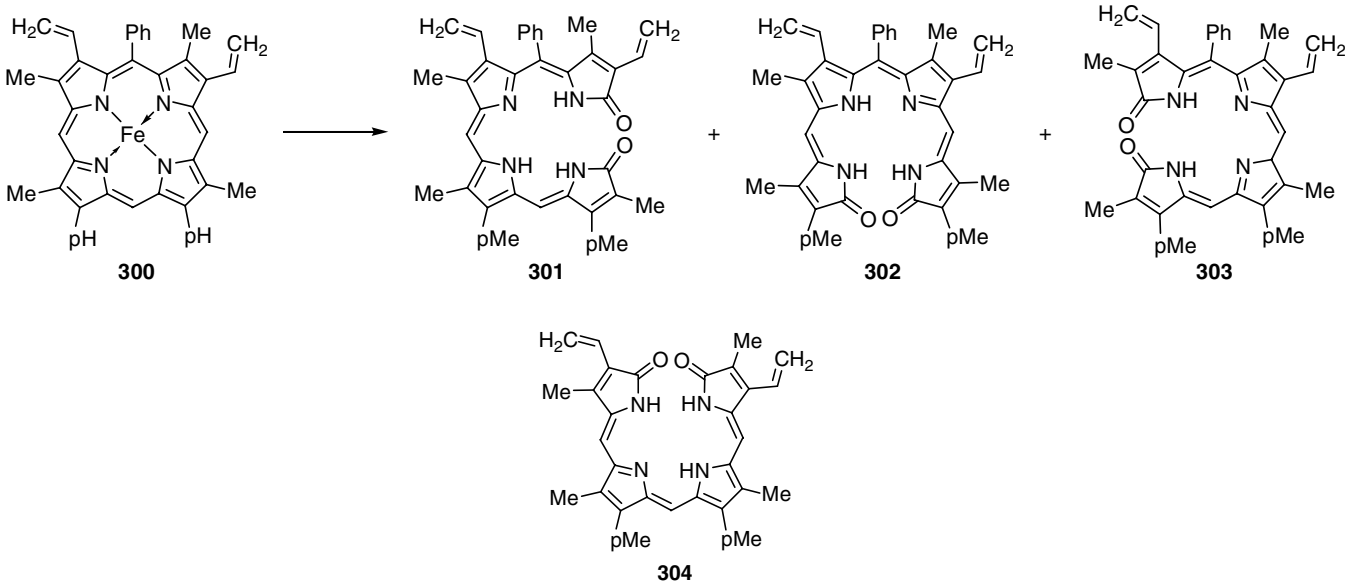
Gerlach and Montforts [162] used a linear tetrapyrrole, bilirubin (**305**, natural heme oxidation product) [155], as starting compound in the synthesis of azaporphyrin **306** (Scheme 46). For this purpose, compound **305** was oxidized to another heme metabolite, biliverdin **307**, with $FeCl_3$ in warm acetic acid; the subsequent esterification and treatment with zinc ace-

**Scheme 44.**

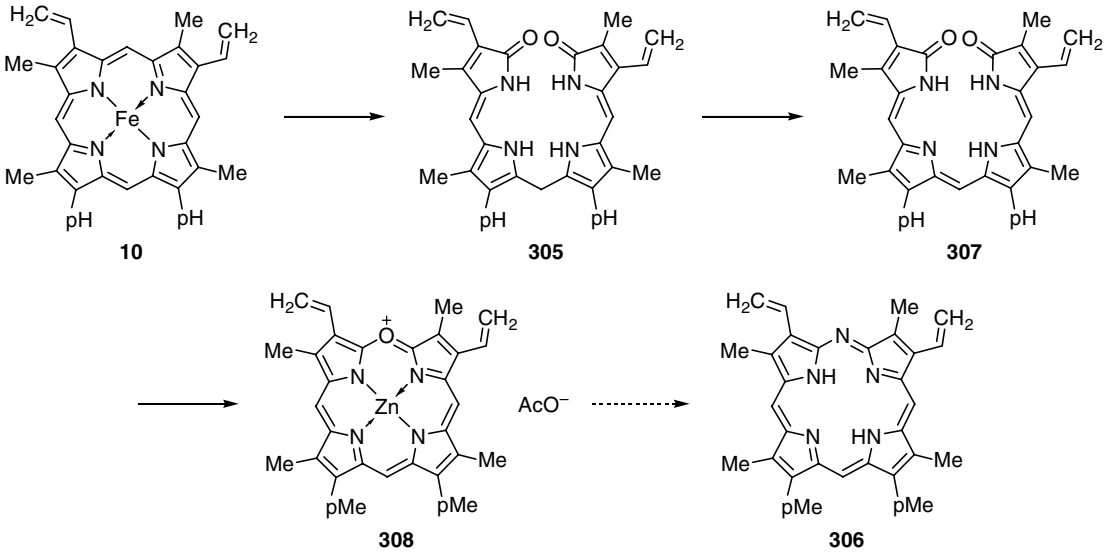



**290**, **294**, $R^1 = R^5$, $R^2 = R^3 = R^4 = H$; **292**, **295**, $R^1 = R^3 = R^4 = H$, $R^2 = R^5$; **293**, **296**, $R^1 = R^2 = R^3 = H$, $R^4 = R^5$; **297**, $R^1 = R^2 = R^4 = H$, $R^3 = R^5$.

**Scheme 45.**



**Scheme 46.**



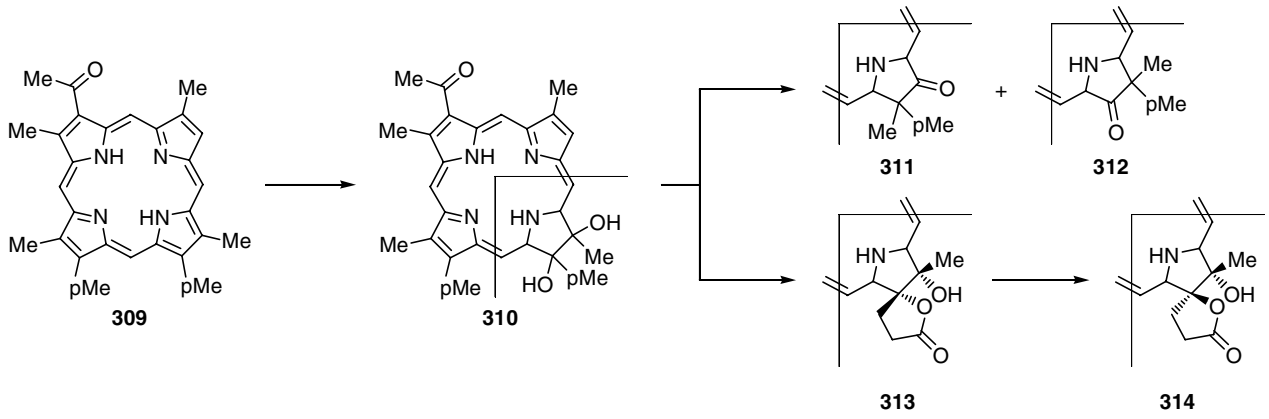

tate and then with acetic anhydride gave oxonium ion **308**. The final stage was amination of **308** with ammonia, followed by treatment with trimethylsilyl polyphosphate.

### *4.2. Modifications Involving 2–3, 7–8, 12–13, and 17–18 Double Bonds.*

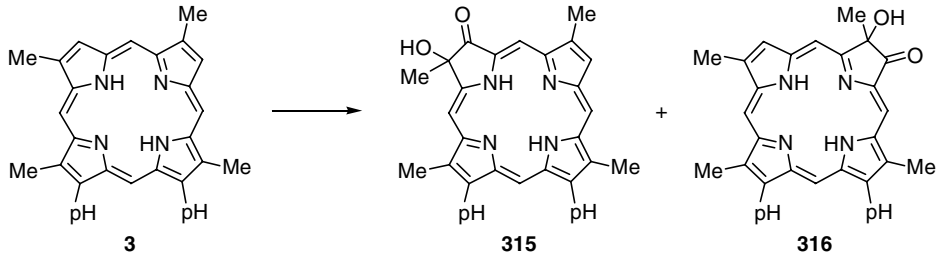
The porphyrin double bonds in positions *2–3*, *7–8*, *12–13*, and *17–18* are oxidized with $OsO_4$ to form chlorin structures with vicinal diol fragments [36, 70, 163]; the oxidation of unsymmetrical octaalkylporphyrin systems leads to the formation of mixtures of isomeric vicinal diols [70, 163, 164]. Regioselective oxidation may be achieved with unsymmetrical tetrapyrroles containing a peripheral electron-withdrawing substituent. In this case, the reaction involves only one double bond in the pyrrole ring located opposite to the pyrrole ring containing electron-withdrawing substituent [70]. For example, the oxidation of 3-acetyldeuteroporphyrin **309** gives 68% of 12,13-dihydroxychlorin **310** [70] (Scheme 47). Vicinal dihydroxychlorins are converted into oxochlorines under conditions of pinacol–pinacolone rearrangement (concentrated sulfuric acid). Chlorin **310** gives rise to a mixture of isomeric chlorins **311** and **312** [70]. Taking into account concomitant migration of peripheral substituents, the formation of oxochlorins is a fairly complex process (for details, see [70, 163]). Vicinal diols are capable of undergoing intramolecular lactonization. Heating of a solution of diol **310** in methanol in the presence of sodium acetate afforded 64% of *cis*-lactone **313** which underwent epimerization over silica gel to give *trans*-lactone **314** [70] (Scheme 47).

A combination of oxidation of the *2–3*, *7–8*, *12–13*, and *17–18* double bonds in porphyrin with subsequent pinacol–pinacolone rearrangement, repetition of this

**Scheme 47.**



**Scheme 48.**



**3** **315** **316**

procedure, and some additional transformations are often performed to determine the structure of some biologically important highly saturated tetrapyrrole compounds [2].

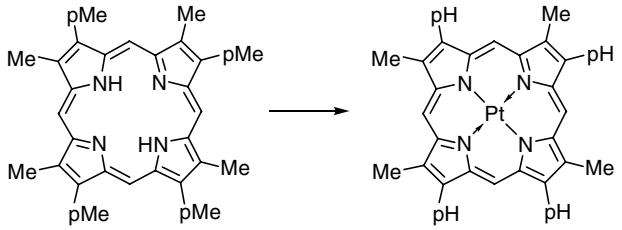
An efficient procedure for regioselective transformation of a porphyrin system via oxidation of the *2–3* and *7–8* double bonds was proposed in [165]. It was found [166] that incubation of deuteroporphyrin IX (**3**) with horse radish peroxidase in the presence of glutathione gives isomeric chlorins **315** and **316** [165] (Scheme 48). Under analogous conditions protoporphyrin IX (**1**) was converted into an unidentified derivative [167]. Factor affecting the formation of chlorins **315** and **316** were discussed in detail in [168].

### *4.3. Metal Complexes and Their Demetalation*

The ability of porphyrins to form coordination compounds with metals is a fundamental property of tetrapyrrole systems. Detailed analysis of the possibility for complex formation with porphyrins, stability of the complexes thus formed, and specificity of their demetalation was given in [32, 169, 170]. The recent data concerning these problems are briefly discussed below. A conventional procedure for the synthesis of porphyrin metal complexes is heating of free bases with metal salts in polar solvents [27, 51, 98, 106, 122, 144, 171, 172]. Reactions with radioactive metal isotopes open the way to radiopharmaceutical agents with a broad spectrum of applications in medicine [22, 28].

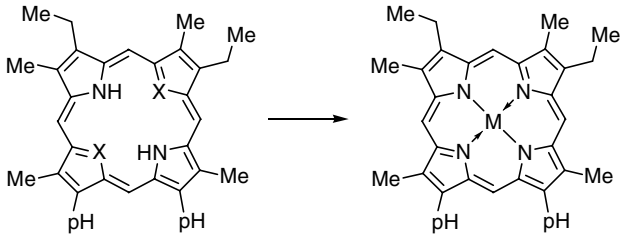
Platinum porphyrin complexes are characterized by a high luminescence quantum yield and are promising as luminescent probes. Platinum complex **317** possesses valuable photophysical properties and is capable of selectively accumulating in tumor cells [27]; it was patented as potential agent for luminescent diagnostics of cancer [19]. Complex **317** was synthesized by heating free base **177** with $K_2PtCl_4$ in benzonitrile, followed by alkaline hydrolysis of the ester groups [27] (Scheme 49). Treatment of dihydrochloride **318** with $SnCl_2$ in the presence of oxygen on heating gave tin(IV) complex **319** (Stannsoporfin) in a good yield; the product is effective in the treatment of physiologic jaundice and psoriasis [40] (Scheme 50). Ishida et al. [173] recently demonstrated prospects in using template catalysis by apocytochrome $b_{562}$ for metalation of porphyrins. Iron(III) complex **12** is widely used as starting compound in the chemistry of protoporphyrin IX. Complex **12** is isolated on a large scale by treatment of defibrinated bovine blood. Specificity of demetalation of protohemin IX (**12**) and other iron(III) porphyrin complexes was reviewed in detail in [9, 33].

**Scheme 49.**



**177** **317**

**Scheme 50.**



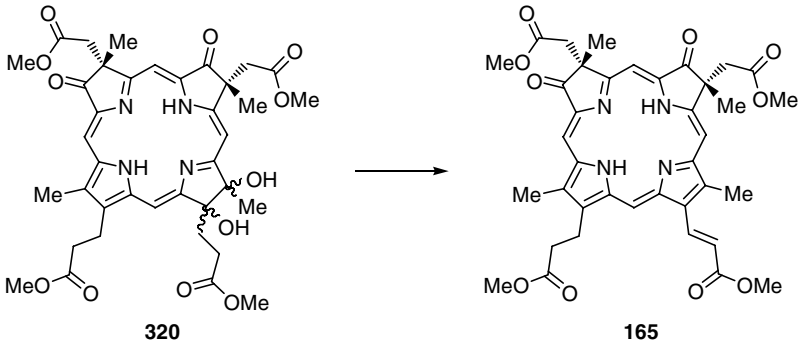
**318** **319**

**318**, X = N·HCl; **319**, M = $[SnCl_2]^{2+}$.

### *4.4. Modifications Involving Rearrangement Processes*

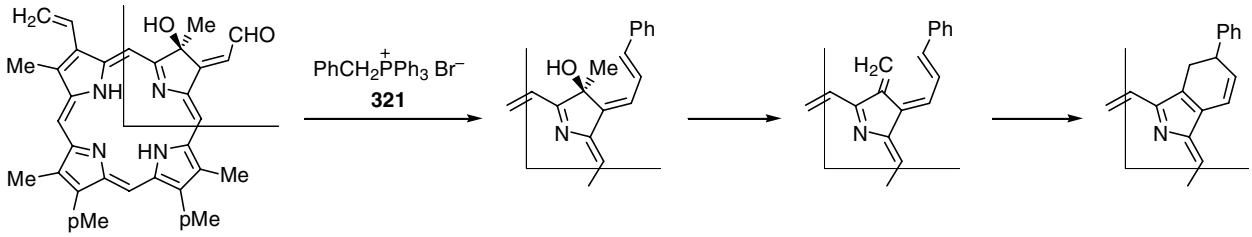
Variation of initial tetrapyrrole structures and conditions makes it possible to obtain tetrapyrrole systems with various modes of conjugation; transformations of partially saturated structures to porphyrins and vice versa are possible. Some aspects of the transformation of chlorins into thermodynamically more stable por-

**Scheme 51.**



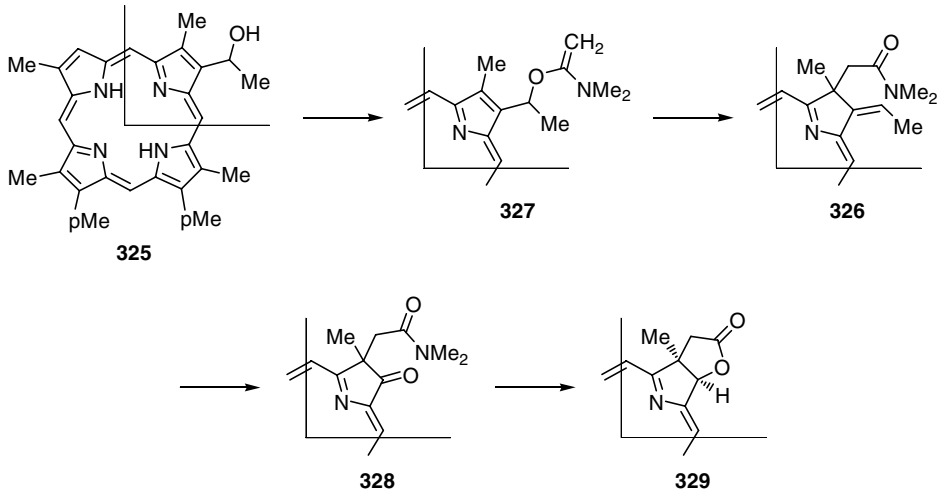
**320** **165**

**Scheme 52.**



**167** **322** **323** **324**

**Scheme 53.**



**325** **327** **326** **328** **329**

phyrin derivatives were considered above (see Section 3.2). There are published data on double dehydration of vicinal diols obtained by oxidation of double bonds with $OsO_4$; here, vinylporphyrin fragment is formed as a result of successive treatment with hydrochloric acid and $H_2SO_4$–MeOH. The corresponding transformation of compound **320** is the final step in the synthesis of porphyrin $d_1$ tetramethyl ester **165** [2] (Scheme 51).

Examples of transformation of the chlorin system into dihydrobenzoporphyrin are known. Treatment of isophotoprotoporphyrin **167** with phosphonium salt **321** in the presence of DBU gives the expected Wittig reaction product **322**, and subsequent heating of compound **322** in 1,2-dichlorobenzene leads to elimination of water molecule and isomerization of intermediate chlorin **323** into stable dihydrobenzoporphyrin **324** [114] (Scheme 52). Transformation of the porphyrin system to chlorin is also possible. Syntheses of chlorin derivatives from vinylporphyrins via Diels–Alder reaction were discussed in Section 3.2. Diels–Alder reactions were also used to convert vinylporphyrins into benzoporphyrins [36] and isobacteriochlorins [9].

Montforts et al. [174, 175] described a new method for building up chlorin system with participation of

hydroxyethyl groups in porphyrins. The Claisen reaction of 8-(1-hydroxyethyl) derivative **325** with *N*,*N*-dimethyl-1,1-dimethoxyethanamine on heating afforded chlorin **326** through intermediate porphyrin **327** [174] (Scheme 53). Further modifications of chlorin **326** were also performed [174, 175]. For example, oxidation of **326** gave ketone **328** which was reduced with $LiAlH(OBu\text{-}t)_3$ and then treated with a base to obtain lactone **329** [175].

## 5. CONCLUSION

Vast experimental data on modifications of protoporphyrin IX and its derivatives have been published over the past decade. The presence in the molecules of these compounds of various peripheral substituents (such as vinyl, formyl, and carbonyl groups) makes it possible to transform the porphyrin macroring into other tetrapyrrole systems, and the ability of tetrapyrroles to form stable complexes with many metals opens wide prospects in their modification using methods of organic and bioorganic chemistry.

The main recent trend in the chemistry of protoporphyrin IX is the application of flexible organic chemistry methods with a view to obtain derivatives possessing practically important properties. In particular, a combination of regioselective introduction of pharmacophoric fragments as peripheral substituents and variation of the central metal ion could give rise to effective agents for diagnostics and therapy of various diseases with the aid of powerful modern photomedical, radiological, X-ray, nuclear magnetic resonance, and radioisotope methods. Low systemic toxicity, valuable photophysical properties, and the ability to selectively accumulate in tumor and other affected cells make protoporphyrin IX derivatives especially promising.

The information collected in the present review on methods of modification of protoporphyrin IX and its derivatives demonstrates their huge synthetic potential and wide prospects in the development of synthetic approaches to compounds possessing a broad spectrum of useful properties, primarily valuable biological activity.

The author thanks Dr. M.S. Nechaev (Faculty of Chemistry, Moscow State University, Moscow, Russia), Dr. A.S. Lermontov (Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, Moscow, Russia), Dr. S.V. Shorunov (Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia), I.O. Konstantinov (Research Institute of Chemical Diversity Ltd., Khimki, Russia), "First Print Yard" joint-stock company (Moscow, Russia), and personally O.I. Konstantinov for their assistance in the preparation of the present review. The review was prepared under financial support by the Russian Foundation for Basic Research (project no. 04-03-32710).

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