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MODIFICATION OF THE PERIPHERAL SUBSTITUENTS IN CHLOROPHYLLS *a* AND *b* AND THEIR DERIVATIVES (REVIEW)

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The extensive published data on methods for the modification of peripheral substituents in chlorophylls a and b and their various semisynthetic derivatives are classified and analyzed. Special attention is paid to specific transformations arising from the presence of the unique macrocyclic tetrapyrrole fragment. Data on certain main pathways to modification of the exocyclic fragment of chlorophylls are also presented.

Keywords: pyropheophorbide, porphyrin, rhodin g_7, pheophetin, pheophorbide, chlorin e_6, chlorophyll, fluorescent diagnostics, photoinduced electron transfer, photosensitizer, photosynthesis.

This article reviews the extensive published data on the principal methods for modification of the peripheral substituents of chlorophyll and their derivatives and also some methods of modifying the exocyclic fragment, based on the classical papers of R. Willstätter, G. Fischer, and the most up-to-date investigations in this field.

The great interest in modification of the peripheral substituents in chlorophyll is due to the broad spectrum of useful characteristics found in their specifically modified derivatives [1]. In particular, they have been used as models for the study of photosynthesis [2, 3]. The unique ability of chlorophyll derivatives to accumulate in tumorous tissues and to cause a photodynamic effect under laser radiation has been successively used in photodynamic therapy (PDT) and fluorescent diagnosis of malignant neoplasms [4-8].

Fundamental data on the chemistry of chlorophylls have been presented in books [9-15] and reviews [16-28], and some pathways to the modification of chlorophylls were discussed in [1, 4, 7, 29-47].

Nomenclature and Classification of the Basic Derivatives of Chlorophylls *a* and *b*

Chlorophylls *a* and *b* are customarily regarded as derivatives of porphin, containing a cyclopentanone ring (exocycle) condensed with a porphyrin macrocycle, various peripheral substituents, a partially hydrogenated pyrrole ring, and a central magnesium atom.

Fischer [10, 11] and IUPAC [28, 48] nomenclature are used for numbering the carbon and nitrogen atoms forming the chlorophyll molecule. In the present review the IUPAC numbering system is used except for some trivial names proposed, mainly by Fischer, for certain derivatives of chlorophylls.

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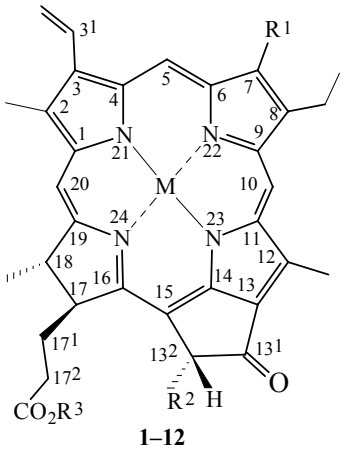
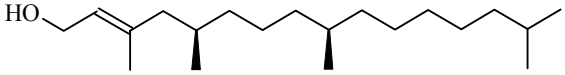
The structural features of chlorophylls and their derivatives make it possible to divide them into two main groups. The first group includes chlorophylls **1** and **2** and the derivatives **3**-**12**, containing an exocyclic fragment (the so-called phorbin derivatives) (Scheme 1). The second group includes the derivatives **14**-**22** not containing an exocyclic fragment (the so-called nonphorbin derivatives) (Scheme 2).



1–12

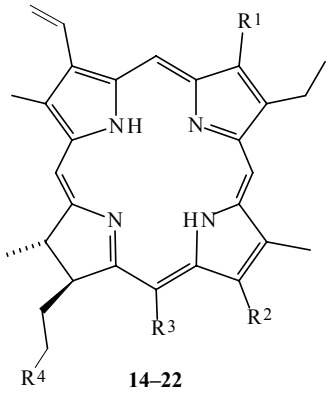
1 chlorophyll *a*: M = Mg, R^1 = Me, R^2 = COOMe, R^3 = Phytyl
2 chlorophyll *b*: M = Mg, R^1 = CHO, R^2 = COOMe, R^3 = Phytyl
3 pheophetin *a*: M = 2H, R^1 = Me, R^2 = COOMe, R^3 = Phytyl
4 pheophorbide *a*: M = 2H, R^1 = Me, R^2 = COOMe, R^3 =H
5 methylpheophorbide *a*: M = 2H, R^1 = R^3 = Me, R^2 = COOMe
6 pyropheophorbide *a*: M = 2H, R^1 = Me, R^2 = R^3 = H
7 methylpyropheophorbide *a*: M = 2H, R^1 = R^3 = Me, R^2 = H
8 pheophetin *b*: M = 2H, R^1 = CHO, R^2 = COOMe, R^3 = Phytyl
9 pheophorbide *b*: M = 2H, R^1 = CHO, R^2 = COOMe, R^3 =H
10 methylpheophorbide *b*: M = 2H, R^1 = CHO, R^2 = COOMe, R^3 =Me
11 pyropheophorbide *b*: M = 2H, R^1 = CHO, R^2 = R^3 = H
12 methylpyropheophorbide *b*: M = 2H, R^1 = CHO, R^2 = H, R^3 = Me

13



Phytyl – the residue of the alcohol phytol **13**

Scheme 1. The nomenclature, names, and structural formulas of chlorophylls *a* and *b* and their main phorbin derivatives.



14–22

14 chlorin e_6: R^1 = Me, R^2 = R^4 = COOH, R^3 = CH_2COOH
15 chlorin e_6 trimethyl ester: R^1 = Me, R^2 = R^4 = COOMe, R^3 = CH_2COOMe
16 chlorin e_4: R^1 = R^3 = Me, R^2 = R^4 = COOH
17 chlorin e_4 dimethyl ester: R^1 = R^3 = Me, R^2 = R^4 = COOMe
18 isochlorin e_4: R^1 = Me, R^2 = H, R^3 = CH_2COOH, R^4 = COOH
19 isochlorin e_4 dimethyl ester: R^1 = Me, R^2 = H, R^3 = CH_2COOMe, R^4 = COOMe
20 phyllochlorin e_6: R^1 = R^3 = Me, R^2 = H, R^4 = COOH
21 rhodin g_7: R^1 = CHO, R^2 = R^4 = COOH, R^3 = CH_2COOH
22 rhodin g_7 trimethyl ester: R^1 = CHO, R^2 = R^4 = COOMe, R^3 = CH_2COOMe

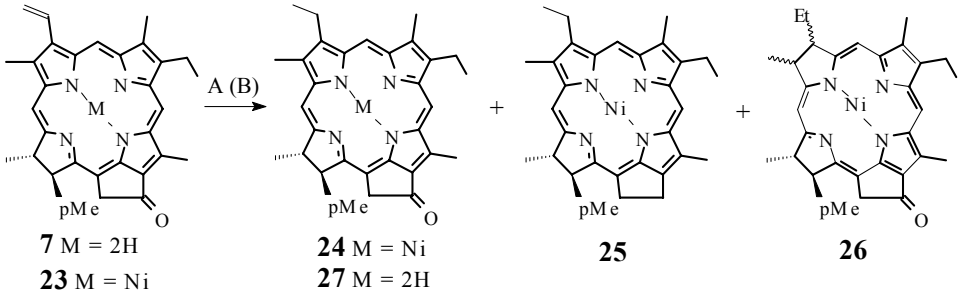
Scheme 2. The names and structural formulas of the main non-phorbin derivatives of chlorophylls *a* and *b*.

Pathways to Modification of the Vinyl Group

The vinyl group readily enters into reduction, oxidation, addition, substitution, and elimination. Under neutral and alkaline conditions it behaves like an isolated double bond, but under acidic conditions its behavior is largely determined by conjugation with the macrocycle.

Reduction of the Vinyl Group

Reduction of the vinyl group to ethyl is realized by means of a wide range of reagents (B_2H_6, $N_2H_4 \cdot H_2O$ [22, 28], PtO_2 [22], Pd/C [49-52], and Raney nickel [53]). The choice of most effective reducing system is determined by the structure of the tetrapyrrole substrate being reduced. Thus, the reduction of the nickel complex **23** at Raney nickel in the Et_2O/EtOH system leads to the formation of three main compounds **24**-**26** ([53] and the literature cited therein), while during reduction of the free base **7** at Pd/C in acetone the derivative **27** is formed with a yield of more than 90% [52] (Scheme 3).



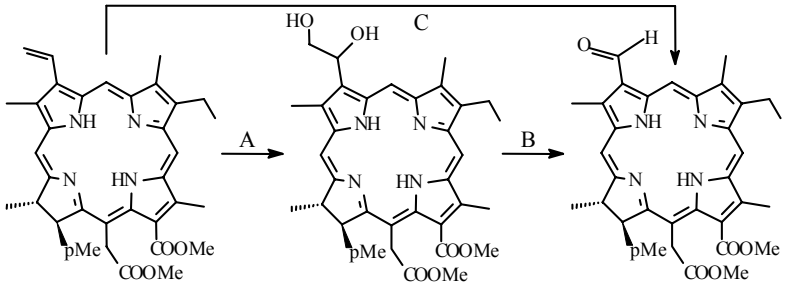
7 M = 2H
23 M = Ni
24 M = Ni
27 M = 2H
25
26

A: Raney nickel in Et_2O/EtOH (for the production of **24**-**26** from **23**).
B: Pd/C in Me_2CO (for the production of **27** from **7**).

Scheme 3. Reduction of the peripheral vinyl group*

Oxidation of the Vinyl Group

Potassium permanganate [22, 54], ozone [55], and noncatalytic [56] and catalytic [57-62] oxidation with osmium tetroxide have been proposed for oxidation of the vinyl group to a formyl substituent. Thus, the reaction of 1 eq. of chlorin **15** with 1 eq. of OsO_4 in pyridine led to the diol **28** with a 100% yield [56]. This was converted by treatment with $NaIO_4$ in aqueous dioxane into the aldehyde **29** with a yield of 84%. An alternative effective method for the production of the aldehyde **29** is the oxidation of vinylchlorin **15** by means of the $OsO_4/NaIO_4$ system [61] (Scheme 4).



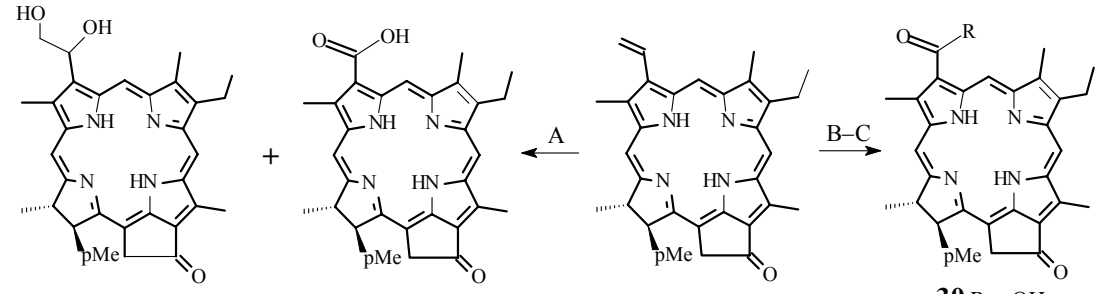
15 **28** **29**

A: OsO_4–Py
B: $NaIO_4$–H_2O–dioxane
C: OsO_4–$NaIO_4$

Scheme 4. Transformation of a peripheral vinyl group into a formyl substituent.

* Here and subsequently the abbreviation p = $CH_2CH_2CO_2$ is used in the formulas, i.e., pMe = $CH_2CH_2CO_2Me$.

The vinyl group of pyropheophorbide **7** is oxidized by potassium permanganate to a carboxyl group with the formation of the acid **30** with yields between 3% [63] and 30% [64]. According to data in [63], the low yield of the acid **30** is due to the parallel formation of the glycol **31**. Two-stage oxidation of the pyropheophorbide **7** was proposed for the production of the derivative **30** with an acceptable yield. The vinylchlorin **7** was first oxidized with high yield to the aldehyde **32**, from which the acid **30** was obtained (yield 81%) by the action of $NaClO_2$ and NH_2SO_3H in the presence of 2-methyl-2-butene [63] (Scheme 5).



A: $KMnO_4$

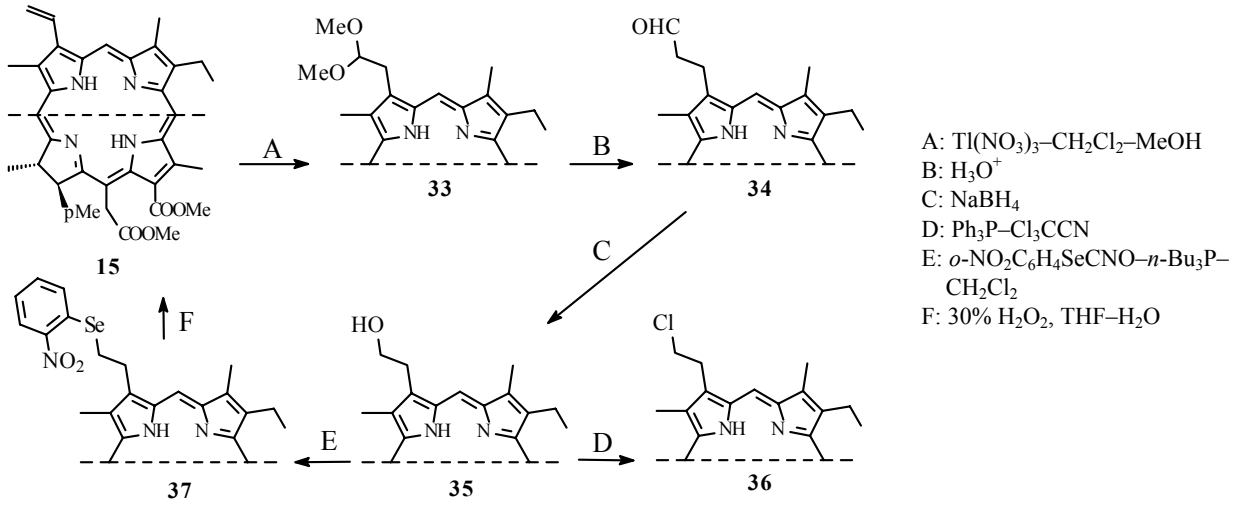
B: OsO_4–NaIO4 (for the production of **32** from **7**);

C: NH_2SO_3H–$NaClO_2$–MeC(Me)CHMe (for the production of **30** from **32**)

Scheme 5. Various versions of the oxidation of a peripheral vinyl group.

The vinyl group of the chlorin **15** is oxidized by $Tl(NO_3)_3$ in $MeOH/CH_2Cl_2$ to the acetal **33**, which is hydrolyzed in an acidic medium to the aldehyde **34**. Reduction of the derivative **34** with $NaBH_4$ leads to the formation of the hydroxyethyl derivative **35** [65]. The sequence of transformations described above can be regarded formally as a method for hydration of the vinyl group in chlorophyll derivatives against the Markovnikov rule [28, 56, 65, 66]. Nucleophilic substitution of the hydroxy group in the 3-(2-hydroxyethyl) substituent of chlorin **35** by a chlorine atom with the formation of the chlorine derivative **36** takes place readily in the Ph_3P/Cl_3CCN system [56].

Recently an effective method was proposed for protection of the vinyl group of chlorophylls using the organoselenium reagent *o*-$O_2NC_6H_4SeCNO$ [67]. The vinyl group can be regenerated from the derivative **37** with a yield of ~100% under the conditions used for isolation of the chlorin **15** (Scheme 6).



A: $Tl(NO_3)_3$–CH_2Cl_2–MeOH

B: H_3O^+

C: $NaBH_4$

D: Ph_3P–Cl_3CCN

E: *o*-$NO_2C_6H_4SeCNO$–*n*-Bu_3P–CH_2Cl_2

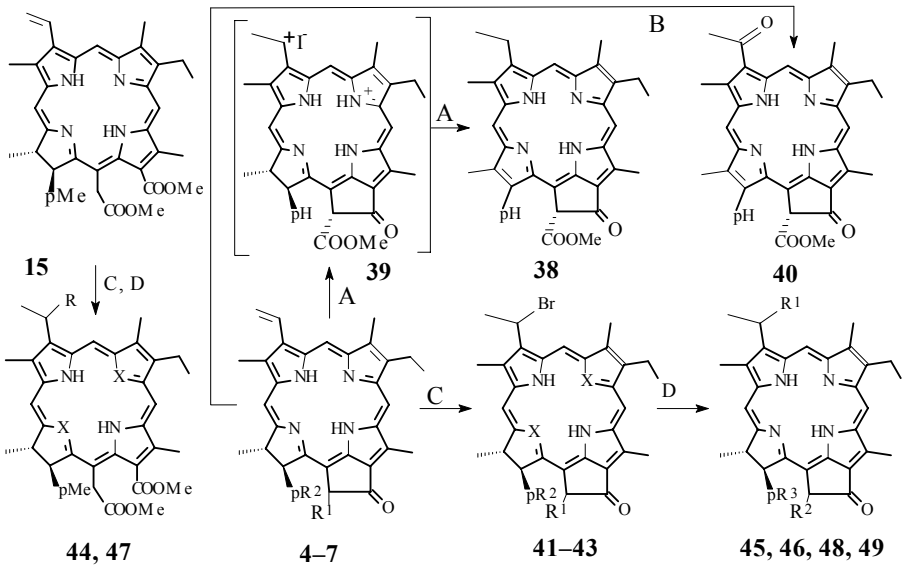
F: 30% H_2O_2, THF–H_2O

Scheme 6. The synthesis and pathways to modification of the 3^2-hydroxyethyl substituent.

Addition to the Vinyl Group

If the vinylchlorin **4** is heated with HI in PH_4I/AcOH, the ethylporphyrin **38** is formed. The principle of the transformation of vinylchlorins into ethylporphyrins (the so-called "HI-isomerization) presumably implies the initial formation of the intermediate **39**, which is then transformed into compound **38** in several stages. Treatment of the chlorin **4** in the HI/AcOH system at room temperature in the presence of oxygen gives the acetylporphyrin **40** with a yield of 20-40% (the so-called "oxo reaction") (for greater detail, see [69]) (Scheme 7).

Hydrobromination of the vinyl group in chlorins **5**-**7**, **15** is realized by the action of a solution of hydrobromic acid in acetic acid. Treatment of the respective perbromides **41**-**44** with alcohol [60, 69], water, or thiol [70] leads to the alkoxy derivatives **45**-**47**, the alcohol **48**, and the mercapto derivative **49** (Scheme 7).

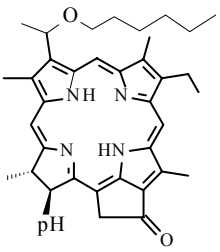


4 R^1 = COOMe, R^2 = H; **5** R^1 = COOMe, R^2 = Me; **6** R^1 = R^2 = H; **7** R^1 = H, R^2 = Me; **14** R^1 = R^2 = R^3 = H;
41 X = N·HBr, R^1 = COOMe, R^2 = Me; **42** X = N·HBr, R^1 = R^2 = H;
43 X = N·HBr, R^1 = H, R^2 = Me; **44** X = N·HBr, R = Br; **45** R^1 = OAlk, R^2 = COOMe, R^3 = Me;
46 R^1 = OAlk, R^2 = H, R^3 = Me; **47** R = OAlk, X = N; **48** R^1 = OH, R^2 = R^3 = H; **49** R^1 = SR^4 (R^4 – sugar residue), R^2 = R^3 = H

A: HI–$PH_4^+I^-$–AcOH–heat (for the production of compound **38** from **4** through the initial formation of **39**);
B: HI–AcOH–oxygen–room temperature (for the production of **40** from **4**);
C: HBr–AcOH;
D: ROH (R = Alk) – for the production of **45**-**47** from **41** and **43**-**44** respectively, **41**, **43**-**44**;
(R = H) – for the production of **48** from **42**; R^4SH (R^4 – sugar residue) – for the production of **49**

Scheme 7. Modification of a peripheral vinyl group with hydrohalogens.

It was noted that functionalization of the vinyl group of chlorophyll derivatives by alcohols is a suitable method for the construction of products for PDT ([6, 7, 60] and the references therein). Thus, compound **50** (commercial name Photochlor®) is undergoing clinical trials in the USA as a prospective product for PDT of cancer ([5, 6] and references therein) (Scheme 8).



50 Photochlor®

Scheme 8

Various pathways have been proposed for the transformation of 3^1-alkoxyethyl [69, 71, 72] and 3^1-hydroxyethyl [22, 70, 73-76] substituents in chlorophyll derivatives.

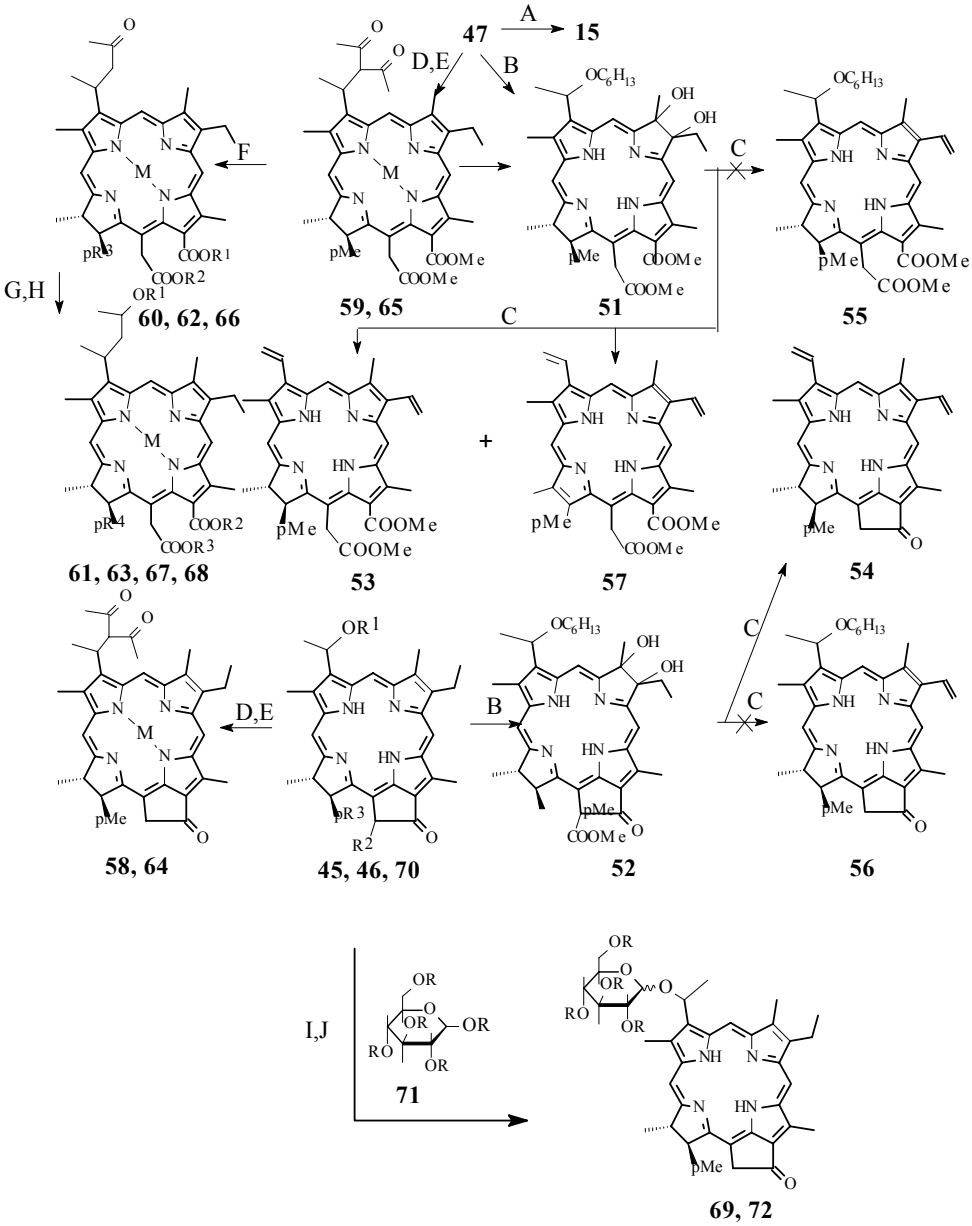
Thermolysis of 3^1-Alkoxyethyl Derivatives. When heated under high vacuum the alkoxyethyl derivative **47** forms the vinylchlorin **15**. Under more rigorous conditions (1,2-dichlorobenzene, 165°C, 5 h) the elimination of alcohol and water occurs in the bacteriochlorins **51** and **52** while decarboxymethylation also occurs in compound **52**, and the corresponding chlorins **53** and **54** are formed. The transformation was discovered during an attempt to realize double dehydration at positions 7 and 8 of bacteriochlorins **51** and **52** in order to produce the easily functionalized 8-vinyl group of compounds **55** and **56**. It was noted that the divinylporphyrin **57** is formed as a result of pyrolysis of the bacteriochlorin **51** [69].

Modification of the 3^1-Alkoxyethyl Substituent by CH-Acids. In the presence of zinc acetate compounds **46** and **47** readily react with the CH acid acetylacetone, forming the zinc complexes **58** and **59** with high yields [71, 72]. Alkaline treatment of the chlorin **59** leads to ketone cleavage of its β-diketonate residue with the formation of the ketone **60**, the reduction of which with $NaBH_4$ gives the alcohol **61** [72]. Demetallation of the metal complexes **58**-**61** with 6 N hydrochloric acid [71, 72] followed by esterification of the intermediates **62** and **63** leads to the free bases **64**-**67**, while acetylation of the hydroxy group of the chlorin **67** gives the acetate **68** [72].

Glycosylation of the 3^1-Hydroxyethyl Substituent. The production of the glycoside pyropheophorbide compound **69** by glycosylation of the 3^1-hydroxyethyl of chlorin **70** with the carbohydrate **71** in the presence of boron trifluoride etherate was reported in [70]. The acetyl groups of the carbohydrate fragment of compound **69** were removed at room temperature in the MeONa–MeOH system, and the O-glycoside derivative **72** was obtained with a yield of 87% (Scheme 9).

Creation of a Stereogenic Center Based on the 3^1-Hydroxyethyl Substituent. In the reaction of a racemic mixture of the 3^1R and 3^1S isomers **70** with vinyl acetate (donor of the acyl group) in toluene in the presence of *Amano PS* or *Toyobo* lipase the corresponding acetate **73** is formed. Its methanolysis in the presence of potassium carbonate leads to a mixture of the initial alcohols rich in the 3^1R isomer **70**. The small diastereomeric excess (44%) of the vinyl acetate **73** is due to the fact that on account of the large size of the chlorin fragment the 3-(1-hydroxyethyl) group of the chlorin **70** cannot bond effectively with the active center of the enzyme, as a result of which the catalytic activity of the lipase is significantly reduced [73] (Scheme 10).

Oxidation of the 3^1-Hydroxyethyl Group in an Acetyl Substituent. With $KMnO_4$ in Me_2CO [22], with $(PyH)_2Cr_2O_7$ [74], and most effectively with the Pr_4NRuO_4–$Me(O)N(CH_2CH_2)_2O$ system [73, 75] the 3^1-hydroxyethyl group is oxidized to acetyl. Thus, treatment of the chlorin **70** with the Pr_4NRuO_4–$Me(O)N(CH_2CH_2)_2O$ system gives a high yield of the acetyl derivative **74** [73]. It is interesting to note that treatment of the chlorin **75**, containing a 3-(1-hydroxyethyl) substituent in the presence of an 8-hydroxymethyl substituent, with $(PyH)_2Cr_2O_7$ leads to the formation of the corresponding 8-formyl derivative **76** with a yield of 79% [76]. In all probability the inertness of the 3-(1-hydroxyethyl) group toward $(PyH)_2Cr_2O_7$ is due to steric hindrances during coordination of the bulky $(PyH)_2Cr_2O_7$ molecule with the relatively inaccessible hydroxy group at position 3^1 of the pyropheophorbide **75** (Scheme 11).



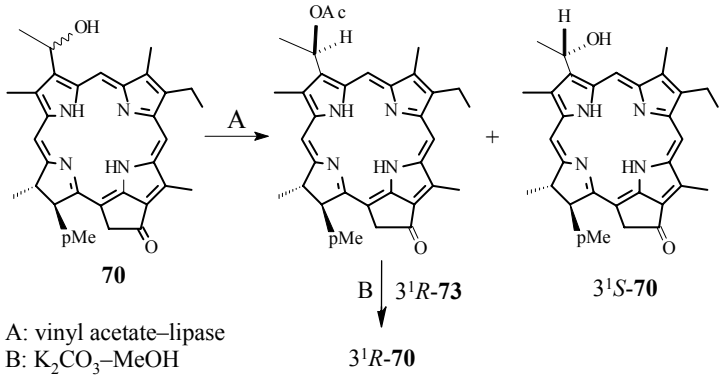
45 $R^1 = C_6H_{13}$, R^2 = COOMe, R^3 = Me; **46** R^1 = Et, R^2 = H, R^3 = Me; **58-61** M = Zn; **60** $R^1 = R^2 = R^3$ = K; **61** R^1 = H, $R^2 = R^3 = R^4$ = K; **62** M = 2H, $R^1 = R^2 = R^3$ = H; **63** M = 2H, $R^1 = R^2 = R^3 = R^4$ = H; **64, 65** M = 2H; **66** M = 2H, $R^1 = R^2 = R^3$ = Me; **67** M = 2H, R^1 = H, $R^2 = R^3 = R^4$ = Me; **68** M = 2H, R^1 = Ac, $R^2 = R^3 = R^4$ = Me; **69**, **71** R = Ac; **70** $R^1 = R^2$ = H, R^3 = Me; **72** R = H

A: Heat under high vacuum; B: OsO_4–H_2S; C: 1,2-Dichlorobenzene, 165°C, 5 h; D: Acetylacetone–$Zn(OAc)_2 \cdot 2H_2O$, 40-70 min; E: 6N HCl; F: KOH–dioxane, 55°C, 4 h, then 6N HCl, 4% H_2SO_4 in MeOH; G: $NaBH_4$–MeOH, 40°C, a few hours, 6N HCl, CH_2N_2 in Et_2O; H: Ac_2O–pyridine, 6 h; I: $BF_3 \cdot Et_2O$, **71;** J: MeONa–MeOH

Scheme 9. Pathways for modification of the 3^1-alkoxy- and 3^1-hydroxyethyl substituent of chlorophyll derivatives.

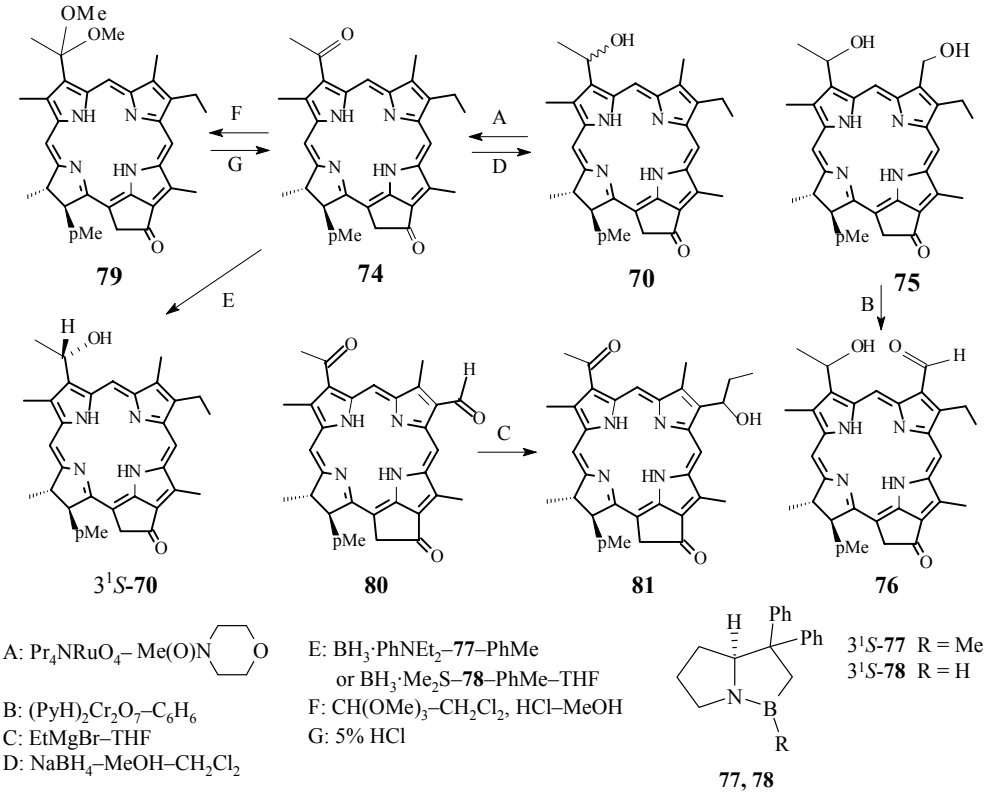
The acetyl readily enters into reduction [73, 75, 77] and nucleophilic addition [75, 77, 78].

Reduction of the Acetyl Group to a 3^1-Hydroxyethyl Substituent. The reduction of the acetyl fragment of chlorin **74** to the 3-(1-hydroxyethyl) derivative **70** takes place readily under the influence of sodium borohydride in methylene chloride/methanol [75]. The alcohol **70** is formed as a mixture of diastereomers.



Scheme 10. The creation of a stereogenic center based on the 3^1-hydroxyethyl group.

The asymmetric reduction of the acetyl group in chlorin **74** with borane in the presence of the chiral oxaborolidines **77** and **78** leads to the selective formation of the chiral derivatives **70**. Oxaborolidines are effective chiral components in such transformations. It was noticed that reduction on the tetrapyrrole substrate in the presence of (*S*)-oxaborolidines leads to the formation of the ($3^1$1*S*)-alcohol **70** as the main compound, although reduction of "normal" prochiral ketones ArCOX, on the other hand, leads to the formation of the *R* alcohols. Such "inversion" of the stereoselectivity is due to the multifunctional nature of the tetrapyrrole chromophore, the different steric effects, and the unusual interactions between the tetrapyrrole and the reducing agents [73] (Scheme 11).



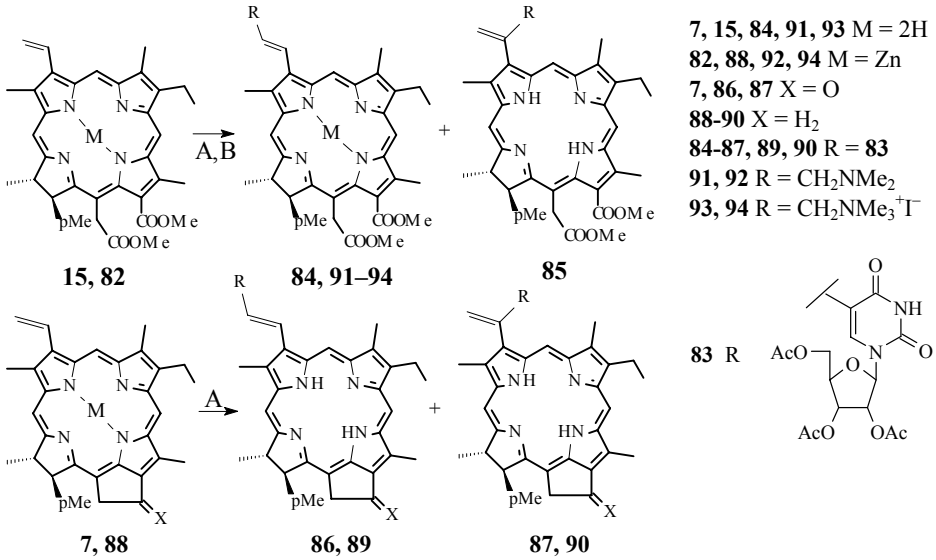
Scheme 11. Oxidation of the 3^1-hydroxyethyl group to an acetyl group and its modification pathways.

Nucleophilic Addition to the Acetyl Group. The acetyl group readily forms diketals [75, 78]. Thus, by the action of $CH(OMe)_3/CH_2Cl_2$ and HCl/MeOH the chlorin **74** is transformed into the derivative **79** [75], brief treatment of which with 5% hydrochloric acid leads to the formation of the initial acetylchlorin **74** with a yield of 100%. This sequence of transformations can be regarded at a method for the protection of the acetyl group. The acetyl group of 3-acetylchlorins is not very reactive towards Grignard reagents. Thus, during the action of ethylmagnesium bromide on the chlorin **80** the alcohol **81**, i.e., the product from attack of the Grignard reagent on the 8-CHO group of the chlorin **80**, is formed with a yield of 60%. According to the ^{1}H NMR spectra, the chlorin **81** is formed as an equimolar mixture of diastereomers. Thus, the ethylmagnesium bromide attacks selectively the most active 8-formyl group in the presence of three other potential points of attack (the 3,13-carbonyls and COOMe in the 17-propionic residue) [77] (Scheme 11).

Substitution at the Vinyl Group

Vinylchlorins react with various organomercury molecules under the conditions of the Heck reaction [79-81]. Thus, treatment of the zinc complex **82** with the modified nucleoside **83** leads to the formation of the *trans* and *gem* isomers **84** and **85** with yields of 29 and 13% respectively; the metal-free pyropheophorbide **7** gives mainly the *trans* isomer **86** with a yield of 17% and only traces of the *gem* isomer **87**, while the introduction of the zinc complex the 13^1-deoxy derivative **88** into the reaction leads to the *trans* and *gem* isomers **89** and **90** in practically equivalent amounts (8 and 9.6% respectively) [81]. In all probability, the yield and the ratio of the obtained isomers are determined mainly by the structure of the original tetrapyrrole (Scheme 12).

It is known that N,N-dimethylmethyleneimmonium iodide (Eschenmoser's salt) is an effective reagent for the introduction of a dimethylaminomethyl group into the pyrrole heterocycle [82]. Thus, if compounds **15** and **82** are used as pyrrole substrates, the corresponding derivatives **91** and **92** are formed with good yields. Investigation of the ^{1}H NMR spectra of the adducts **91** and **92** showed that the dimethylaminomethyl group condenses with the vinyl group only in the *trans* position. Quaternization of the amines **91** and **92** with methyl iodide leads to the water-soluble methiodides **93** and **94** [83, 84] (Scheme 12).

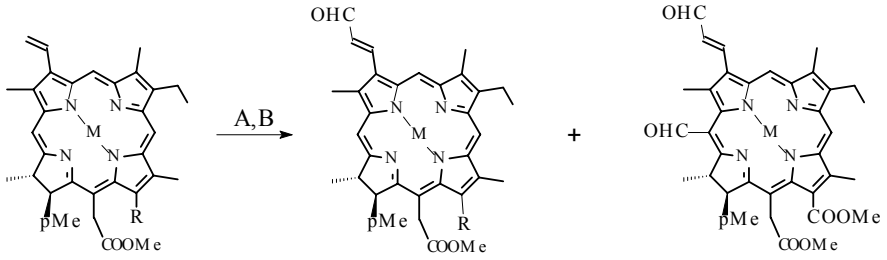


A: RHgCl (R = **83**)–$LiPdCl_3$ (for the production of **84** and **85**, **86** and **87**, and **89** and **90** from **82**, **7**, and **88** respectively); $H_2C{=}NMe_2^+I^-$ (for the production of **91** and **92** from **15** and **82** respectively)

B: MeI (for the production of **93** and **94** from **91** and **92** respectively)

Scheme 12. The introduction of nucleoside residues and a dimethylaminomethyl group along the periphery of the chlorin macrocycle.

The enhanced electron density at the peripheral vinyl group gives rise to activity in the Vilsmeier reaction. Thus, during brief heating to 100°C in a mixture of phosphorus oxychloride and DMFA followed by demetallation of the intermediates **97** and **98**, and **99** respectively the metal complexes **95** and **96** give the respective formyl derivatives **100** and **101** and **102**. It was noted that if the metal complex **95** is used as substrate the products from monoformylation **100** and diformylation **101** are formed. Under analogous conditions the metal complex **96** forms compound **102** – the result of exclusive attack at the vinyl group of the chlorin **96** [85]. Selective functionalization of the vinyl group can also be achieved in the case where the Vilsmeier reaction is conducted at a copper complex. Thus, the formyl derivative **100** is obtained during formylation of the metal complex **103** by the $POCl_3$/DMF system after demetallation of the intermediate **104** [50, 56] (Scheme 13).



95, 96, 103 | **97, 99, 100, 102, 104, 105** | **98, 101**

95 M = FeCl, R = COOMe
96 M = FeCl, R = H
97 M = FeCl, R = COOMe
98 M = FeCl

99 M = FeCl, R=H
100 M = 2H, R = COOMe
101 M = 2H
102 M = 2H, R = H

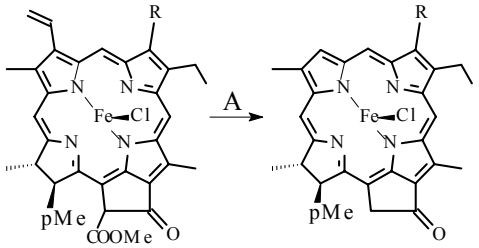
103 M = Cu, R = COOMe
104 M = Cu, R = COOMe

A: $POCl_3$/DMF (for the production of compounds **97** and **98**, **99**, and **104** from **95**, **96**, and **103** respectively).
B: Acid treatment (for the production of **100**, **101**, **102** from **97** and **104**, **98**, and **99** respectively).

Scheme 13. Versions of the introduction of an aldehyde along the periphery of the chlorin macrocycle using the Vilsmeier reaction.

Elimination of the Vinyl Group

Electrophilic elimination of the vinyl group of vinylchlorins (so-called devinylation) is easily realized by heating them in molten resorcinol. The main side processes occurring during devinylation are 13^2-demethoxycarbonylation (see the section on "Demethoxycarbonylation at Position 13^2 of the Exocycle),



105 R = Me
107 R = CHO

106 R = Me
108 R = H

A: Heating in molten resorcinol

Scheme 14: The elimination of a peripheral vinyl group.

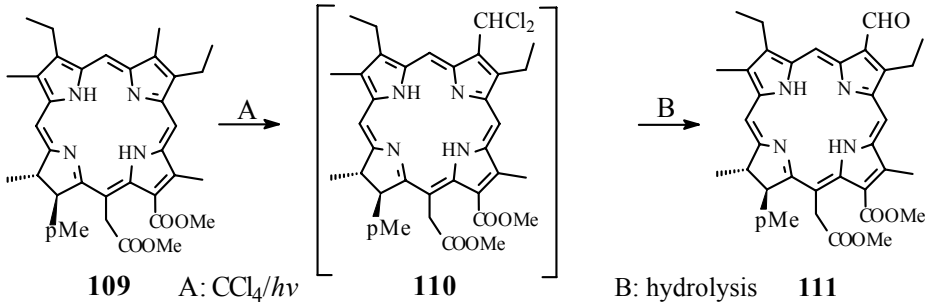
oxidation of the chlorin macrocycle to the thermally more stable porphyrin derivative, and additional deformylation in the case of the devinylation of derivatives of the *b* series. Thus, when the metal complex **105** is heated in molten resorcinol the divinylchlorin **106** is formed, while if the metal complex of the *b* series **107** is used 3-devinyl-7-deformylchlorin **108** is formed [22] (Scheme 14).

Pathways for Modification of a Formyl Group

Versions of the Introduction of a Formyl Group

The main methods for the introduction of a formyl group into the chlorin macrocycle include oxidation of the vinyl group (for greater detail, see the section on "Oxidation of the Vinyl Group"), oxidation of the 15-CH_2COOH group (see the section on "Pathways for Modification of the Carboxyl Groups of the Products from Opening of the Exocycle"), and the Vilsmeier reaction (see [52, 65, 67, 87-89] and the section on "Substitution at the Vinyl Group").

Photochemical modification of the peripheral substituents has also been proposed for the introduction of a formyl [90, 91]. Thus, the formyl derivative **111** is obtained with a good yield by irradiation of the chlorin **109** in carbon tetrachloride solution followed by hydrolysis of the intermediate dichloromethyl derivative **110**. It is assumed that the mechanism of formation of the intermediate **110** rests on sensitization of the carbon tetrachloride, partial photolysis to the Cl· radical, and possible stereospecific substitution of the methyl group of the chlorin **109** at position 7 (Scheme 15).

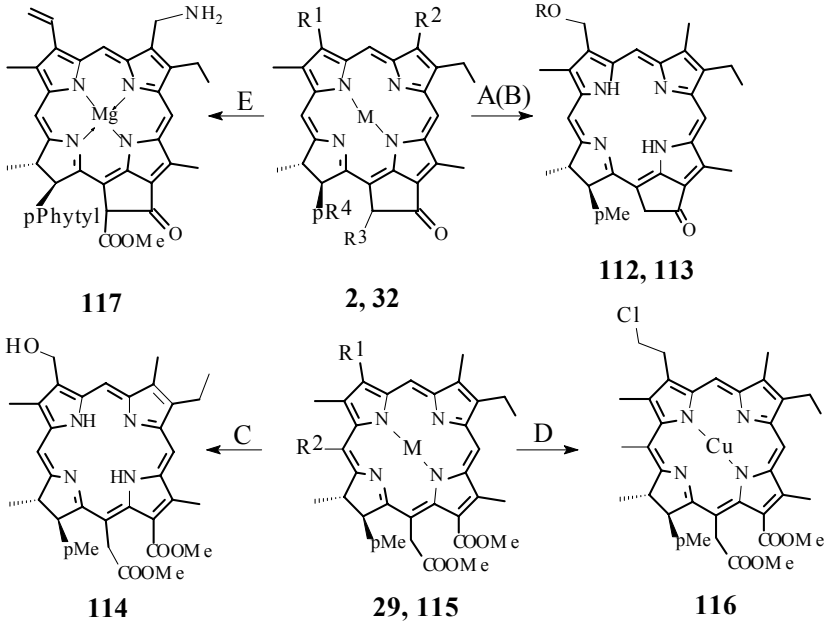


Scheme 15. The photochemical method of introduction of a formyl group.

Reduction of the Formyl Group

The formyl group is easily reduced to a hydroxymethyl group by the action of $NaBH_4$ or $Al(O\text{-}i\text{-}Pr)_3$ [22]. With the use of these reducing agents on a tetrapyrrole substrate containing several carbonyl groups it is difficult to achieve selectivity in the reduction of the formyl group [28]. The selective reduction of the formyl group of the pyropheophorbide **32** to a hydroxymethyl substituent with the formation of the derivative **112** is achieved by the action of *t*-$BuNH_2 \cdot BH_3$ [92], $Bu_4NBH(OAc)_3$ [55], or $NaBH_3CN$ [63]. The reductive alkylation of the aldehyde group of the chlorin **32** to the methoxymethyl derivative **113** can be achieved is conducted with an acceptable yield by the action of the $MeOH/H_2SO_4/Et_3SiH$ system [92]. The aldehyde **29** is transformed by the action of sodium borohydride into the alcohol **114** [71]. The reduction of the aldehyde group in the *meso* position by means of sodium borohydride under the conditions of high acidity leads to a methyl group [50, 65]. Thus, treatment of the metal complex **115** with the $NaBH_4$/AcOH system gives a high yield of the derivative **116**

[65]. Reductive amination of the aldehyde group in chlorins has also been described [93, 94]. Thus, treatment of the chlorophyll **2** with the NH_4OAc–$NaBH_3CN$–MeOH system gives the aminomethyl derivative **117** with a yield of 80% [94] (Scheme 16).

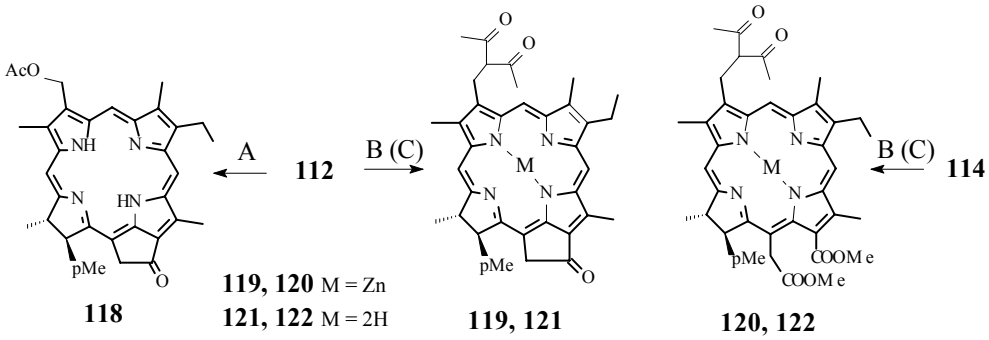


117 **2, 32** **112, 113** **114** **29, 115** **116**

2 M = Mg, R^1 = CH=CH_2, R^2 = CHO, R^3 = COOMe, R^4 = Phytyl; **29** M = 2H, R^1 = CHO, R^2 = H;
32 M = 2H, R^1 = CHO, R^2 = R^4 = Me, R^3 = H; **112** R = H; **113** R = Me; **115** M = Cu, R^1 = CH_2CH_2Cl, R^2 = CHO
A: *t*-$BuNH_2 \cdot BH_3$, $Bu_4N^+BH(OAc)_3^-$ or $NaBH_3CN$ (for the production of **112** from **32**);
B: MeOH–H_2SO_4–Et_3SiH (for the production of **113** from **32**); C: $NaBH_4$ (for the production of **114** from **29**);
D: $NaBH_4$–AcOH (for the production of **116** from **115**); E: NH_4OAc–$NaBH_3CN$–MeOH (for the production of **117** from **32**)

Scheme 16. The various versions of reduction of the aldehyde group.

Methods for modification of the hydroxymethyl group in chlorins **112** and **114** were proposed. Thus, the acetoxy derivative **118** was obtained by treating the alcohol **112** with acetyl chloride in pyridine [63]. The reaction of the chlorins **112** and **114** with the CH-acid acetylacetone in the presence of zinc acetate gave the metal complexes **119** and **120**, the brief treatment of which with 6 N hydrochloric acid led to the free bases **121** and **122** [71] (Scheme 17).



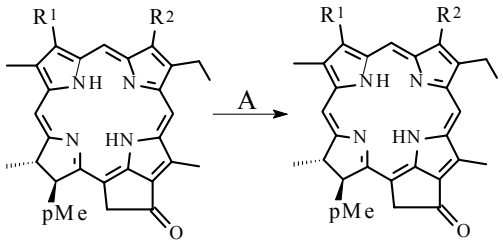
118 **119, 120** M = Zn **121, 122** M = 2H **119, 121** **120, 122**

A: $Zn(OAc)_2 \cdot 2H_2O$–acetylacetone, 110°C (for the production of **119** and **120** from **112** and **114** respectively);
AcCl–pyridine (for the production of **118** from **112**)
B: 6N hydrochloric acid (for the production of **121** and **122** from **119** and **120** respectively)

Scheme 17. Pathways for modification of the hydroxymethyl group.

Oxidation of the Formyl Group

By oxidizing the aldehyde groups of chlorophylls it is possible to introduce a carboxyl group at various positions of the chlorin ring. Thus, the aldehydes **12** and **32** are oxidized to the carboxy derivatives **123** and **30** by the action of NH_2SO_3H and $NaClO_2$ in the presence of 2-methyl-2-butene [63] (Scheme 18).



12, 32 **30, 123**

12 R^1 = CH=CH_2, R^2 = CHO
30 R^1 = COOH, R^2 = Me
32 R^1 = CHO, R^2 = Me
123 R^1 = CH=CH_2, R^2 = COOH

A: NH_2SO_3H–$NaClO_2$–$H_3CC(Me)$=CHMe
(for the production of **30** and **123** from **32** and **12** respectively)

Scheme 18. Oxidation of the formyl groups of chlorophyll derivatives to carboxyl substituents.

The insertion of a carboxyl group at position 3 or 7 of the chlorophyll macrocycle opens up wide possibilities for its further modification. Thus, it can be easily transformed into an amide [63, 95-97], ester, or anhydride [63, 97] group.

Nucleophilic Addition to the Formyl Group

The aldehyde group of the chlorophyll **2** and other formylchlorins contains a powerful nucleophilic center, giving rise to the ease of its reaction with a wide range of nucleophiles.

The Production of Imino Derivatives

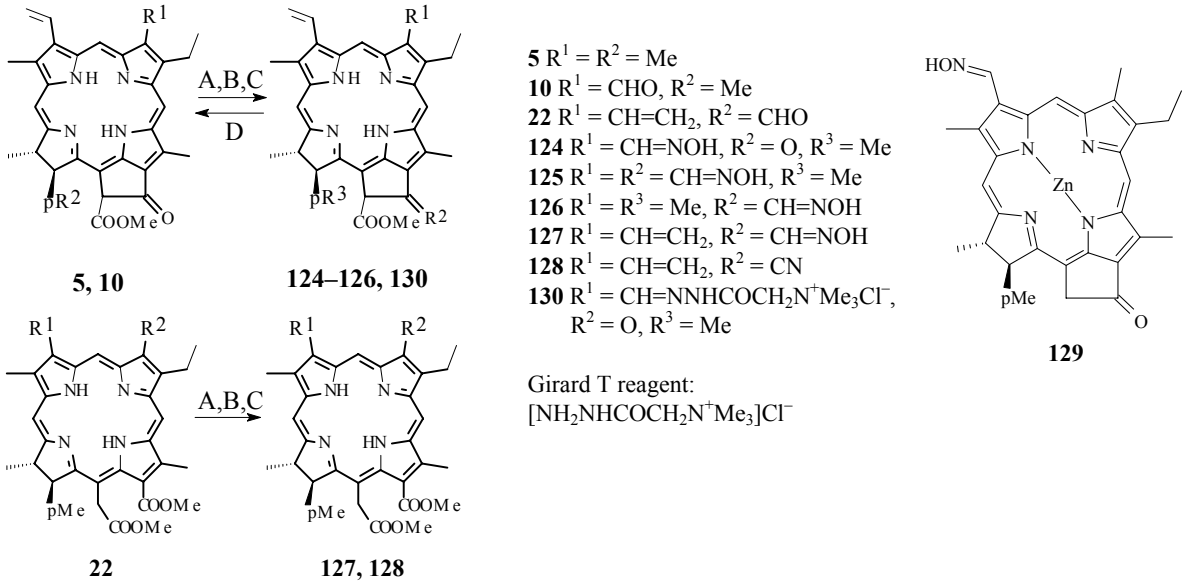
The reaction of the aldehyde **10** with $NH_2OH·HCl$ in pyridine at room temperature leads to the formation of the aldoxime **124** [98]. By increasing the temperature it is possible to obtain oximes at position 13^1 in various chlorophyll derivatives. Under these conditions compound **10** forms the 3,13^1-dioxime **125** [98], while the derivative **5** forms the 13^1-monoxime **126** [99]. Under analogous conditions the aldehyde **22** is transformed into the aldoxime **127**, the heating of which in acetic anhydride gives the cyano derivative **128** [85]. The production of the oxime **129** was reported in [100].

A method was proposed for separating the chlorins of series *a* and *b* using the Girard T reagent [49, 101]. Thus, the hydrazide **130** is formed regioselectively during the action of this reagent on a mixture of the chlorins **5** and **10** in the presence of acetic acid. In view of the high polarity of the hydrazide **130** compared with compound **5** the compounds are easily separated by column chromatography. Acid solvolysis of the hydrazide **130** with a $MeOH/Me_2CO/H_2SO_4$ mixture leads to the initial aldehyde **10**. Thus, with the Girard T reagent it is possible to separate phorbin derivatives of the *a* and *b* series effectively [49] (Scheme 19).

Imino derivatives are also obtained on the basis of the formyl group at position 15 (see the section on "Pathways for Modification of the Carboxyl Groups of the Products from Opening of the Exocycle").

Production of Vinyl Derivatives

With the right strategy by the Wittig [51, 55, 56, 58, 102-106], Knoevenagel [104], McMurry [107-109], and other condensations [57, 105, 110] it is possible to construct effectively various vinyl derivatives based on the formyl group of chlorophylls.



A: $NH_2OH·HCl$–pyridine, room temperature (for the production of **124** from **10**)
B: $NH_2OH·HCl$–pyridine, 100°C (for the production of **125-127** from **10**, **5**, and **22** respectively)
C: Ac_2O, heat (for the production of **128** from **127**); Girard T reagent
AcOH (for the production of **130** from **10**)
D: MeOH–Me_2CO–H_2SO_4 (for the production of **10** from **130**)

Scheme 19. The production of imino derivatives based on the formyl group of chlorophyll derivatives.

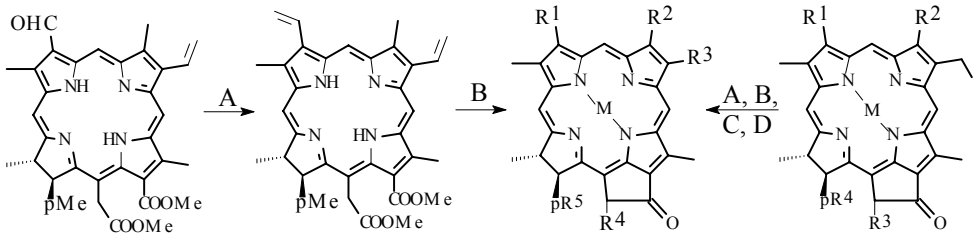
The Wittig Reaction. Treatment of the metal complex **131** with phosphorane ($Ph_3P=CH_2$) leads to the formation of the vinyl derivative **132** with a yield of 32% [55], but if the chlorophyll **2** is used as formyl substrate the 7-vinyl derivative **133** is formed with a yield of 60% [102]. The metal-free derivatives of chlorophylls also react with phosphorane [55, 56, 103, 104] and its homologs [51, 104], and here the phorbin derivatives **10**, **12**, **32**, and **134** form the respective ethylidenechlorins **135**, **136**, **7**, and **5** with low yields, while the nonphorbin chlorin **137** forms the derivative **53** with a yield of more than 80% [56, 103].

Two effective pathways were proposed for the production of vinylphorbin derivatives. The first involves preliminary construction of the divinylchlorin **53** from the formylchlorin **137** by the Wittig reaction, and its cyclization with a strong base leads to the phorbin structure **138** with a yield of 82% (see the section on "Recyclization of the Exocycle") [56]. The second approach involves transformation of the aldehyde group of the phorbin chlorins **32** and **134** into the reactive phosphonium salts **139** and **140**, which are converted into the derivatives **7** and **5** with good yields by the action of paraformaldehyde in the presence of epoxypropane. For this the aldehyde group of the chlorins **32** and **134** is reduced to the hydroxymethyl derivatives **112** and **141**, treatment of which with the Ph_3P/CBr_4 system gives the phosphonium salts **139** and **140** [55] (Scheme 20).

The Wittig reaction was studied in greatest detail for the formyl substrate **32** in [104].

The Knoevenagel Reaction. The base-catalyzed reaction of the aldehyde **32** with malononitrile, dimethyl malonate, and methyl cyanoacetate leads to the corresponding vinyl derivatives **142-145** [104]. It was shown that the yields of compounds **142-145** are determined by the nucleophilic activity of the employed activated methylene components and by the steric effects during the joint coordination of the bulky aldehyde molecule **32** with the nucleophile (Scheme 21).

The McMurry Reaction. An effective method for the synthesis of homodimers [107-109] and heterodimers [108] of various tetrapyrroles whose monomers are linked by a system of double bonds is the McMurry reaction [112, 113]. Tetrapyrroles containing a carbonyl group, which can be at various positions of

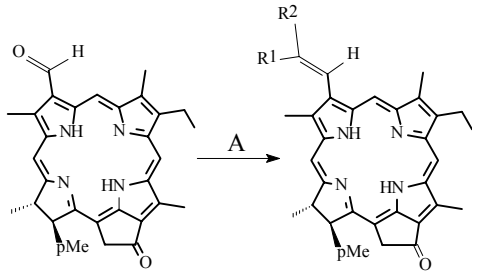


137 **53** **5, 7, 132,133, 135,136, 138** **2, 10, 12, 32, 112, 131, 134, 139–141**

2 M = Mg, R^1 = CH=CH_2, R^2 = CHO, R^3 = COOMe, R^4 = Phytyl; **5** M = H, R^1 = CH=CH_2, R^2 = R^5 = Me, R^3 = Et, R^4 = COOMe;
7 M = 2H, R^1 = CH=CH_2, R^2 = R^5 = Me, R^3 = Et, R^4 = H; **10** M = 2H, R^1 = CH=CH_2, R^2 = CHO, R^3 = COOMe, R^4 = Me;
12 M = 2H, R^1 = CH=CH_2, R^2 = CHO, R^3 = H, R^4 = Me; **32** M = 2H, R^1 = CHO, R^2 = R^4 = Me, R^3 = H;
112 M = 2H, R^1 = CH_2OH, R^2 = R^4 = Me, R^3 = H; **131** M = Zn, R^1 = CHO, R^2 = R^4 = Me, R^3 = H;
132 M = Zn, R^1 = CH=CH_2, R^2 = R^5 = Me, R^3 = Et, R^4 = H; **133** M = Mg, R^1 = R^2 = CH=CH_2, R^3 = Et, R^4 = COOMe, R^5 = Phytyl;
134 M = 2H, R^1 = CHO, R^2 = R^4 = Me, R^3 = COOMe; **135** M = 2H, R^1 = CH=CH_2, R^2 = CH=CHMe, R^3 = Et, R^4 = COOMe, R^5 = Me;
136 M = 2H, R^1 = CH=CH_2, R^2 = CH=CHMe, R^3 = Et, R^4 = H, R^5 = Me; **138** M = 2H, R^1 = R^3 = CH=CH_2, R^2 = R^5 = Me, R^4 = COOMe;
139 M = 2H, R^1 = $Ph_3P^+CH_2Br^-$, R^2 = R^4 = Me, R^3 = H; **140** M = 2H, R^1 = $Ph_3P^+CH_2Br^-$, R^2 = R^4 = Me, R^3 = COOMe;
141 M = 2H, R^1 = CH_2OH, R^2 = R^4 = Me, R^3 = COOMe

A: Ph_3P=CH_2 (for the production of **5**, **7**, **53**, **132**, and **133** from **134**, **32**, **137**, **131**, and **2** respectively)
Ph_3P=CHMe (for the production of **135** and **136** from **10** and **12** respectively);
B: $NaN(SiMe_3)_2$ (for the production of **138** from **53**); $Bu_4NBH(OAc)_3$ (for the production of **112** and **141** from **32** and **134** respectively);
C: Ph_3P–CBr_4 (for the production of **139** and **140** from **112** and **141** respectively);
D: paraformaldehyde–1,2-epoxypropane (for the production of **5** and **7** from **140** and **139** respectively)

Scheme 20. Functionalization of the aldehyde groups of chlorophylls and their derivatives using the Wittig reaction.



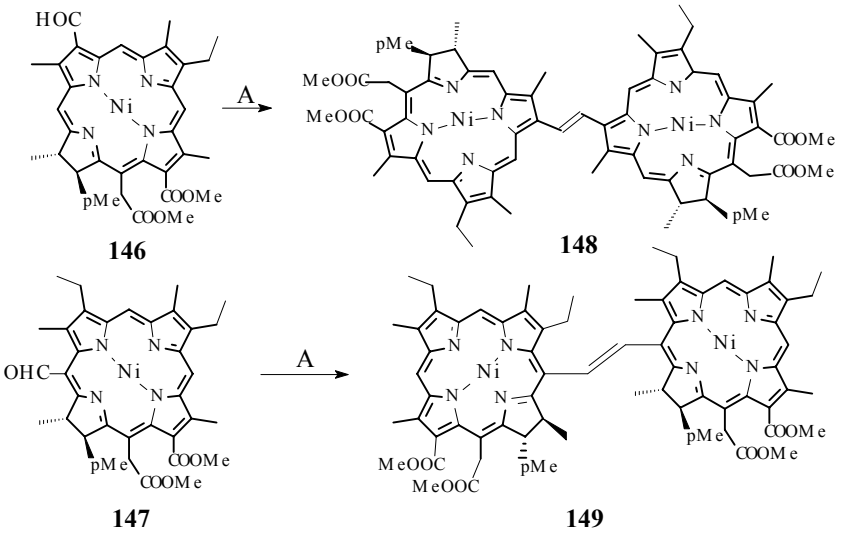
32 **142–145**

142 R^1 = R^2 = CN (76%)
143 R^1 = R^2 = COOMe (52%)
144 R^1 = CN, R^2 = COOMe (78%)
145 R^1 = COOMe, R^2 = CN (0%)

A: $NCCH_2CN$ (for the production of **142** from **32**)
$MeOOCCH_2COOMe$, Et_3N (for the production of **143** from **32**)
$NCCH_2COOMe$, Et_3N (for the production of **144** and **145** from **32**)

Scheme 21. Reaction of the aldehyde group of chlorophyll derivatives with CH-acids in the Knoevenagel reaction.

the macrocycle, are most often used as substrates for the production of such dimers. Thus, the corresponding symmetrical *trans*-ethylene dimers **148** and **149** are formed when the nickel complexes **146** and **147** are heated with $TiCl_3$(1,2-dimethoxyethane)$_{1.5}$ and a zinc-copper couple in 1,2-dimethoxyethane [107] (Scheme 22).

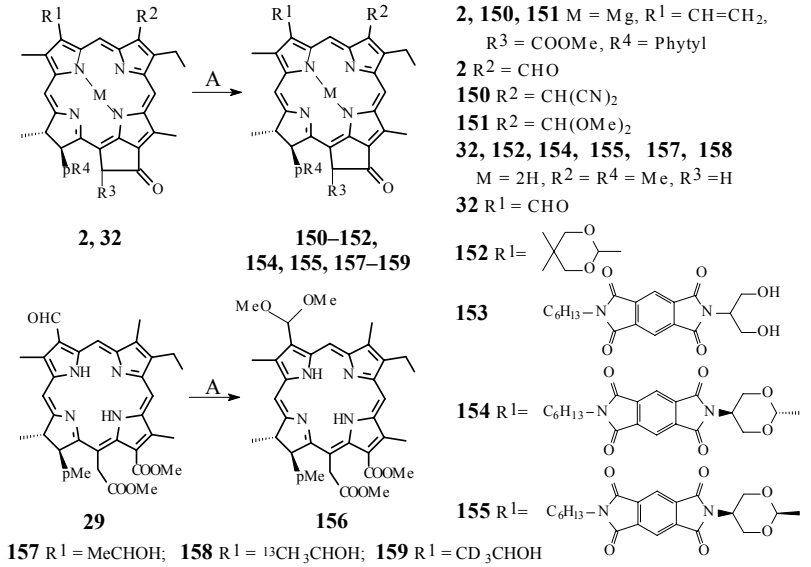


A: $TiCl_3$(1,2-dimethoxyethane)$_{1.5}$–Zn-Cu (for the production of **148** and **149** from **146** and **147** respectively)

Scheme 22. Reductive dimerization of the formyl derivatives of chlorins under the conditions of the McMurry reaction.

Production of Cyanohydrins and Acetals

The formyl group of chlorophyll **2** reacts with HCN and methanol with the formation of the cyanohydrin **150** and the acetal **151** respectively [22]. The aldehyde groups of the metal-free derivatives of chlorophylls also form acetals in reaction with active nucleophilics [56, 78, 103, 114, 115]. Thus, treatment of the chlorin **32** with 2,2-dimethyl-1,3-propanediol in the presence of *p*-$MeC_6H_4SO_3H$ leads to the formation of the cyclic acetal **152** with a quantitative yield, but if the polycyclic diol **153** is used as nucleophile the stereoisomeric acetals **154** and **155** are formed with yields of 79% [114]. The dimethyl acetal **156** is formed with a yield of 92% when the aldehyde **29** is treated with trimethyl orthoformate in methanol in the presence of toluenesulfonic acid [56].



2, 150, 151 M = Mg, R^1 = $CH=CH_2$, R^3 = COOMe, R^4 = Phytyl
2 R^2 = CHO
150 R^2 = $CH(CN)_2$
151 R^2 = $CH(OMe)_2$
32, 152, 154, 155, 157, 158 M = 2H, R^2 = R^4 = Me, R^3 =H
32 R^1 = CHO

152 R^1=

153

154 R^1=

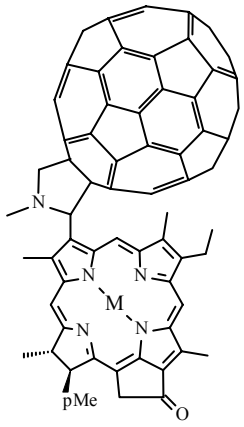
155 R^1=

A: HCN (for the production of **150** from **2**);
MeOH (for the production of **151** from **2**);
p-$MeC_6H_4SO_3H$–$HOCH_2C(Me_2)_2CH_2OH$
(for the production of **152** from **32**);
p-$MeC_6H_4SO_3H$–**153**
(for the production of **154** and **155** from **32**);
$HC(OMe)_3$–MeOH–TsOH
(for the production of **156** from **29**);
MeMgI (for the production of **157** from **32**);
$^{13}CH_3MgI$ (for the production of **158** from **32**);
CD_3MgI (for the production of **159** from **32**)

Scheme 23. The production of cyanohydrins and acetals based on the formyl group and their chemical characteristics.

Strong polarization of the C=O group of chlorophylls facilitates its reaction with the Grignard reagent. Thus, during the action of methylmagnesium iodide on the formyl derivative **32** the corresponding alcohols **157-159** are formed regioselectively with yields of 75-81% in the form of a racemic mixture of diastereomers [116] (Scheme 23).

Other Condensations. A method proposed by Prato and coworkers was used for the synthesis of fullerenepyropheophorbide dimers [117]. It involves the addition of an azomethine ylide at the 6–6 bond of fullerene. Thus, heating of the formylchlorin **32** with fullerene and N-methylglycine in toluene leads to the formation of the epimers **160** with a yield of 49%, and their treatment with zinc acetate in chloroform/methanol gives the zinc complex **161** with a yield of 86% [118] (Scheme 24).



160 M=2H **161** M=Zn

Scheme 24. The fullerene–pyropheophorbide dimer.

Pathways for Modification of the 17-2-Alkoxycarbonylethyl) Group of Chlorophylls

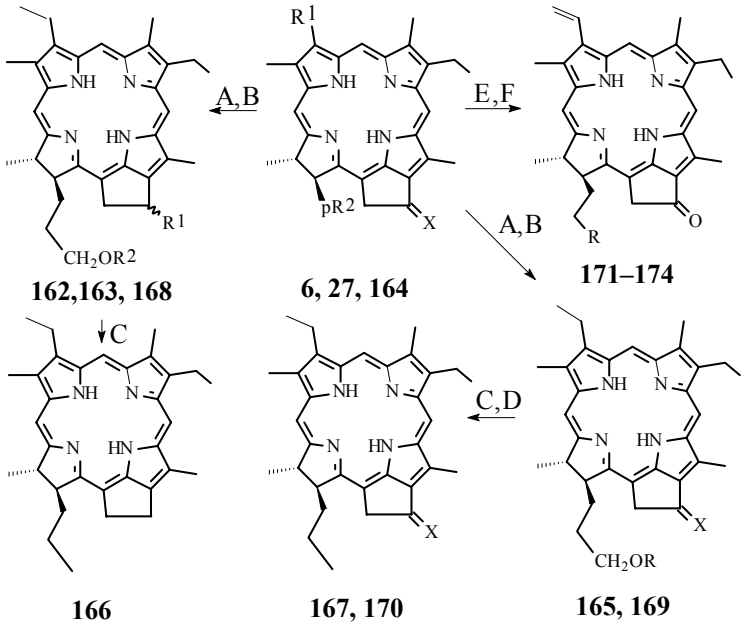
Reduction of the Ester Group

Under the influence of lithium aluminum hydride both carbonyl fragments of the chlorin **27** are reduced with the formation of compounds **162** and **163**. It was noted that here the 17-CH_2CH_2COOMe group is reduced smoothly to a 17-$CH_2CH_2CH_2OH$ group, while the 13^2-carbonyl fragment is reduced both to an alcohol and to a methylene group, and it is this that secures the presence of the two main reduction products **162** and **163** from the chlorin **27**. Previous protection of the 13^2-carbonyl fragment of the chlorin **27** in the form of the ketal **164** makes it possible by the action of lithium aluminum hydride to realize the regioselective reduction of the ester group of the chlorin **27** to the hydroxy derivative **165** [119] (Scheme 25).

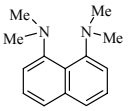
Pathways were also proposed for the transformation of the alcohol groups of the chlorins **163** and **165** to methyl groups with the formation of compounds **166** and **167**. For this purpose the alcohols **163** and **165** are first treated with the $MsCl/Et_3N$ system in methylene chloride with the formation of the mesityl derivatives **168** and **169**, and they are then reduced with lithium aluminum hydride, giving the methyl derivatives **166** and **167** with a yield of more than 50%. The protecting group in the chlorin **170** is removed by treatment with hydrochloric acid in acetone, leading to the formation of the chlorin **167** [119] (Scheme 25).

The transformation of the carboxyl group of the chlorin **6** into the aminoethyl derivative **171** was realized by the Curtius reaction under mild conditions: The carboxy derivative **6** was heated with *t*-BuOH in the presence of diphenylphosphoryl azide and triethylamine. By losing a molecule of nitrogen the corresponding

azide **172** rearranges to the isocyanate **173**, which in reaction with *t*-BuOH *in situ* forms the *tert*-butylurethane **174**. The yield of the urethane **174** was increased to 30% after replacement of triethylamine by the significantly more effective proton acceptor **175**, which prevented the formation of NH_3 and on this account reduced the yield of the side compounds. The quaternized amine **171** was obtained with a yield of 65% by acid hydrolysis of the urethane **174** in ethyl acetate [120] (Scheme 25).



6 R^1 = $CH{=}CH_2$, R^2 = H, X = O; **27** R^1 = Et, R^2 = Me, X = O; **162** R^1 = OH, R^2 = H; **163** R^1 = R^2 = H;
164 R^1 = Et, R^2 = Me, X = $O(CH_2)_2O$; **165** R = H, X = $O(CH_2)_2O$; **167** X = O; **168** R^1 = H, R^2 = Ms; **169** R = Ms, X = $O(CH_2)_2O$;
170 X = $O(CH_2)_2O$; **171** R = $NH_3^+Cl^-$; **172** R = N_3; **173** X = NCO; **174** R = NHC(O)Bu; **175**



A: $LiAlH_4$, 0°C (for the production of **162** and **163** from **27**); $LiAlH_4$, -78°C (for the production of **165** from **164**);
B: MsCl–Et_3N (for the production of **168** and **169** from **163** and **175** respectively);
C: $LiAlH_4$, 0°C (for the production of **166** from **168**); $LiAlH_4$, -7°C (for the production of **167** from **169**);
D: HCl–acetone (for the production of **170** from **167**);
E: $N_3PO(OPh)_2$–*t*-BuOH–**175** (for the production of **172**-**174** from **6**);
F: 3M HCl–EtOAc (for the production of **171** from **174**)

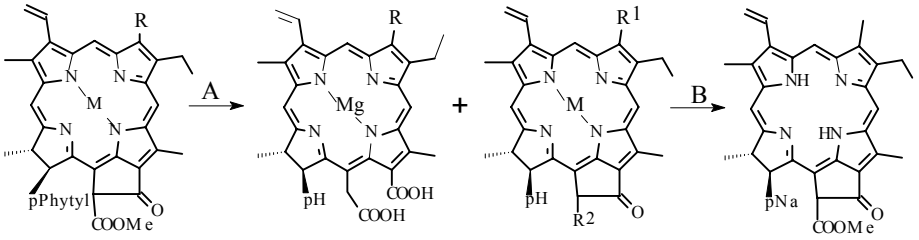
Scheme 25. Various versions of the reduction of the ester group

Hydrolysis of the Ester Group

Effective hydrolysis of the ester group takes place in an acidic and an alkaline medium and also under the influence of enzymes.

Acid Hydrolysis. If an ether solution of the chlorophyll **1** is shaken with 30% hydrochloric acid for 5-30 min the phytylpropionate residue is hydrolyzed, and the magnesium atom is removed from the chlorophyll molecule with the formation of the pheophorbide **4** [121, 122]. Hydrolysis of the chlorophyll **2** to the pheophorbide **9** requires a higher concentration of hydrochloric acid than the hydrolysis of chlorophyll **1** to pheophorbide **4**. This fact and also the difference in the distribution coefficients ether–hydrochloric acid has been successfully used for the separation of compounds of series *a* and *b* [123]. According to data in [124], the

hydrolysis of the phytol residue of pheophetins **3** and **8** in the hydrochloric acid–ether system is accompanied by hydrolysis of the 13^2-CO_2Me fragment to a 13^2-CO_2H group and its subsequent elimination with the formation of the corresponding derivatives **6** and **11**. It was proposed to use 80% aqueous trifluoroacetic acid at 0°C for regioselective hydrolysis of the phytylpropionate residue of the chlorins **3** and **8**, and this made it possible to obtain the chlorins **4** and **9** with a yield of more than 90% [124] (Scheme 26).



1–3, 8 **178,179** **4, 6, 9, 11, 176,177, 180** **181**

1 M = Mg, R = Me; **2** M = Mg, R = CHO; **3** M = 2H, R = Me; **4** M = 2H, R^1 = Me, R^2 = COOMe;
6 M = 2H, R^1 = Me, R^2 = H; **8** M = 2H, R= CHO; **9** M = 2H, R^1= CHO, R^2 = COOMe;
11 M = 2H, R^1= CHO, R^2 = H; **176** M = Mg, R^1 = Me, R^2 = COOH;
177 M = Mg, R^1 = CHO, R^2 = COOH; **178** R = Me; **179** R = CHO; **180** M = Mg, R^1 = Me, R^2 = COOH

A: hydrochloric acid–ether (for the production of **4** and **9** from **1** and **2** respectively; the side formation of **6** and **11** from **3** and **8** respectively); 80% CF_3COOH, 0°C (for the production of **4** and **9** from **3** and **8** respectively); a cold solution of alkali (for the production of **176** and **178** and **177** and **179** from **1** and **2** respectively); the enzyme chlorophyllase–aqueous acetone (for the production of **180** from **1**).
B: a dilute solution of sodium hydroxide (for the production of **181** from **4**).

Scheme 26. The various versions of the hydrolysis of the ester group.

Alkaline Hydrolysis. Treatment of the chlorophylls **1** and **2** in a cold solution of alkali leads to elimination of the phytol residue with retention of the magnesium ion in the macrocycle. Side reactions are hydrolysis of the 13^2-CO_2Me group to a carboxy group with the formation of the chlorophyllins **176** and **177** and the products from opening of the exocycle **178** and **179** [37] (Scheme 26). The methylpropionate residue of chlorophyll derivatives **7** is hydrolyzed by the action of an aqueous solution of lithium hydroxide in THF–methanol to a carboxyl group with a yield of 80-82% [60].

Enzymatic Hydrolysis. The highly effective hydrolysis of the phytylpropionate residue of chlorophylls is achieved by the action of the enzyme chlorophyllase ([125] and the references therein), discovered by Willstätter and Stoll more than 90 years ago [126]. According to data in [127], incubation of chlorophyll **1** with chlorophyllase in aqueous acetone at 22°C leads after 70 min to the formation of the chlorophyllide **180** with a yield of 96% [see the section on "Various Versions of the Production of Esters Based on the 17-(2-hydroxy(alkoxy)carbonylethyl) Group of Chlorophylls"].

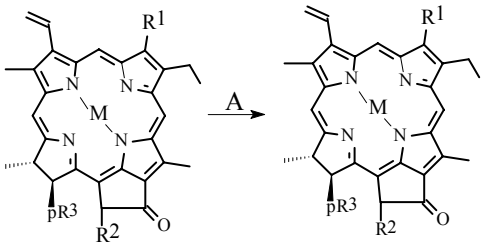
The 17-(2-Hydroxycarbonylethyl) group readily forms salts with strong bases. Thus, under the influence of a dilute solution of sodium hydroxide the pheophorbide **4** and its various derivatives are converted into the corresponding water-soluble sodium salts **181** with high yields [128, 129] (Scheme 26).

Various Versions of the Production of Esters Based on the 17-2-Hydroxy(alkoxy)carbonylethyl) Group of Chlorophylls

The pheophetins **3** and **8** are converted by the action of methanol in the presence of sulfuric acid [49] into the corresponding methyl esters **5** and **10**. Esterification of the acid **4** with diazomethane gives the methyl ester **5** [52].

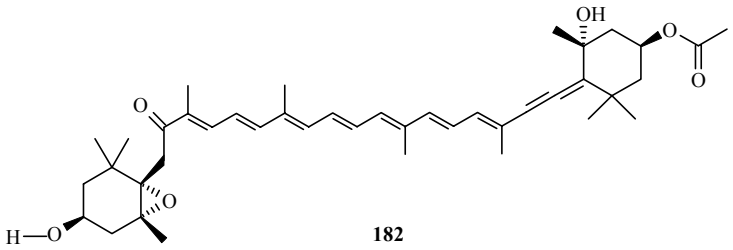
Transesterification of the methyl esters to their $C_{(5)}$–$C_{(10)}$ homologs is realized by the action of ROH/H_2SO_4 [59]. In order to obtain esters containing long-chain and/or labile fragments the strategy of preliminary activation of the ester (carboxyl) group is used, or the reaction is conducted with highly active esterifying systems under mild conditions [59, 66, 97, 124, 130-133]. Thus, the reaction of the pheophorbide **6** with the polyene alcohol fucoxanthin **182** in the presence of 2-chloro-1-methylpyridinium iodide and 4-dimethylaminopyridine leads to the formation of the ester **183** with an acceptable yield [97].

With the enzyme chlorophyllase (see the section on "Hydrolysis of the Ester Group") as transesterification catalyst it is possible to obtain esters under mild conditions, starting from chlorophylls and their derivatives ([127, 134] and references cited therein). Thus, the incubation of chlorophyll **1** in the presence of chlorophyllase with the methyl ester of the amino acid serine leads to the formation of the ester **184** with a yield of 70-80% [134]. It was shown that the derivative **184** exhibits high anticancer activity [134] (Scheme 27).



1, 3, 4, 6, 8 **5, 10, 183, 184**

1 M = Mg, R^1 = Me, R^2 = COOMe, R^3 = Phytyl
3 M = 2H, R^1 = Me, R^2 = COOMe, R^3 = Phytyl
4 M = 2H, R^1 = Me, R^2 = COOMe, R^3 = H
5 M = 2H, R^1 = R^3 = Me, R^2 = COOMe
6 M = 2H, R^1 = Me, R^2 = R^3 = H
8 M = 2H, R^1 = CHO, R^2 = COOMe, R^3 = Phytyl
10 M = 2H, R^1 = CHO, R^2 = COOMe, R^3 = Me



182

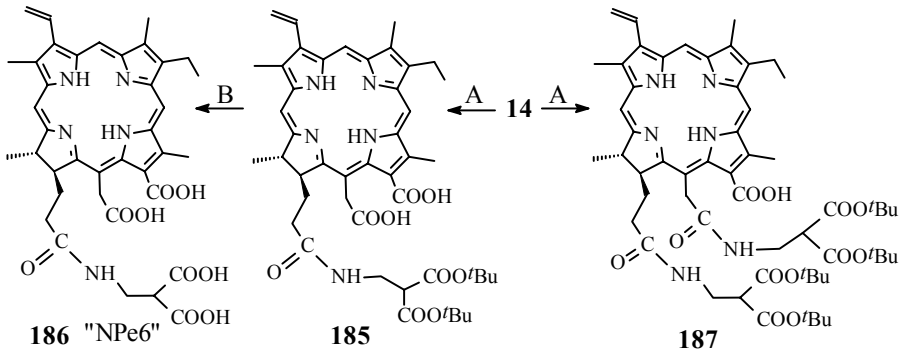
183 M = 2H, R^1 = Me, R^2 = H, R^3 = fucoxanthin residue **182**; **184** M = Mg, R^1 = Me, R^2 = COOMe, R^3 = $CH_2CH(NH_2)COOMe$

A: MeOH–acid (for the production of **5** and **10** from **3** and **8** respectively); CH_2N_2–Et_2O (for the production of **5** from **4**); **182**–2-chloro-1-methylpyridinium iodide–4-dimethylaminopyridine (for the production of **183** from **6**); enzyme chlorophyllase–$HOCH_2CH(NH_2)COOMe$ (for the production of **184** from **1**)

Scheme 27. Esterification of the 17^2-carboxyl and transesterification of the 17^2-ester group.

The Production of Amide Derivatives Based on the 17-2-Hydroxycarbonylethyl) Group of Chlorophylls

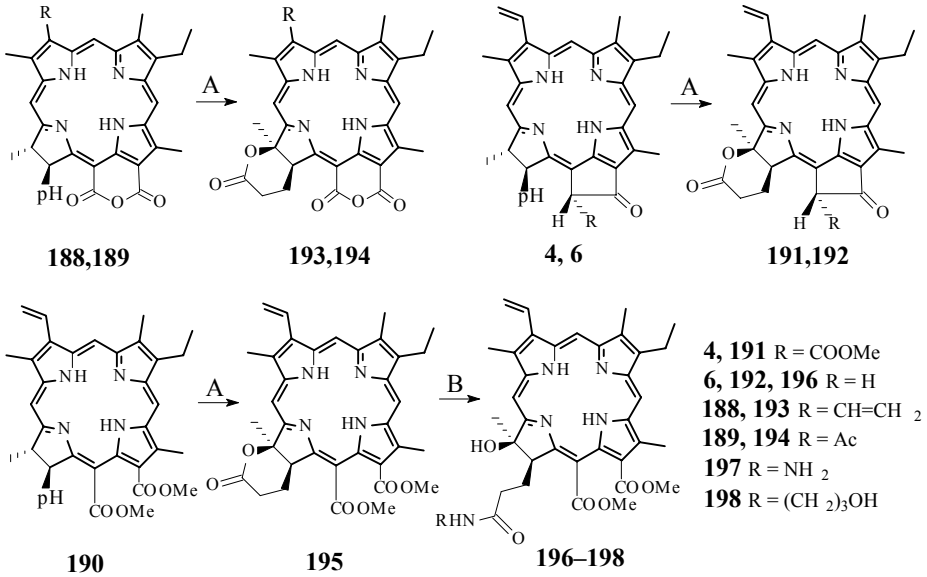
The creation of an amide bond on the basis of the 17-(2-hydroxycarbonylethyl) group of chlorophylls and their derivatives is an effective method for the production of prospective compounds for use in medicine ([132, 135-137] and references therein) and in industry [158]. The optimum strategy for such bioconjugates is to use the procedures of peptide chemistry. Thus, compound **185** is obtained in the reaction of the chlorin **14** with di-*tert*-butyl aspartate in the presence of dicyclohexylcarbodiimide. The protection of the carboxyl groups in the amino acid residue of the adduct **185** is removed by the action of trifluoroacetic acid, and the amide derivative **186** is obtained ([4] and references therein); this is an effective product (commercial name NPe6) for the treatment of various forms of cancer by PDT ([4-6, 8, 142] and references therein). It was noted that the diamide **187** is a side product in the production of the amide **185** (Scheme 28).



A: $H_2NCH_2CH(COO\text{-}t\text{-}Bu)_2$–dicyclohexylcarbodiimide; B: CF_3COOH

Scheme 28. The strategy for the synthesis of the effective product "NPe6" for the treatment of various forms of cancer by PDT.

An alternative approach was also developed for the production of 17^2-amide derivatives. Thus, treatment of various chlorophyll derivatives **4**, **6**, **188-190**, containing a free 17^2-carboxyl group, with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone leads to the formation of the lactones **191-195** [159, 160]. Opening of the lactone **195** with N-nucleophiles gives good yields of the amides **196-198** [161] (Scheme 29).



A: 2,3-Dichloro-5,6-dicyanobenzoquinone (for the production of **191-195** from **4**, **6**, and **188-190** respectively);
B: NH_3, N_2H_4, or $HO(CH_2)_3NH_2$ (for the production of **196-198** respectively from **195**).

Scheme 29. Stereoselective synthesis of the lactone cycle in ring D and production of 17^2-amide derivatives by its opening with N-nucleophiles.

Pathways for the Modification of the Exocyclic Fragment

The main problem in the isolation and modification of chlorophylls is the high reactivity of their exocyclic fragment. The strong activation of the hydrogen atom at position 13^2 by the two carbonyl groups gives rise to the ease of enolization with the participation of the $C(13^1)$–$C(13^2)$ bond. For specific modification of the

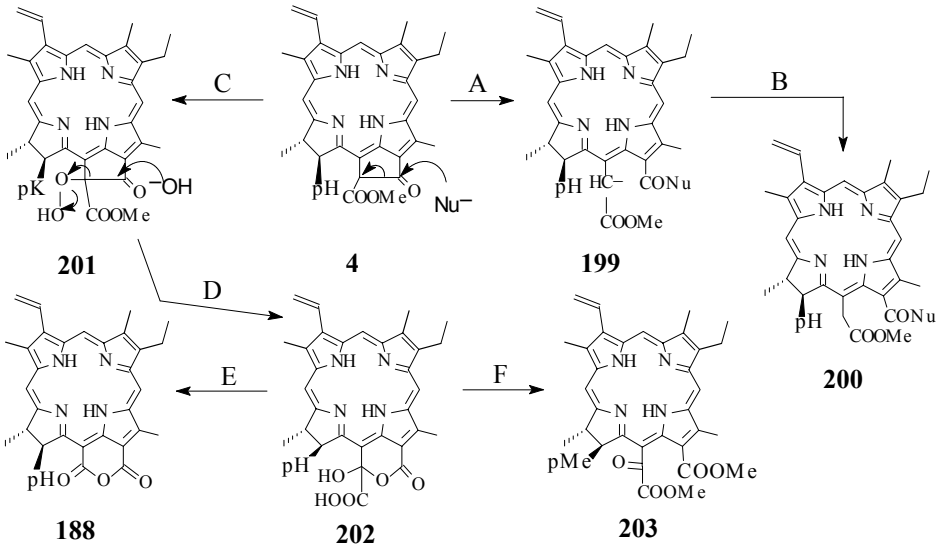
exocycle it is necessary to take account of the ability of its enolate anion to undergo rapid and irreversible oxidation by atmospheric oxygen (the so-called "allomerization" process [9]) in the presence of bases and/or metals (for greater detail, see [22, 28]). In this review some of the basic pathways for the modification of the exocycle without the participation of atmospheric oxygen are examined in greatest detail.

Opening of the Exocyclic Fragment

Mechanisms of Opening of the Exocycle. The exocycle in chlorophylls and their derivatives is easily opened with cleavage of the C(13^1)–C(13^2) bond by the action of various nucleophiles. The ease of opening of the exocycle is due to the presence of a resonance-stabilized and sterically accessible nucleophilic center at carbon atom 13^1.

The mechanism of opening of the exocycle without the involvement of oxygen is regarded as base-catalyzed nucleophilic addition to the 13^1-carbonyl group of the phorbin **4**, which is transformed into compound **200** through the intermediate formation of the carbanion **199** [28, 162].

The key stage in the opening of the exocycle with the participation of oxygen is probably fragmentation of the initially formed hydroperoxide **201** under the acidic conditions with the formation of the so-called "unstable chlorin" **202** [11]. Evaporation of the solvent leads to cyclization of the chlorin **202** to the purpurin **188**, while during esterification of compound **202** with diazomethane its exocyclic fragment is opened with the formation of the derivative **203** [49] (Scheme 30).



A: Nu^-; B: NuH; C: atmospheric oxygen, KOH; D: Acidification. E: Evaporation.; F: CH_2N_2–Et_2O

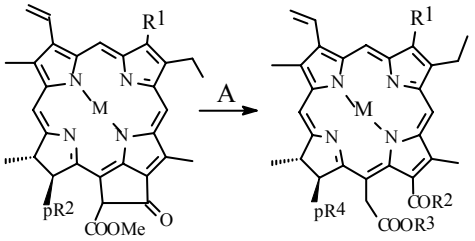
Scheme 30. Versions of the opening of the exocyclic fragment.

Opening of the Exocycle by the Action of O-Nucleophiles. Alkaline hydrolysis of the chlorophylls **1** and **2** in the absence of oxygen leads to the formation of the magnesium complexes **178** and **179** respectively [22, 25]. The chlorins **14** and **21** are obtained similarly from the free bases **4** and **9** [22].

Opening of the pheophorbides **5** and **10** by the action of the methoxide ion leads to the formation of the chlorins **15** and **22**. Thus, the chlorins **15** and **22** are formed when the pheophorbides **5** and **10** are kept in an atmosphere of nitrogen for 24 h in the Py/CH_2N_2/MeOH system [22]. Methanolysis of the exocyclic fragment of the pheophorbides **5** and **10** in the MeONa/THF/MeOH system makes it possible to obtain good yields of the trimethyl esters of the chlorins **15** [50] and **22** [51]. Brief treatment of the pheophorbides **5** and **10** with a 0.5%

solution of potassium hydroxide in methanol in the presence of pyridine leads to the formation of the triesters **15** and **22** respectively with yields of more than 70% [162] (Scheme 31).

Opening of the Exocycle by the Action of N-Nucleophiles. Under the influence of a wide range of amines the exocycle of chlorophylls **1** and **2** and their derivatives **3**, **5**, and **8** open readily with the formation of the corresponding 13^1-carboxamides **204-208** [22, 25, 147, 163-167]. It was shown that the effectiveness of aminolysis of the exocycle is determined by the basicity of the employed amine and by steric effects during coordination of the nucleophilic center 13^1 with the nitrogen-containing nucleophilic [22, 25, 163]. It was noted that the rate of formation of the 13^1-carboxamides in most cases is increased in the presence of water or ethanol [166] (Scheme 31).



1–5, 8–10 **14, 15, 21, 22, 178, 179, 204–208**

1 M = Mg, R^1 = Me, R^2 = Phytyl; **2** M = Mg, R^1 = CHO, R^2 = Phytyl; **3** M = 2H, R^1 = Me, R^2 = Phytyl;
4 M = 2H, R^1 = Me, R^2 = H; **5** M = 2H, R^1 = R^2 = Me; **8** M = 2H, R^1 = CHO, R^2 = Phytyl; **9** M = 2H, R^1 = CHO, R^2 = H;
10 M = 2H, R^1 = CHO, R^2 = Me; **14** M = 2H, R^1 = Me, R^2 = OH, R^3 = R^4 = H; **15** M = 2H, R^1 = R^3 = R^4 = Me, R^2 = OMe;
21 M = 2H, R^1 = CHO, R^2 = OH, R^3 = R^4 = H; **22** M = 2H, R^1 = CHO, R^2 = OMe, R^3 = R^4 = Me;
178 M = Mg, R^1 = Me, R^2 = OH, R^3 = R^4 = H; **179** M = Mg, R^1 = CHO, R^2 = OH, R^3 = R^4 = H;
204 M = Mg, R^1 = Me, R^2 = NR^5R^6, R^3 = Me, R^4 = Phytyl; **205** M = Mg, R^1 = CHO, R^2 = NR^5R^6, R^3 = Me, R^4 = Phytyl;
206 M = 2H, R^1 = R^3 = Me, R^2 = NR^5R^6, R^4 = Phytyl; **207** M = 2H, R^1 = R^3 = R^4 = Me, R^2 = NR^5R^6;
208 M = 2H, R^1 = CHO, R^2 = NR^5R^6, R^3 = Me, R^4 = Phytyl; **204-208** R^5, R^6 = H, Alk, Ar, Hetero

A: Alkali, absence of O_2 (for the production of **14**, **21**, **178**, and **179** from **4**, **9**, **1**, and **2** respectively);
pyridine–CH_2N_2–MeOH, MeONa–THF–MeOH or KOH–MeOH–pyridine (for the production of **15** and **22** from **5** and **10** respectively);
R^1R^2NH (for the production of **204-208** from **1-3**, **5**, and **8** respectively).

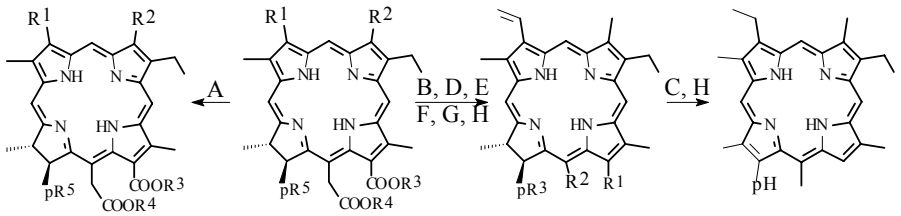
Scheme 31. Nucleophilic opening of the exocycle without the participation of oxygen.

Pathways for Modification of the Carboxyl Groups of the Products from Opening of the Exocycle

The carboxyl groups of the chlorins **14** and **21** can be easily transformed into ester groups. Thus, the reaction of the chlorins **14** and **21** with diazomethane leads to the trimethyl esters **15** and **22** respectively. Esterification of the chlorin **14** with bromomethyl acetate in the presence of N,N-diisopropylethylamine gives the triester **209** [168]. It was shown that compound **209** has significant anticancer activity ([169] and references therein).

The free carboxyl groups of the chlorin **14** are decarboxylated in the order 15-CH_2COOH > 13-COOH, and the chlorins **16** and **20** are formed in succession. During pyrolysis of the chlorin **20** the stable phylloporphyrin XV **210** is formed [37].

The monoacid **211** is produced by selective hydrolysis of the triester **15** [22]. By activation of the 13-COOH group of the chlorin **211** with dicyclohexylcarbodiimide it is possible to obtain the biologically active amides **212** [170]. During hydrolysis the 13-COOH group of the chlorin **211** is eliminated with the formation of the chlorin **19**. Hydrolysis of the diester **19** gives the diacid **18**, pyrolysis of which in pyridine gives the chlorin **20** and the porphyrin **210** [22] (Scheme 32).



15, 22, 209 **14, 21** **16, 18–20, 211, 212** **210**

14 $R^1 = CH{=}CH_2$, $R^2 = Me$, $R^3 = R^4 = R^5 = H$
15 $R^1 = CH{=}CH_2$, $R^2 = R^3 = R^4 = R^5 = Me$
16 $R^1 = COOH$, $R^2 = Me$, $R^3 = H$
18 $R^1 = R^3 = H$, $R^2 = CH_2COOH$
19 $R^1 = H$, $R^2 = CH_2COOMe$, $R^3 = Me$
20 $R^1 = R^3 = H$, $R^2 = Me$

21 $R^1 = CH{=}CH_2$, $R^2 = CHO$, $R^3 = R^4 = R^5 = H$
22 $R^1 = CH{=}CH_2$, $R^2 = CHO$, $R^3 = R^4 = R^5 = Me$
209 $R^1 = CH{=}CH_2$, $R^2 = Me$, $R^3 = R^4 = R^5 = CH_2OC(O)Me$
211 $R^1 = COOH$, $R^2 = CH_2COOMe$, $R^3 = Me$
212 $R^1 = C(O)NHR$, $R^2 = CH_2COOMe$, $R^3 = Me$,
R is a residue of steroids and other hormones

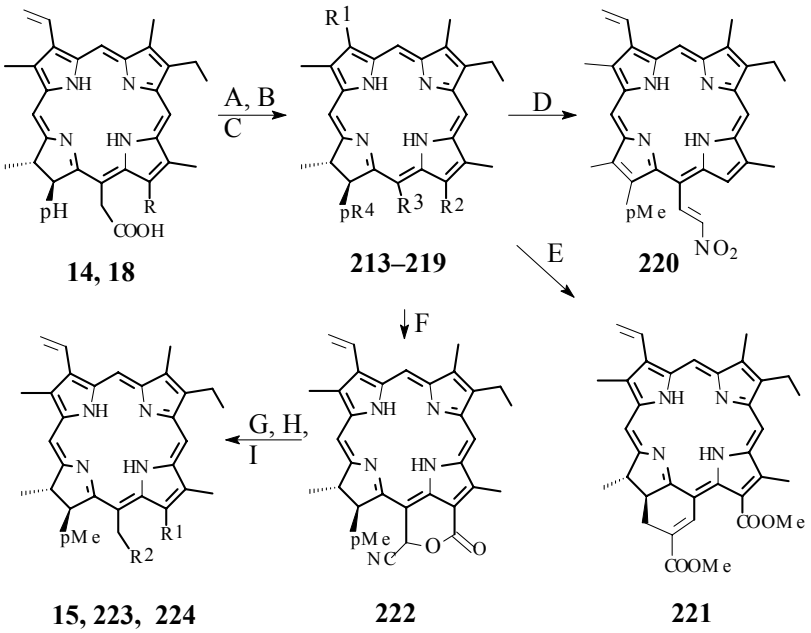
A: CH_2N_2 (for the production of **15** and **22** from **14** and **21** respectively); $AcOCH_2Br–EtN(i\text{-}Pr)_2$ (for the production of **209** from **14**.
B: Hydrolysis (for the production of **16** and **20** from **14**). C: Pyrolysis (for the production of **210** from **20**).
D: Hydrolysis (for the production of **211** from **15**). E: dicyclohexylcarbodiimide–RNH_2 (for the production of **212** from **211**).
F: Pyrolysis (for the production of **19** from **211**). G: Hydrolysis (for the production of **18** from **19**).
H: Pyrolysis (for the production of **20** and **210** from **18**).

Scheme 32. Esterification and pyrolysis of the carboxyl groups of the products from opening of the exocycle.

The final product from pyrolysis of the chlorins of the *b* series is the porphyrin **210**, indicating reduction of the 7-CHO group in chlorins of the *b* series under rigorous conditions [11].

In spite of the similarity of the structures of chlorins **14** and **18** their chemical characteristics different significantly. Thus, treatment of the chlorin **14** with potassium permanganate followed by esterification of the intermediate **213** leads to the formation of the formyl derivative **214** with a yield of less than 10%. Under similar conditions the chlorin **18** is not transformed into the analogous formyl derivative **215**, but the chlorin **216**, i.e., the product from oxidation of the vinyl and 13-CH_2COOH groups of the chlorin **18**, is formed with a yield of more than 20%. When heated with hydroxylamine hydrochloride in aqueous pyridine the aldehyde **214** undergoes deformylation with the formation of rhodochlorin **217**. In the case of the formyl derivative **216** the aldoxime **218** is obtained, and this gives a good yield of the nitrile **219** when heated with acetic anhydride [85]. It was noted that the nitromethylene derivative **220** is formed in the reaction of nitromethane with the formyl derivative **214** in the presence of pyridine and ethylamine [22] (Scheme 33).

The presence of three C-nucleophilic centers, situated on one side of the chlorin macrocycle, opens up great possibilities for its further modification. It is important to note that planned modification of the chlorin **214** is possible both in the pyrrole ring C and in ring D. Thus, under the influence of the sodium methoxide/methanol system the chlorin **214** enters into intramolecular aldol condensation with the formation of the pentacyclic derivative **221**, and here modification of pyrrole ring D is realized [22]. The principle of the construction of an additional ring on the basis of ring C was used by Woodward as one of the last stages in the total synthesis of chlorophyll **1** [171-174]. Thus, the cyanolactone **222** is produced during treatment of the chlorin **214** with hydrogen cyanide, and its reduction by the zinc/acetic acid system followed by esterification of the intermediate **223** gives the nitrile **224**. The derivative **15** is formed during solvolysis of the nitrile **224** by the acetic acid–methanol system (Scheme 33).



14 R = COOH; **15** $R^1 = R^2$ = COOMe; **18** R = H; **213** R^1 = CH=CH_2, R^2 = COOH, R^3 = CHO, R^4 = H; **214** R^1 = CH=CH_2, R^2 = COOMe, R^3 = CHO, R^4 = Me; **215** R^1 = CH=CH_2, R^2 = H, R^3 = CHO, R^4 = Me; **216** R^1 = COOMe, R^2 = H, R^3 = CHO, R^4 = Me; **217** R^1 = CH=CH_2, R^2 = COOMe, R^3 = H, R^4 = Me; **218** R^1 = COOMe, R^2 = H, R^3 = CH=NOH, R^4 = Me; **219** R^1 = COOMe, R^2 = H, R^3 = CN, R^4 = Me; **223** R^1 = COOH, R^2 = CN; **224** R^1 = COOMe, R^2 = CN

A: $KMnO_4$ (for the production of **213** from **14**); esterification (for the production of **214** from **213**); $KMnO_4$, esterification (for the production of **216** from **18**).
B: $NH_2OH \cdot HCl$, heat (for the production of **217** and **218** from **214** and **216** respectively).
C: Ac_2O, heat (for the production of **219** from **218**). D: $MeNO_2$–$EtNH_2$–pyridine (for the production of **220** from **214**).
E: MeONa–MeOH (for the production of **221** from **224**). F: HCN (for the production of **222** from **214**).
G: Zn–AcOH (for the production of **223** from **222**). H: Esterification (for the production of **224** from **223**).
I: AcOH–MeOH (for the production of **15** from **224**).

Scheme 33. Further versions of modification of the carboxyl groups in the products from opening of the exocycle.

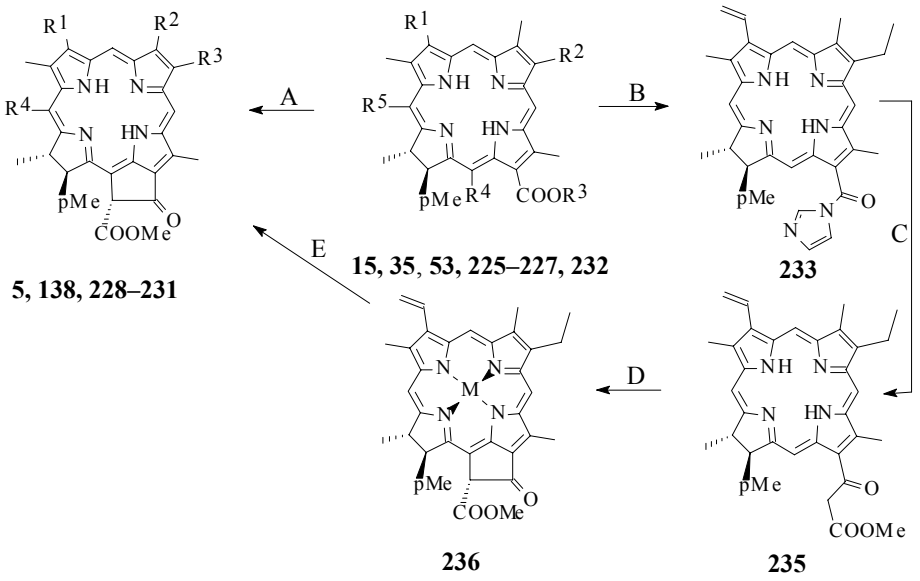
Recyclization of the Exocycle

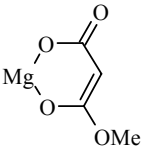
Base-Catalyzed Recyclization of the Exocycle. By the action of strong bases under anaerobic conditions various derivatives of chlorophylls **15**, **35**, **53**, and **225-227**, containing 13-COOMe and 15-CH_2COOMe fragments, undergo smooth cyclization to the respective pheophorbides **5**, **228**, **138**, and **229-231** [50, 51, 56, 65]. Thus, brief heating of the chlorin **226** with *t*-BuOK in the *t*-BuOH–Py system leads to the pheophorbide **230** with a yield of 97% [65]. It is assumed that recyclization of the exocycle takes place according to the mechanism of the Dieckmann condensation [51] (Scheme 34).

Recyclization of the exocycle is the best method for the production of phorbins **138**, **228-321**, the direct synthesis of which from the pheophorbides **5** and **10** is ineffective (see also "Production of Vinyl Derivatives").

Photolytic Recyclization of the Exocycle. An alternative way of constructing the exocyclic fragment of chlorophyll is based on the use of the chlorin **232**, containing a 13-COOH fragment and a vacant position 15, as starting compound [175]. Thus, treatment of the chlorin **232** with N,N'-carbonyldiimidazole leads to the carboxyimidazole **233**, the reaction of which with the chelate **234** gives the β-keto ester **235**. Cyclization of the

nonphorbin chlorin **235** to the phorbin metal complex **236** is achieved by the successive treatment of 2 eq. of $Tl(CF_3COO)_3$ and photolysis. The metal complex **236** is demetallated by the action of SO_2 and hydrochloric acid, resulting in the formation of the pheophorbide **5**. It is important to note that this multistage path for the construction of the exocyclic fragment was previously developed and optimized for model porphyrin systems [176-180] (Scheme 34).



5 $R^1 = CH{=}CH_2$, $R^2 = Me$, $R^3 = Et$, $R^4 = H$; **15** $R^1 = CH{=}CH_2$, $R^2 = Et$, $R^3 = Me$, $R^4 = CH_2COOMe$, $R^5 = H$;
35 $R^1 = CH_2CH_2OH$, $R^2 = Et$, $R^3 = Me$, $R^4 = CH_2COOMe$, $R^5 = H$; **53** $R^1 = R^2 = CH{=}CH_2$, $R^3 = Me$, $R^4 = CH_2COOMe$, $R^5 = H$;
138 $R^1 = R^3 = CH{=}CH_2$, $R^2 = Me$, $R^4 = H$; **225** $R^1 = Et$, $R^2 = CH{=}CH_2$, $R^3 = Me$, $R^4 = CH_2COOMe$, $R^5 = H$;
226 $R^1 = CH_2CH_2Cl$, $R^2 = Et$, $R^3 = R^5 = Me$, $R^4 = CH_2COOMe$; **227** $R^1 = R^2 = Et$, $R^3 = R^5 = Me$, $R^4 = CH_2COOMe$;
228 $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = Et$, $R^4 = H$; **229** $R^1 = Et$, $R^2 = Me$, $R^3 = CH{=}CH_2$, $R^4 = H$; **230** $R^1 = CH_2CH_2Cl$, $R^2 = R^4 = Me$,
$R^3 = Et$; **231** $R^1 = R^3 = Et$, $R^2 = R^4 = Me$; **232** $R^1 = CH{=}CH_2$, $R^2 = Et$, $R^3 = R^4 = R^5 = H$; **234**  ; **236** $M = Tl^{3+}CF_3COO^-$

A: Base (for the production of **5**, **228**, **138**, and **229-231** from **15**, **35**, **53**, and **225-227** respectively).
B: N,N'-Carbonyldiimidazole (for the production of **233** from **232**). C: **234** (for the production of **235** from **233**).
D: $Tl(CF_3COO)_3$, photolysis (for the production of **236** from **235**). E: SO_2 and hydrochloric acid (for the production of **5** from **236**).

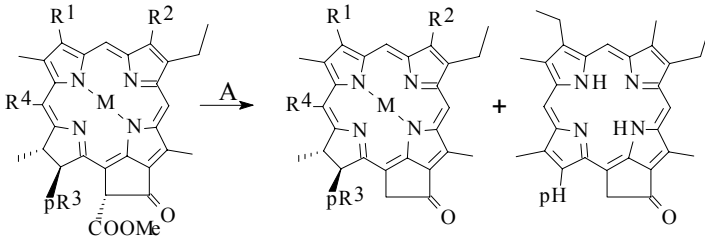
Scheme 34. Pathways for recyclization of the exocyclic fragment.

Demethoxycarbonylation at Position 13^2 of the Exocycle.

When heated in high-boiling solvents, phorbin-containing derivatives of chlorophylls containing a COOMe group in the cyclopentanone fragment **1**, **3-5**, **10**, **228**, **230**, **231**, and **237** readily lose it and form the corresponding stable pyro derivatives **238**, **239**, **6**, **7**, **12**, and **240-243**. The 13^2-COOMe fragment is easily eliminated both on the metal complexes **1** and **237** [181, 182] and on the nonmetal derivatives **3-5**, **10**, **228**, **230**, and **231** [11, 43, 49, 50, 65, 181]. It was noted that thermal isomerization of the pyro derivative **6** to the stable phylloerythrin **244** occurs as a side reaction during prolonged heating of the pheophorbide in pyridine [11].

A universal solvent for the demethoxycarbonylation of pheophorbides of series *a* and *b* is collidine (2,4,6-trimethylpyridine) [49]. Thus, the use of collidine makes it possible to obtain the pyropheophorbide **7** with a yield of more that 90%. The pyrolysis time of the pheophorbide amounts to 90 min, and the formation of side products is not observed. Under analogous conditions the pheophorbide **10** is transformed into the pyropheophorbide **12** with a yield of more than 80% [49].

An effective method for demethoxycarbonylation of compound **5** was proposed in the patent [183]. Thus, pyrolysis of the chlorin **5** in a two-phase system consisting of water and a high-boiling solvent leads to the formation of the pyro derivative **7** with a quantitative yield, and the use of a two-phase system has been applied to the large-scale production of the pyro derivative **7** (Scheme 35).



1, 3–5, 10, 228, 230, 231, 237 → **6,7, 12, 238–243** + **244**

1, **238** M = Mg, R^1 = CH=CH_2, R^2 = Me, R^3 = Phytyl, R^4 = H; **3**, **239** M = 2H, R^1 = CH=CH_2, R^2 = Me, R^3 = Phytyl, R^4 = H;
4, **6** M = 2H, R^1 = CH=CH_2, R^2 = Me, R^3 = R^4 = H; **5**, **7** M = 2H, R^1 = CH=CH_2, R^2 = R^3 = Me, R^4 = H;
10, **12** M = 2H, R^1 = CH=CH_2, R^2 = CHO, R^3 = Me, R^4 = H; **228**, **240** M = 2H, R^1 = CH_2CH_2OH, R^2 = R^3 = Me, R^4 = H;
230, **241** M = 2H, R^1 = CH_2CH_2Cl, R^2 = R^3 = R^4 = Me; **231**, **242** M = 2H, R^1 = Et, R^2 = R^3 = R^4 = Me;
237, **243** M = Mg, R^1 = Et, R^2 = R^3 = Me, R^4 = H

A: Heating in a high-boiling solvent (for the production of **238**, **239**, **6**, **7**, **12**, and **240**-**243** from **1**, **3**-**5**, **10**, **228**, **230**, **231**, and **237** respectively; side formation of **244** during the pyrolysis of **4**)

Scheme 35. Demethoxycarbonylation at position 13^2 of chlorophylls and their phorbin derivatives.

Analysis of the data on methods for modification of the peripheral substituents of chlorophylls *a* and *b* demonstrates their truly boundless synthetic potential and the promise of these reactions in the development of designed methods for the synthesis of derivatives possessing a wide range of useful characteristics.

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REFERENCES

1. K. Kadish, K. M. Smith, and R. Guilard (editors), *The Porphyrin Handbook*, Academic Press, Vol. 6, Boston, MA (2000).
2. D. Gust and T. A. Moore, in: K. Kadish, K. M. Smith, and R. Guilard (editors), *The Porphyrin Handbook*, Vol. 8, Academic Press, Boston, MA, 2000, p. 153.
3. N. V. Konovalova, R. P. Evstigneeva, and V. N. Luzgina, *Usp. Khim.*, **70**, 1059 (2001).
4. E. D. Sternberg, D. Dolphin, and C. Bruckner, *Tetrahedron*, **54**, 4151 (1998).
5. T. D. Mody, *J. Porphyrins and Phthalocyanines*, **4**, 362 (2000).
6. R. K. Pandey, *J. Porphyrins and Phthalocyanines*, **4**, 368 (2000).

7. R. K. Pandey and G. Zheng, in: K. Kadish, K. M. Smith, and R. Guilard (editors), *The Porphyrin Handbook*, Vol. 6, Academic Press, Boston, MA (2000), p. 157.
8. I. MacDonald and T. J. Dougherty, *J. Porphyrins and Phthalocyanines*, **5**, 105 (2001)
9. R. Willstätter and A. Stoll, *Untersuchungen über Chlorophyll*, J. Springer, Berlin (1913).
10. H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. 2, Part 1, Akad. Verlagsges., Leipzig (1937).
11. H. Fischer and A. Stern, *Die Chemie des Pyrrols*, Vol. 2, Part 2, Akad. Verlagsges., Leipzig (1940).
12. L. P. Vernon and G. R. Seely (editors), *The Chlorophylls*, Academic Press, London (1966).
13. G. P. Gurinovich, A. N. Sevchenko, and K. N. Solov'ev, *Spectroscopy of Chlorophyll and Related Compounds* [in Russian], Nauka i Tekhnika, Minsk (1968).
14. G. S. Marks, *Heme and Chlorophyll*, Van Nostrand, London, (1969).
15. H. Scheer, *Chlorophylls*, CRC Press, Boca Raton Ann Arbor, Boston, London, (1991).
16. A. Stoll and E. Wiedemann, *Fortschr. Chem. Org. Naturst.*, **1**, 159 (1938).
17. A. Stoll and E. Wiedemann, *Fortschr. Chem. Forsch.*, **2**, 538 (1952).
18. J. C. Kephart, *Econ. Bot.*, **9**, 3 (1955).
19. S. Aronoff, in: W. Ruhland (editor), *Handbuch der Pflanzenphysiologie*, Vol. 5, Part 1, Springer-Verlag, Berlin (1960), p. 234.
20. A. S. Holt, in: T. W. Goodwin (editor), *Chemistry and Biochemistry of Plant Pigments*, Academic Press, London, (1965), p. 3.
21. S. Aronoff, in: L. P. Vernon and G. R. Seely (editors), *The Chlorophylls*, Academic Press, London, (1966), p. 3.
22. G. R. Seely, in: L. P. Vernon and G. R. Seely (editors), *The Chlorophylls*, Academic Press, London (1966), p. 67.
23. H. H. Inhoffen, *Pure and Appl. Chem.*, **17**, 443 (1968).
24. H. H. Inhoffen, *Fortschr. Chem. Org. Naturst.*, **26**, 284 (1968).
25. A. H. Jackson, in: T. W. Goodwin (editor), *Chemistry and Biochemistry of Plant Pigments*, Vol. 1, 2nd ed., Academic Press, London (1975), p. 1.
26. H. Brockmann, Jr., in: D. Dolphin (editor), *The Porphyrins*, Vol. 2, Academic Press, New York (1978), p. 288.
27. A. H. Jackson, in: R. H. Thomson (editor), *The Chemistry of Natural Products*, Blackie, Glasgow (1985), p. 395.
28. P. H. Hynninen, in: H. Scheer (editor), *Chlorophylls*, CRC Press, Boca Raton Ann Arbor, Boston, London (1991), p. 145.
29. J. E. Falk, *Porphyrins and Metalloporphyrins*, Elsevier, Amsterdam (1964).
30. A. Treibs, *Das Leben und Wirken van Hans Fischer*, Hans Fischer Gesellschaft, München, 1971.
31. K. M. Smith (Ed.), *Porphyrins and Metalloporphyrins*, Elsevier, Amsterdam (1975).
32. J.-H. Fuhrhop, in: K. M. Smith (editor), *Porphyrins and Metalloporphyrins*, Elsevier, Amsterdam (1975), p. 593.
33. F. R. Hopf and D. G. Whitten, in: K. M. Smith (editor), *Porphyrins and Metalloporphyrins*, Elsevier, Amsterdam (1975), p. 667.
34. J. H. Fuhrhop and K. M. Smith, in: K. M. Smith (editor), *Porphyrins and Metalloporphyrins*, Elsevier, Amsterdam (1975), p. 757.
35. K. M. Smith, in: S. Coffey (editor), *Rodd's Chemistry of Carbon Compounds*, Vol. 4 B, 2nd ed., Elsevier, Amsterdam (1977) (237).
36. D. Dolphin (editor), *The Porphyrins*, Academic Press, New York (1978).
37. R. K. DiNello and C. K. Chang, in: D. Dolphin (editor), *The Porphyrins*, Vol. 1, Academic Press, New York (1978), p. 289.
38. H. Scheer, in: D. Dolphin (editor), *The Porphyrins*, Vol. 2, Academic Press, New York (1978), p. 1.

39. H. Scheer and H. H. Inhoffen, in: D. Dolphin (editor), *The Porphyrins*, Vol. 2, Academic Press, New York (1978), p. 45.
40. F. R. Hopf and D. G. Whitten, in: D. Dolphin (editor), *The Porphyrins*, Vol. 2, Academic Press, New York (1978), p. 161.
41. J. W. Buchler, in: D. Dolphin (editor), *The Porphyrins*, Vol. 2, Academic Press, New York (1978), p. 389.
42. K. M Smith, in: P. G. Sammes (editor): *Comprehensive Organic Chemistry*, Vol. 4, Pergamon Press, Oxford (1979), p. 321.
43. O. I. Koifman, K. A. Askarov, B. D. Berezin, and N. S. Enikolopyan, in: N. S. Enikolopyan (editor), *Porphyrins: Structure, Properties, Synthesis* [in Russian], Nauka, Moscow (1985), p. 175.
44. G. V. Ponomarev and G. V. Kirillova, in: *Porphyrins: Structure, Properties, Synthesis* [in Russian], Nauka, Moscow (1985), p. 239.
45. K. M. Smith, in: K. Kadish, K. M. Smith, and R. Guilard (editors), *The Porphyrin Handbook*, Vol. 1, Academic Press, Boston, MA (2000), p. 1.
46. M. D. G. H. Vicente, in: K. Kadish, K. M. Smith, and R. Guilard (editors), *The Porphyrin Handbook*, Vol. 1, Academic Press, Boston, MA (2000), p. 149.
47. H. J. Callot and R. Ocampo, in: K. Kadish, K. M. Smith, and R. Guilard (editors), *The Porphyrin Handbook*, Vol. 1, Academic Press, Boston, MA (2000), p. 349.
48. G. B. Moss, *Pure and Appl. Chem.*, **59**, 779 (1987).
49. G. W. Kenner, S. W. McCombie, and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2517 (1973).
50. K. M. Smith, G. M. F. Bisset, and M. J. Bushell, *Bioorg. Chem.*, **9**, 1 (1980).
51. K. M. Smith, M. J. Bushell, J. Rimmer, and J. F. Unsworth, *J. Am. Chem. Soc.*, **102**, 2437 (1980).
52. K. M. Smith, D. A. Goff, and D. J. Simpson, *J. Am. Chem. Soc.*, **107**, 4946 (1985).
53. K. M. Smith and D. A. Goff, *J. Am. Chem. Soc.*, **107**, 4954 (1985).
54. A. S. Holt and H. V. Morley, *Can. J. Chem.*, **37**, 507 (1959).
55. R. Fischer, N. Engel, A. Henseler, and A. Gossauer, *Helv. Chim. Acta*, **11**, 1046 (1994).
56. B. Gerlach, S. E. Brantley, and K. M. Smith, *J. Org. Chem.*, **63**, 2314 (1998); *Chem. Abstr.*, **128**, 243863 (1998).
57. M. R. Wasielewski, D. G. Johnson, M. P. Neimczyk, G. L. Gaines, M. P. O'Neil, and W. A. Svec, *J. Am. Chem. Soc.*, **112**, 6482 (1990).
58. G. P. Wiederrecht, W. A. Svec, M. P. Niemczyk, and M. R. Wasielewski, *J. Phys. Chem.*, **99**, 8918 (1995).
59. H. Tamiaki, S. Miyata, Y. Kureishi, and R. Tanikaga, *Tetrahedron*, **52**, 12421 (1996).
60. R. K. Pandey, A. B. Sumlin, S. Constantine, M. Aoudia, W. R. Potter, D. A. Bellnier, W. B. Henderson, M. A. Rodgers, K. M. Smith, and T. J. Dougherty, *Photochem. and Photobiol.*, **64**, 194 (1996); *Chem. Abstr.*, **125**, 142405 (1996).
61. R. K. Pandey, M. Isaac, I. MacDonald, C. J. Medforth, M. O. Senge, T. J. Dougherty, and K. M. Smith, *J. Org. Chem.*, **62**, 1463 (1997).
62. A. F. Mironov, *Ros. Khim. Zh.*, **5**, 23 (1998).
63. A. Osuka, Y. Wada, and S. Shinoda, *Tetrahedron*, **52**, 4311 (1996); *Chem. Abstr.*, **124**, 289075 (1996).
64. D. Gust, T. A Moore, A. L. Moore, and P. A. Liddel, in: *Methods in Enzymology* (Ed. L. Packer), Vol. 213, Academic Press, N. Y. (1992), p. 87.
65. K. M. Smith, J. M. F. Bisset, and M. J. Bushell, *J. Org. Chem.*, **45**, 2218 (1980).
66. M. R. Wasielewski, W. A. Svec, and B. T. Cope, *J. Am. Chem. Soc.*, **100**, 1961 (1978).
67. S. E. Brantley, B. Gerlach, M. M. Olmstead, and K. M. Smith, *Tetrahedron Lett.*, **38**, 937 (1997); *Chem. Abstr.*, **126**, 185929 (1997).
68. P. H. Hynninen, *Liebigs Ann. Chem.*, 835 (1990).
69. G. Zheng, T. J. Dougherty, and R. K. Pandey, *J. Org. Chem.*, **64**, 3751 (1999); *Chem. Abstr.*, **131**, 73470 (1999).

70. A. A. Aksenova, Yu. L. Sebyakin, and A. F. Mironov, *Russian J. Bioorg. Chem.*, **27**, 124 (2001).
71. V. Yu. Pavlov, A. V. Reshetnickov, and G. V. Ponomarev, *Abstracts of 1-st International Conference on Porphyrins and Phthalocyanines*, Dijon, France (2000), p. 519.
72. A. V. Reshnikov, T. A. Babushkina, G. V. Kirillova, and G. V. Ponomarev, *Khim. Geterotsikl. Soedin.*, 213 (2001).
73. H. Tamiaki, M. Kouraba, K. Takeda, S.-i. Kondo, and R. Tanikaga, *Tetrahedron: Asymmetry*, **9**, 2101 (1998); *Chem. Abstr.*, **129**, 230557 (1998).
74. A. F. Mironov, *Proceedings of SPIE, The International Society for Optical Engineering*, **2728**, 150 (1996); *Chem. Abstr.*, **124**, 201808 (1996).
75. H. Tamiaki, T. Miyatake, and R. Tanikaga, *Tetrahedron Lett.*, **38**, 267 (1997).
76. H. Tamiaki, M. Omoda, and M. Kubo, *Bioorg. Med. Chem. Lett.*, **9**, 1631 (1999); *Chem. Abstr.*, **131**, 228575 (1999).
77. H. Tamiaki, T. Tomida, and T. Miyatake, *Bioorg. Med. Chem. Lett.*, **7**, 1415 (1997); *Chem. Abstr.*, **127**, 81273 (1997).
78. H. Falk, G. Hoornaert, H.-P. Isenring, and A. Eschenmoser, *Helv. Chim. Acta*, **58**, 2347 (1975).
79. I. K. Morris, K. M. Snow, N. W. Smith, and K. M. Smith, *J. Org. Chem.*, **55**, 1231 (1990).
80. X. Jiang, R. K. Pandey, and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1607 (1996).
81. X. Jiang, R. K. Pandey, and K. M. Smith, *Tetrahedron Lett.*, **36**, 365 (1995).
82. M. Ono, R. Lattman, K. Inomata, C. Lehmann, T. Früh, and A. Eshenmoser, *Croat. Chem. Acta*, **58**, 627 (1985).
83. R. K. Pandey, F.-Y. Shiau, N. W. Smith, T. J. Dougherty, and K. M. Smith, *Tetrahedron*, **48**, 7591 (1992).
84. K. M. Smith, R. K. Pandey, F.-Y. Shiau, N. W. Smith, P. Iakovides, and T. J. Dougherty, *Proceedings of SPIE, The International Society for Optical Engineering*, **1645**, 274 (1992).
85. A. W. Nichol, *J. Chem. Soc. (C)*, 903 (1970).
86. V. Wray, U. Jürgens, and H. Brockmann, Jr., *Tetrahedron*, **35**, 2275 (1979).
87. H. Brockmann, Jr., U. Jürgens, and M. Thomas, *Tetrahedron Lett.*, **23**, 2133 (1979).
88. U. Jürgens and H. Brockmann, Jr., *Liebigs Ann. Chem.*, 472 (1982).
89. S. Mettath, M. Shibata, J. L. Alderfer, M. O. Senge, K. M. Smith, R. Rein, T. J. Dougherty, and R. K. Pandey, *J. Org. Chem.*, **63**, 1646 (1998).
90. U. Jürgens and H. Brockmann, Jr., *J. Chem. Res. S.*, 181 (1979).
91. U. Jürgens and H. Brockmann, Jr., *J. Chem. Res. M.*, 2379 (1979).
92. H. Tamiaki, M. Amakawa, Y. Shimono, R. Tanikaga, A. R. Holzwarz, and K. Schaffner, *Photochem. and Photobiol.*, **63**, 92 (1996).
93. H. Tamiaki, A. R. Holzwarth, and K. Schaffner, *Photosynth. Res.*, **41**, 245 (1994).
94. R. C. Davis, S. L. Ditson, A. F. Fentiman, and R. M. Pearlstein, *J. Am. Chem. Soc.*, **103**, 6823 (1981).
95. P. A. Liddell, D. Barrett, L. R. Makings, P. J. Pessiki, D. Gust, and T. A. Moore, *J. Am. Chem. Soc.*, **108**, 5350 (1986).
96. D. Gust, T. A. Moore, A. L. Moore, A. A. Krasnovsky, Jr., P. A. Liddell, D. Nicodem, J. DeGraziano, P. Kerrigan, L. R. Makins, and P. J Pessiki, *J. Am. Chem. Soc.*, **115**, 5684 (1993).
97. A. Osuka, S. Shinoda, S. Marumo, H. Yamada, T. Katoh, I. Yamazaki, Y. Nishimura, Y. Tanaka, S. Taniguchi, T. Okada, K. Nozaki, and T. Ohno, *Bull. Chem. Soc. Japan*, **68**, 3255 (1995); *Chem. Abstr.*, **124**, 55637 (1996).
98. A. Stoll and E. Wiedemann, *Helv. Chim. Acta*, **17**, 456 (1934).
99. A. Stoll and E. Wiedemann, *Helv. Chim. Acta*, **17**, 163 (1934).
100. S. Knapp, B. Huang, T. J. Emge, S. Sheng, K. Krogh-Jespersen, I. A. Potenza, and H. J. Schugar, *J. Am. Chem. Soc.*, **121**, 7977 (1999).
101. H. R. Wetherell and M. J. Hendrickson, *J. Org. Chem.*, **24**, 710 (1959).

102. T. J. Michalski, J. E. Hunt, J. C. Hindman, and J. J. Katz, *Tetrahedron Lett.*, **26**, 4875 (1985).
103. B. Gerlach and K. M. Smith, *Tetrahedron Lett.*, **37**, 5431 (1996).
104. H. Tamiaki and M. Kouraba, *Tetrahedron*, **53**, 10677 (1997); *Chem. Abstr.*, **127**, 205387 (1997).
105. M. R. Wasielewski, *Chem. Rev.*, **92**, 435 (1992).
106. G. P. Wiederrecht, M. P. Niemczyk, W. A. Svec, and M. R. Wasielewski, *J. Am. Chem. Soc.*, **118**, 81 (1996).
107. L. Jaquinod, D. J. Nurco, C. J. Medforth, R. K. Pandey, T. P. Forsyth, M. M. Olmstead, and K. M. Smith, *Angew. Chem. Int. Ed. Engl.*, **35**, 1013 (1996).
108. R. Paolesse, R. K. Pandey, T. P. Forsyth, L. Jaquinod, K. R. Gerzevske, D. J. Nurco, M. O. Senge, S. Licoccia, T. Boschi, and K. M. Smith, *J. Am. Chem. Soc.*, **118**, 3869 (1996).
109. L. Jaquinod, M. O. Senge, R. K. Pandey, T. P. Forsyth, and K. M. Smith, *Angew. Chem. Int. Ed. Engl.*, **35**, 1840 (1996).
110. D. J. Johnson, M. P. Niemczyk, D. W. Minsek, G. R. Wiederrecht, W. A. Svec, G. L. Gaines, and M. R. Wasielewski, *J. Am. Chem. Soc.*, **115**, 5692 (1993).
111. G. Zheng, R. K. Pandey, T. P. Forsyth, A. N. Kozyrev, T. J. Dougherty, and K. M. Smith, *Tetrahedron Lett.*, **38**, 2409 (1997); *Chem. Abstr.*, **126**, 277323 (1997).
112. J. E. McMurry, T. Lectka, and J. G. Rico, *J. Org. Chem.*, **54**, 3748 (1989).
113. J. E. McMurry, *Chem. Rev.*, **89**, 1513 (1989).
114. A. Osuka, S. Marumo, Y. Wada, I. Yamazaki, T. Yamazaki, Y. Shirakava, and Y. Nishimura, *Bull. Chem. Soc. Japan*, **68**, 2909 (1995); *Chem. Abstr.*, **124**, 29485 (1996).
115. H. Tamiaki, M. Kubo, and T. Oba, *Tetrahedron*, **56**, 6245 (2000).
116. H. Tamiaki, Y. Shimono, A. Graham, M. Rattray, and R. Tanikaga, *Bioorg. Med. Chem. Lett.*, **6**, 2085 (1996).
117. M. Maggini, G. Scorrano, and M. Prato, *J. Am. Chem. Soc.*, **115**, 9798 (1993).
118. J. Helaja, A. Y. Tauber, Y. Abel, N. V. Tkachenko, H. Lemmetyinen, I. Kilpelainen, and P. Hynninen, *J. Chem. Soc., Perkin Trans. 1*, 2403 (1999); *Chem. Abstr.*, **131**, 336858 (1999).
119. R. J. Abraham, A. E. Rowan, N. W. Smith, and K. M. Smith, *J. Chem. Soc., Perkin Trans. 2*, 1047 (1993).
120. A.-S. Fabiano, D. Allouche, Y.-H. Sanejouand, and N. Paillous, *Photochem. and Photobiol.*, **66**, 336 (1997).
121. P. H. Hynninen, *Acta Chem. Scand.*, **27**, 1771 (1973).
122. P. H. Hynninen, M. R. Wasielewski, and J. J. Katz, *Acta Chem. Scand.*, B., **33**, 637 (1979).
123. P. H. Hynninen and S. Lotjonen, *Synthesis*, 539 (1980).
124. M. R. Wasielewski and W. A. Svec, *J. Org. Chem.*, **45**, 1969 (1980).
125. R. Gaffar, S. Kermasha, and B. Bisakowski, *J. Biotechnology*, **75**, 45 (1999).
126. R. Willstätter and A. Stoll, *Liebigs Ann. Chem.*, **380**, 148 (1911).
127. T. J. Michalski, J. E. Hunt, C. Bradshaw, A. M. Wagner, J. R. Norris, and J. J. Katz, *J. Am. Chem. Soc.*, **110**, 5888 (1988).
128. I. Sakata, S. Nakajima, K. Koshimizu, N. Samejima, K. Inohara, and H. Takata, *Eur. Pat. Appl.* EP 142732; *Chem. Abstr.*, **103**, 123271 (1985).
129. M. Nakazato, Jpn. Patent 04139186; *Chem. Abstr.*, **117**, 178303 (1992).
130. S. G. Boxer and R. R. Bucks, *J. Am. Chem. Soc.*, **101**, 1883 (1979).
131. S. G. Boxer and G. L. Closs, *J. Am. Chem. Soc.*, **98**, 5406 (1976).
132. M. Karasawa, T. Otani, M. Uchimoto, K. Aizawa, and H. Kawabe, Eur. Pat. Appl. EP 322198; *Chem. Abstr.*, **112**, 76802 (1990).
133. P. Wongsinkongman, A. Brossi, H.-K. Wang, K. F. Bastow, and K.-H. Lee, *Bioorg. Med. Chem.*, **10**, 583 (2002).

134. V. Rosenbach-Belkin, L. Chen, L. Fiedor, I. Tregub, F. Pavlotsky, V. Blumfeld, Y. Salomon, and A. Scherz, *Photochem. and Photobiol.*, **64**, 174 (1996).
135. J. C. Bommer and B. F. Burnham, Eur. Pat. Appl. EP 200218; *Chem. Abstr.*, **106**, 85048 (1987).
136. A. Dagan, S. Gatt, S. Cerbu-Karabat, J.-C. Maziere, C. Maziere, R. Santus, E. L. Engelhardt, K. A. Yeh, C. C. Stobbe, M. C. Penning, and J. D. Chapman, *Int. J. Cancer*, **63**, 831 (1995).
137. D. Kessel, *J. Photochem. and Photobiol.*, B., **39**, 81, (1997).
138. N. S. Soukos, M. R. Hamblin, and T. Hasan, *Photochem. and Photobiol.*, **65**, 723 (1997).
139. T. V. Akhlynina, D. A. Jans, A. A. Rosenkranz, N. V. Statsyuk, I. Y. Balashova, G. Toth, I. Pavo, A. B. Rubin, and A. S. Sobolev, *J. Biol. Chem.*, **272**, 20328 (1997).
140. L.-M. Wong Kee Song, K. K. Wang, and A. R. Zinsmeister, *Cancer*, **82**, 421 (1998).
141. N. S. Soukos, L. A. Ximenez-Fyvie, M. R. Hamblin, S. S. Socransky, and T. Hasan, *Antimicrob. Agents Chemother.*, **42**, 2595 (1998); *Chem. Abstr.*, **130**, 22293 (1999).
142. S. W. Taber, V. H. Fingar, C. T. Coots, and T. J. Wieman, *Clin. Cancer Res.*, **4**, 2741 (1998); *Chem. Abstr.*, **130**, 179373 (1999).
143. R. K. Pandey, A. N. Kozyrev, and T. J. Dougherty, US Patent 5864035; *Chem. Abstr.*, **130**, 139207 (1999).
144. T. V. Akhlynina, D. A. Jans, N. V. Statsyuk, I. Y. Balashova, G. Toth, I. Pavo, A. Rosenkranz, B. S. Naroditsky, and A. S. Sobolev, *Int. J. Cancer*, **81**, 734 (1999).
145. J. Kbadem, A. A. Veloso, F. Tolentino, T. Hasan, and M. Hamblin, *Investigative Ophthalmology & Visual Science*, **40**, 3132 (1999).
146. B. Robinson, A. R. Morgan, and H. L. Narciso, Jr., PCT Int. Appl. WO 97 05127; *Chem. Abstr.*, **126**, 211973 (1997).
147. G. Zheng, M. Aoudia, D. Lee, M. A. Rodgers, K. M. Smith, T. J. Dougherty, and R. K. Pandey, *J. Chem. Soc., Perkin Trans. 1*, 3113 (2000).
148. C. R. Rovaldi, A. Pievsky, N. A. Sole, P. M. Friden, D. M. Rothstein, and P. Spacciapoli, *Antimicrob. Agents Chemother.*, **44**, 3364 (2000).
149. A. Gijsens, L. Missiaen, W. Merlevede, and P. Dewitte, *Cancer Res.*, **60**, 2197 (2000).
150. I. Sheyhedin, T. Okunaka, H. Kato, Y. Yamamoto, N. Sakaniwa, C. Konaka, and K. Aizawa, *Lasers in Surgery and Medicine*, **26**, 83 (2000).
151. M. Del Governatore, M. R. Hamblin, E. E. Piccinini, G. Ugolini, and T. Hasan, *British J. Cancer*, **82**, 56 (2000).
152. J. Usuda, T. Okunaka, K. Furukawa, T. Tsuchida, Y. Kuroiwa, Y. Ohe, N. Saijo, K. Nishio, C. Konaka, and H. Kato, *Int. J. Cancer*, **93**, 475 (2001).
153. T. Nagae, K. Aizawa, N. Uchimura, D. Tani, M. Abe, K. Fujishima, S. E. Wilson, and S. Ishimaru, *Lasers in Surgery and Medicine*, **28**, 381 (2001).
154. K. Mori, S. Yoneya, K. Anzail, S. Kabasawa, T. Sodeyama, G. A. Peyman, and D. Moshfeghi, *Retina - The Journal of Retinal and Vitreous Diseases*, **21**, 499 (2001).
155. J. Kopecek, P. Kopeckova, T. Minko, Z. R. Lu, and C. M. Peterson, *J. Controlled Release*, **74**, 147 (2001).
156. J. G. Shiah, Y. Sun, P. Kopeckova, C. M. Peterson, R. C. Straight, and J. Kopecek, *J. Controlled Release*, **74**, 249 (2001).
157. S. I. Ogura, Y. Fujita, T. Kamachi, and I. Okura, *J. Porphyrins and Phthalocyanines*, **5**, 486 (2001).
158. Y. Kureishi, H. Shiraishi, and H. Tamiaki, *J. Electroanal. Chem.*, **496**, 13 (2001).
159. A. F. Mironov, A. V. Efremov, O. A. Efremova, and R. Bonnett, *Tetrahedron Lett.*, **38**, 6775 (1997).
160. A. F. Mironov and A. V. Nechaev, *Russian J. Bioorg. Chem.*, **27**, 141 (2001).
161. A. V. Nechaev, *Author's Abstract of Thesis for Candidate of Chemical Sciences* [in Russian], Moscow (2002).
162. S. Lötjönen and P. H. Hynninen, *Synthesis*, 541 (1980).

163. A. Weller and R. Livingston, *J. Am. Chem. Soc.*, **76**, 1575 (1954).
164. F. C. Pennington, S. D. Boyd, H. Horton, S. W. Taylor, D. G. Wolf, J. J. Katz, and H. H. Strain, *J. Am. Chem. Soc.*, **89**, 3871 (1967).
165. P. A. Ellsworth and C. B. Storm, *J. Org. Chem.*, **43**, 281 (1978).
166. F. C. Pennington, N. B. Boettcher, and J. J. Katz, *Bioorg. Chem.*, **3**, 204 (1974).
167. L. Ma and D. Dolphin, *Tetrahedron*, **52**, 849 (1996).
168. R. D. Poterz and S. A. Chernomorsky, US Patent 5599831; *Chem. Abstr.*, **126**, 154558 (1997).
169. D. Kessel and R. D. Poretz, *Photochem. and Photobiol.*, **71**, 94 (2000).
170. S. C. Mohr and R. Ray, PCT Int. Appl. WO 97 34637; *Chem. Abstr.*, **127**, 304808 (1997).
171. R. B. Woodward, *Angew. Chem.*, **72**, 651 (1960).
172. R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Duller, J. Hannah, F. P. Hauck, S. Ito, A. Langemann, E. Le Goff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, and H. Volz, *J. Am. Chem. Soc.*, **82**, 3800 (1960).
173. R. B. Woodward, *Pure and Appl. Chem.*, **2**, 383 (1962).
174. R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Gloss, H. Duller, J. Hannah, F. P. Hauck, S. Ito, A. Langemann, E. Le Goff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, and H. Volz, *Tetrahedron*, **46**, No. 22, 7599 (1990).
175. K. M. Smith and W. M. Lewis, *Tetrahedron*, **37**, 399 (1981).
176. M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J. Am. Chem. Soc.*, **91**, 1232 (1969).
177. G. W. Kenner, S. W. McCombie, and K. M. Smith, *J. Chem. Soc., Chem. Commun.*, 844 (1972).
178. M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J. Chem. Soc., Perkin Trans. 1*, 512 (1974).
179. M. T. Cox, A. H. Jackson, G. W. Kenner, S. W. McCombie, and K. M. Smith, *J. Chem. Soc. Perkin Trans. 1*, 516 (1974).
180. G. W. Kenner, S. W. McCombie, and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 527 (1974).
181. F. C. Pennington, H. H. Strain, V. A. Svec, and J. J. Katz, *J. Am. Chem. Soc.*, **86**, 1418 (1964).
182. A. Y. Tauber, R. K. Kostiainen, and P. H. Hynninen, *Tetrahedron*, **50**, 4723 (1994).
183. B. C. Robinson, A. S. Phadke, S.-J. S. H. Lee, and D. Sengupta, US Patent 5973141; *Chem. Abstr.*, **131**, 299317 (1999).