Discovery and Synthesis of Less Common Natural Hydroporphyrins

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I. Introduction

Of the porphinoids occurring in nature the most biologically important and the most widespread are heme (**3a**) (the red blood pigment), chlorophyll *a* (**4**) (the green pigment involved in plant photosynthesis), the bacteriochlorophylls (**7**) (of the bacterial photosynthetic apparatus), and vitamin B_{12} (**8**) (the "antipernicious" red pigment essential for numerous biochemically important rearrangement reactions). The basic functions of these cofactors are determined by the incorporation of different metal ions into the centers of their macrotetracycles. Fine tuning of the functions is regulated by the different oxidation levels of the macrocyclic ligand systems. The final adaptation of the cofactors to their various molecular environments in the cells is effected by variation in the peripheral substitution patterns of the chromophores. In the iron-containing red blood pigment heme (**3a**), which transports oxygen and electrons, this takes the form of a completely unsaturated 18π aromatic porphyrin chromophore **1**. The common structural units in the class of photosynthetic pigments are the chlorin (**2**) and bacteriochlorin (**5**) frameworks with partially saturated pyrrole rings and photochemically inert central magnesium ions. The photophysical properties, especially the longer wavelength absorption of the chlorins and bacteriochlorins resulting from this structural modification, make them naturally suited as pigments for photosynthesis. The central metal ion of vitamin B_{12} (**8**) provides an example of how the special reactivity of organometallic compounds is used in nature. The highly reduced corrin chromophore **6** precisely adjusts the reactivity required in the central cobalt ion.

Until the mid-1970s the four classic porphinoid and corrinoid structures with their porphyrin, chlorin, bacteriochlorin, and corrin skeletons were the only representatives of the class of porphinoid natural products (Chart 1).[1-8] Although other partially hydrogenated porphinoid structures were conceivable and some had in fact been prepared by the reduction of porphyrins,[9,10] none of these reduced porphyrins had hitherto been found in nature. Over the past 20 years, essentially two developments have been responsible for augmenting the range of naturally occurring porphinoids with novel, interesting structures. The first line of development originates from the investigation of vitamin B_{12} biosynthesis. Novel hydroporphinoid structures have been discovered in the search for intermediates that could form part of the biosynthetic chain between the key building block of porphyrin biosynthesis, uroporphyrinogen III (**153**), and vitamin B_{12} (**8**).[11-13] At the same time some of these structures, which play an important role in vitamin B_{12} biosynthesis, were identified as cofactors of redox enzymes of microorganisms and plants.[8] The second development is characterized by the deliberate search for new porphinoid structures in marine organisms and microorganisms, which has actually resulted in the discovery of previously unknown hydroporphinoid compounds. In both cases isolation, identification, and structural elucidation of the novel structures, which often only occur as traces, had only just become possible due to the simultaneous development of new separation techniques and Fourier transform NMR spectroscopy. The novel structures with unusual biological activities have also attracted the attention of synthetic organic chemists, who have developed synthetic pathways and thus been able to produce sufficient amounts of material for subsequent investigations.

II. Chlorins

A. Discovery of New Naturally Occurring Chlorins

Chlorophyll *a* (**4**, Chart 1), the green photosynthesis pigment, is the prototype of the chlorin class of natural products. It was first isolated by Willstätter[14] at the

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Franz-Peter Montforts was born in Hohenlimburg, Germany, in 1948. He studied at the University of Münster, Germany, where he received his Diplom degree in chemistry in 1972. From 1972 to 1976 he worked as scientific staff member in the Institute of Organic Chemistry in Münster. In 1974 he received his doctoral degree in Organic Chemistry under Prof. Dr. Burchard Franck. After a postdoctoral fellowship (1977–1978) with Prof. Dr. Albert Eschenmoser at the ETH Zürich, Switzerland, he moved for his Habilitation (1983) in organic chemistry to the Institute of Organic Chemistry at the University of Frankfurt, Germany. In the faculty of Chemistry in Frankfurt he held the position of a Hochschulassistent and Privatdozent. In 1986 he was appointed to his present position, professor of organic chemistry at the University of Bremen, Germany. He is recipient of the "Siemens Medal" of the "Werner von Siemens Ring Stiftung" (1981) and of the award of the "Verband der Chemischen Industrie" (1983). His current research interests are concerned with the chemistry and selective synthesis of natural products, focusing on partial and total synthesis of new tetrapyrrolic structures. The special interest for photodynamic tumor therapy (PDT) and artificial photosynthesis originates from the research in tetrapyrrole chemistry.

Benjamin Gerlach was born in Bremen, Germany in 1966. He received his chemistry diploma in 1990 and his Ph.D. in 1993 from the University of Bremen. In 1990, he joined the Fraunhofer-Institut für angewandte Materialforschung (IfaM) in Bremen working on the organic chelatists behavior on alumina surfaces. During his doctoral work on porphyrin and chlorin synthesis in Prof. Montforts' group he became fellow of a Chemiefonds-Stipendium by the Fonds der Chemischen Industrie. Currently he is working as a postdoctoral fellow in the group of Prof. Dr. B. Kräutler at the University of Innsbruck, Austria. There he is engaged in the structural elucidation and synthesis of catabolites from chlorophylls.

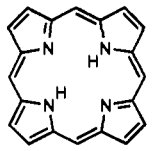
turn of the century. The common structural unit in this class is the chlorin framework **2** with a partially saturated pyrrole ring, which is derived from the completely unsaturated porphyrin. The photophysical properties of the chlorins resulting from this structural alteration render them naturally suitable as pigments for photosynthesis and also make them of interest in medical applications, as for example in photodynamic tumor therapy (PDT).[15,16]

Frank Höper was born in Bremen, Germany in 1965. He received his Diplom degree in chemistry in 1990 and his Ph.D. in 1993 from the University of Bremen. Since 1991 he has been working in the Institute of Organic Chemistry, University of Bremen, as a scientific staff member. His research interests include the enantioselective synthesis of porphyrins and chlorins, together with the asymmetric allylboration reaction.

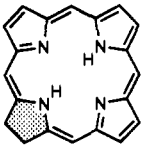
Novel chlorin structures have recently been isolated from various marine organisms and their substitution pattern suggests their biogenesis from chlorophyll *a* (**4**) as being most likely (Chart 2). The nickel-containing tunichlorin (**9**) was discovered by Rinehart et al.[17] in the tunicate *Trididemnum solidum* which occurs in the Caribbean Sea. Structural elucidation was carried out by UV/vis, CD, MS, and ^{1}H NMR spectroscopy on dimethyltunichlorin (**107**) (see Scheme 12), which is prepared by etherification of the 3-hydroxymethyl group and esterification of the 17-propionic acid side chain. Dimethyltunichlorin synthesized from tunichlorin (**9**) is in all respects identical to dimethyltunichlorin prepared from chlorophyll *a* (**4**) by partial synthesis (see Scheme 12). However, the biological function of tunichlorin (**9**) is still unknown. Cyclopheophorbide (**10**) and chlorophyllone *a* (**11**), which are closely related to each other, occur in the sponge *Darwinella oxeata* and in the short-necked clam *Ruditapes philippinarum*. Cambie et al.[18] have isolated cyclopheophorbide and determined its structure by X-ray diffraction. It is worth noting, that the structure of naturally occurring cyclopheophorbide, which was first isolated in 1986, is identical to that of the cyclopheophorbide prepared from chlorophyll *a* (**4**) by partial synthesis (see Scheme 12) in Eschenmoser's laboratory[19] some years before. Structural elucidation of chlorophyllone *a* (**11**), an oxidation product of **10**, was achieved by classical spectroscopic methods.[20] Both compounds exhibit antioxidative properties and protect the animals containing the chlorin derivatives **10** and **11** against unwanted oxidation processes. As can be deduced from their occurrence in animals, pigments **10** and **11** have no photosynthetic activity. Another group of chlorins, which are not related to the chlorophylls, is characterized by geminally disubstituted structural parts in the saturated pyrrole rings. In terms of their substitution pattern and biological activity the chlorins **12**, **13**, and **14** (Chart 3) differ markedly from each other.

Bonellin (**12**) is the green sex-differentiating pigment of *Bonellia viridis*, a marine animal found throughout the Mediterranean and belonging to the *Echiuroida* class of animals. *Bonellia viridis* possesses a remarkable sex dimorphism, which is induced by bonellin. Any of the initially asexual larvae that come into contact with

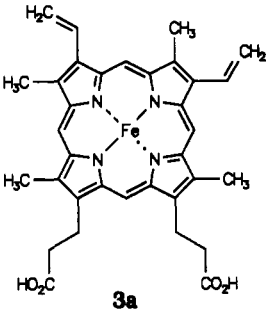
Chart 1. The Most Important Representatives of Porphinoid and Corrinoid Natural Products



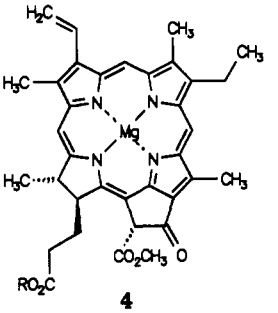
1
Porphyrin



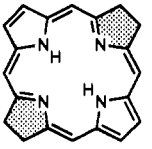
2
Chlorin



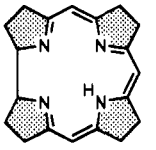
3a
Heme



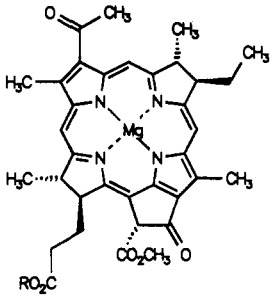
4
Chlorophyll a



5
Bacteriochlorin

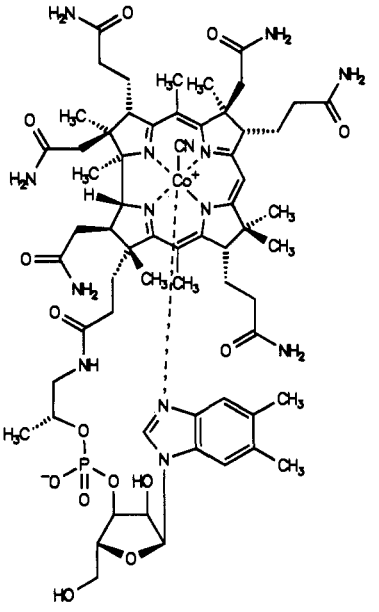


6
Corrin



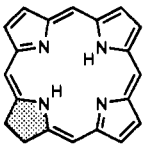
R = Phytyl

7
Bacteriochlorophyll

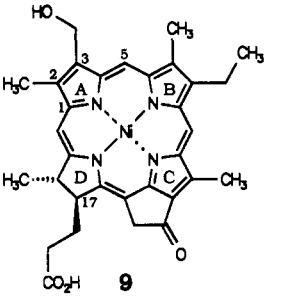


8
Vitamin B_{12}

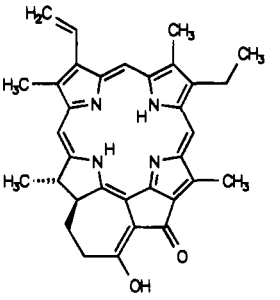
Chart 2. Less Common Chlorins Derived from Chlorophyll *a* (4)



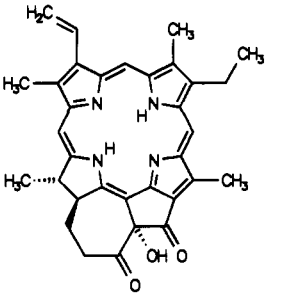
2
Chlorin



9
Tunichlorin

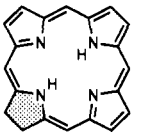


10
Cyclopheophorbide

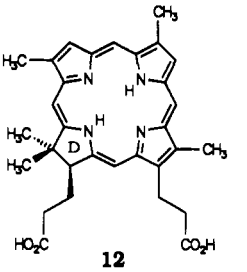


11
Chlorophyllone a

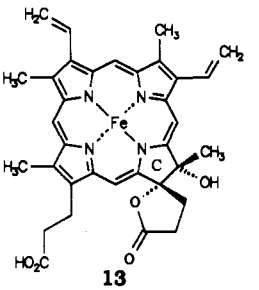
Chart 3. Less Common Geminally Disubstituted Chlorins



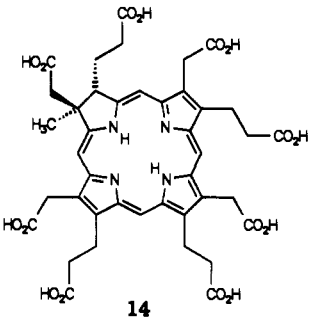
2
Chlorin



12
Bonellin



13
Heme d



14
Factor I

the body wall of the female, which contains the green bonellin, develop into males of about 1–3 mm in size. After contact with bonellin the males live inside the body cavity of the larger females (15 cm). The female of the species develop from those larvae which have had no contact with bonellin.[21-24] Although pure crystalline bonellin (12) was first isolated by Lederer et al.[25] in 1939, it was not until 1976 that Pelter et al.[26] determined the constitutional formula of bonellin by modern spectroscopic methods. Chemical degradation was used to elucidate the absolute configuration of bonellin (12) by Montforts et al.[27] The ring D degradation product of bonellin (12) was found to be constitutionally and configurationally identical to the already familiar ring C degradation product of vitamin B_{12} (8). Factor I (14) was first isolated as its octamethyl ester by Müller et al.[28] and by Arigoni et al.[29] from bacteria that produce vitamin B_{12}, such as *Propionibacterium shermanii* and *Clostridium tetanomorphum*. Its reduced form [precorrin 1 (155), see Scheme 22] is the first link in the biosynthetic chain between uroporphyrinogen III (153) and vitamin B_{12} (8).[28-30] Apart

from this, factor I (14) has no other biological function. The structural determination of factor I was greatly simplified by the fact that 14 originates during the biosynthetic pathway to vitamin B_{12}. Structural alternatives for factor I (14) were thus restricted.[28-30]

In contrast to bonellin (12) and factor I (14), heme *d* (13) is bishydroxylated in the periphery of ring C, which lends it the characteristic geminally disubstituted structural part and the typical chlorin chromophore. The absolute and relative configurations of heme *d* (13) have still not been determined. The correct configurational formula of heme *d*[31] may therefore be a stereoisomer of formula 13. In addition, there is no certainty as to whether the spirocyclic lactone structure is the natural structural element or whether it is generated during isolation.

As is typical in many bacteria, the respiratory chain of *Escherichia coli* contains two terminal oxidases, cytochrome *o* and cytochrome *d*. Heme *d* (13) is the prosthetic group of the terminal oxidase cytochrome *d*.[32] Cytochrome *o* prevails in the early exponential phase during aerobic growth of the culture. Cytochrome *d* plays an important role in the late exponential phase, or when cells are grown with a limited oxygen supply. The K_m value[33] for the oxygen-binding of cytochrome *d* is about 8 times lower than that of cytochrome *o*. This allows the bacteria to grow under conditions of low oxygen supply.

B. Synthesis of Chlorins

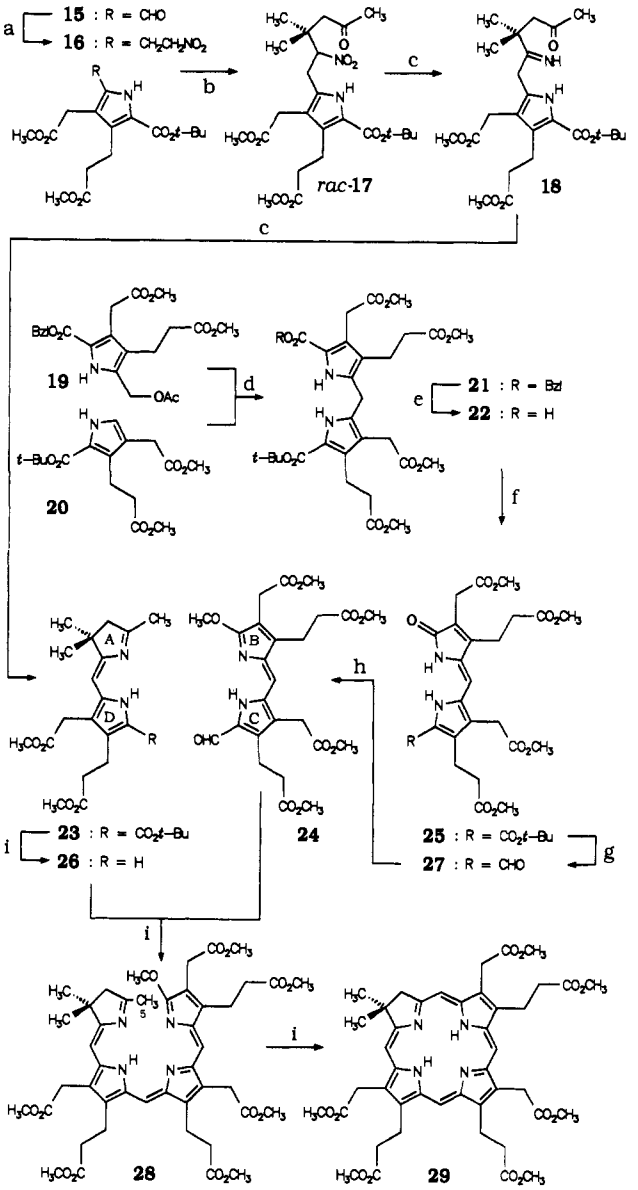
1. Total Synthesis of Model Compounds

Although methods for the preparation of chlorins were available when the discovery of less common chlorins began, Woodward's synthesis[34] of chlorophyll *a* (4) was in fact the only selective totally synthetic pathway. However, the geminally dialkylated structural parts typical of factor I (14) and bonellin (12) cannot be created with Woodward's approach.

The laboratories of Battersby[35] and Montforts[36] developed selective methods for the total synthesis of chlorins on model systems, such as 29 (Scheme 1) and 47 (Scheme 3), which contain the characteristic dialkylated parts in the saturated five-membered rings of the chlorin system. The knowledge gained from these investigations was later used to synthesize the naturally occurring chlorins.

In a model synthesis,[35c,f] a nitro-Michael addition of the readily available nitroalkyl pyrrole 16 to mesityl oxide was used to introduce the geminally dialkylated structural element into an AD component *rac*-17 for the desired chlorin. Reduction of the nitro function in *rac*-17 leads, via the imine structure 18, to the desired AD dimer 23. On the other hand, the BC part 21 is produced from the monopyrroles 19 and 20. Selective cleavage of the benzyl ester of 21 and subsequent bromination of 22 yield the bicyclic lactam 25. During the course of the reaction the B pyrrole ring is brominated under decarboxylation, the dipyrrole methane is oxidized and the bromine in the pyrrolic position is substituted to form a lactam function. The complete BC part 24 is obtained by acid-catalyzed formylation and subsequent methylation, with the acid first being responsible for ester cleavage and then decarboxylation. The AD dimer 23 and the BC dimer 24 were combined

Scheme 1. Total Synthesis of a Model Chlorin: Photochemical Route[a]

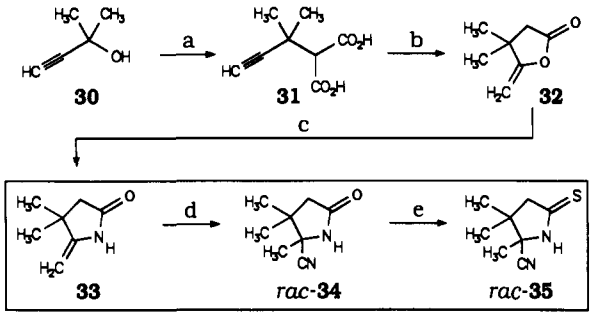


[a] (a) (1) $MeNO_2$, $MeNH_3^+Cl^-$, KOAc, MeOH, room temperature, 5 h; (2) $NaBH_4$, MeOH/DMF (10/1), HOAc, room temperature. (b) Mesityl oxide, $Bu_4N^+F^-$, DMF, room temperature, 3 h. (c) (1) NaOMe, THF, MeOH, room temperature, 5 min; (2) $TiCl_3$, NH_4OAc, H_2O, THF, room temperature, 5.5 h. (d) TsOH, CH_2Cl_2, 18 °C, 2 h. (e) H_2, Pd/C, MeOH. (f) HCO_2Na, HCO_2H, Br_2, 0 °C, 15 min. (g) TFA, 50 °C, 1 h, $HC(OMe)_3$, 0 °C, 20 min, H_2O. (h) $(Me)_3O^+BF_4^-$, CH_2Cl_2, *i*-Pr_2NEt, 18 °C, 20 min. (i) (1) TFA, 18 °C, 2.75 h, THF, *i*-Pr_2NEt; (2) *hν* (vis), <0.3 Torr, 20 °C, 6.2 h.

by treatment with acid to form the linear tetrapyrrole 28. Again, the acid brings about ester cleavage, decarboxylation, and condensation. In the final stage the linear tetrapyrrole 28 undergoes photochemically induced cyclization to give the chlorin 29. A plausible mechanism for the ring closure of 28 to 29 includes the formation of the 5-enamine tautomer of 28, which cyclizes in a photochemical $18\pi-\sigma$ isomerization process followed by elimination of methanol.

The photochemical cyclization process of the model synthesis was also successfully applied to other model syntheses[35] and to syntheses of naturally occurring hydroporphyrins, such as factor I (14) (see Schemes 4–6), bonellin (12),[37] and sirohydrochlorin (112, see Scheme 18).

Scheme 2. Geminally Dimethylated Building Blocks for Syntheses of Different Hydroporphyrins (See Also Scheme 14)[a]

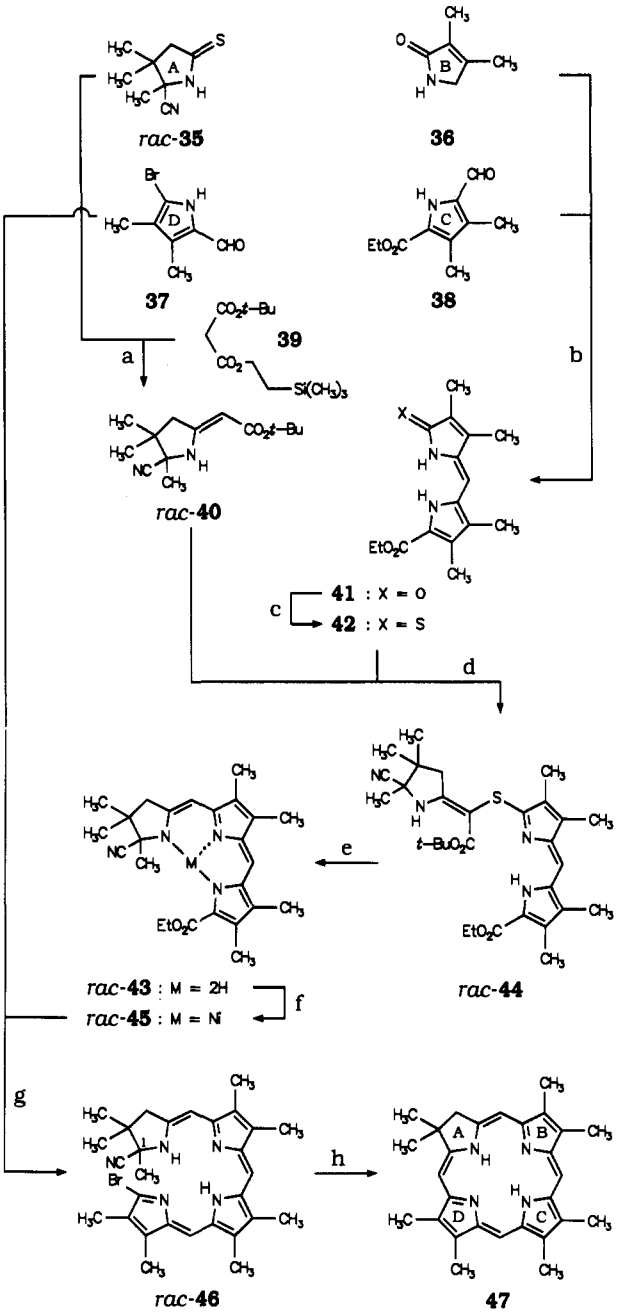


[a] (a) (1) $CaCl_2$, hydroquinone, HCl, 20 °C, 45 min; (2) $H_2C(CO_2Et)_2$, EtOH, NaOEt, 65 °C, 45 min, reflux, 30 min, 40 °C, overnight; (3) NaOH, EtOH, 90 °C. (b) 150 °C, TsOH, distillation. (c) NH_3, −40 °C, 5 h. (d) KCN, $KHCO_3$, H_2O, room temperature, 30 min, 50 °C, 30 min. (e) P_2S_5, THF, reflux, 2 h.

The geminally dimethylated lactams **33**, *rac*-**34**, and the thiolactam *rac*-**35** (Scheme 2) have proven successful as important building blocks in numerous syntheses of hydroporphinoid compounds. The saturated ring systems, which were orignally devised by Eschenmoser et al.[38] for the synthesis of model corrins, can be obtained in a few reaction steps via a malonic ester synthesis starting from alkinol **30**, which is commercially available on a large scale.

In the model synthesis of the chlorin **47** (Scheme 3)[36] the thiolactam *rac*-**35** was used as building block for the saturated ring of the chlorin. The sulfide contraction procedure allows the thiolactam *rac*-**35** to be connected to one of its neighboring rings. The procedure was devised by Eschenmoser et al.[39] while investigating the syntheses of vitamin B_{12} and corrins. Later on the method proved to be extremely efficient for the construction of hydroporphinoid structures. Paramount in the synthesis of chlorin **47**[36] is the 2-pyrrolinone **36**, in which the lactam function can be coupled with the thiolactam *rac*-**35** by methods adopted from corrin chemistry, while condensation with pyrrolealdehyde **38** can occur in the 5-position, according to the principles of bile-pigment synthesis. The pyrrolinone **36** and the aldehyde **38** undergo a base-catalyzed reaction to give the bicyclic lactam **41**, which is converted into its thio analogue **42**. The thiolactam *rac*-**35** is converted by reaction with the selectively cleavable malonic ester **39**, via sulfide contraction, into the vinylogous urethane *rac*-**40**. Coupling of *rac*-**40** and thiolactam **42** via bromination yields the tricyclic sulfide *rac*-**44**. On losing the *tert*-butylester group, the sulfide *rac*-**44** is converted into the tricycle *rac*-**43** in a variant of the sulfide contraction, developed by Eschenmoser et al.[40] for an isobacteriochlorin synthesis (see Scheme 16). The extremely oxygen-sensitive tricycle *rac*-**43** is stabilized by complexation with nickel(II). The nickel in *rac*-**45** also activates the ester function by participating in the complexation, so that a mild selective hydrolysis becomes possible to cleave the ester function. The crude product of ester hydrolysis undergoes direct acid-catalyzed condensation with the bromopyrrolealdehyde **37**, involving decarboxylation and decomplexation, to give the tetracycle *rac*-**46**. Reaction with potassium *tert*-butyl alkoxide in the presence of zinc(II), which acts as a template and can be readily removed acidolytically from the cyclized ligand system that is

Scheme 3. Total Synthesis of a Model Chlorin: Sulfide Contraction Route[a]



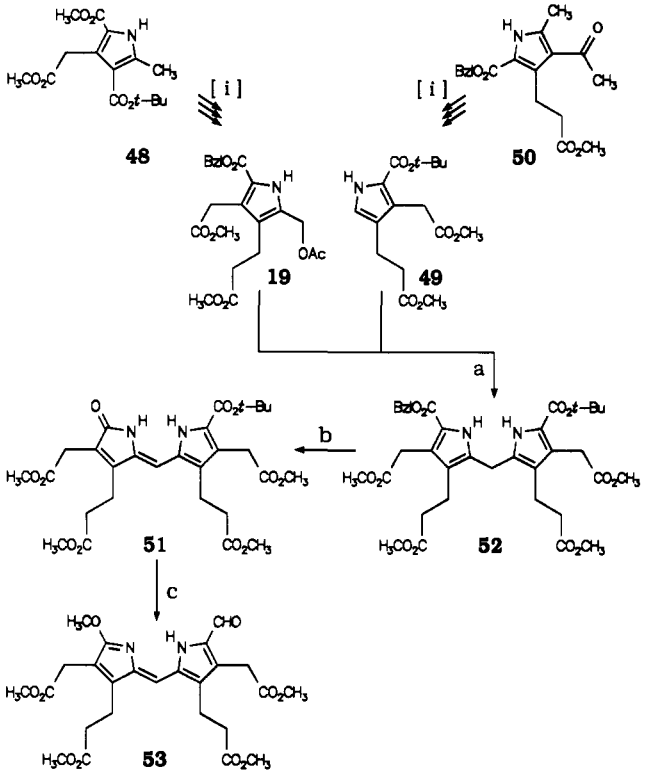
[a] (a) (1) $(PhCO_2)_2$, K_2CO_3, MeCN, 0 °C to room temperature; (2) $P(OEt)_3$, 80 °C; (3) $(n\text{-}Bu)_4NF$, THF, reflux; (4) 2 N HCl/CH_2Cl_2, HPLC. (b) DBU, molecular sieves 3 Å, THF, reflux. (c) P_2S_5, $NaHCO_3$, THF, room temperature. (d) (1) NBS, CH_2Cl_2, room temperature; (2) DBU, MeCN, room temperature. (e) $P(CH_2CH_2CN)_3$, TFA, benzene, reflux. (f) $Ni(OAc)_2 \cdot H_2O$, AcONa, MeOH/THF (2/1), room temperature. (g) (1) THF, KOH, MeOH/H_2O (9/1), reflux; (2) TsOH, $CHCl_3$, reflux. (h) (1) $Zn(OAc)_2 \cdot H_2O$, KO*t*-Bu, HO*t*-Bu, 70 °C; (2) 25% HCl/CH_2Cl_2.

formed, finally results in the cyclization of the linear tetracycle *rac*-**46** to the chlorin **47**. The base liberates an enamine double bond in position 1 by HCN elimination and the enamine cyclizes with the loss of bromide. The concept for the synthesis of the chlorin **47** has so far been applied to the syntheses of bonellin (see Scheme 8) and a hexadehydrocorrin.[41]

2. *Total Synthesis of Naturally Occurring Chlorins*

The construction of geminally dialkylated moieties in the saturated ring of factor I (**14**) and bonellin (**12**)

Scheme 4. C–D Dimeric Building Block for the Total Synthesis of Factor I Octamethyl Ester (67)[a]

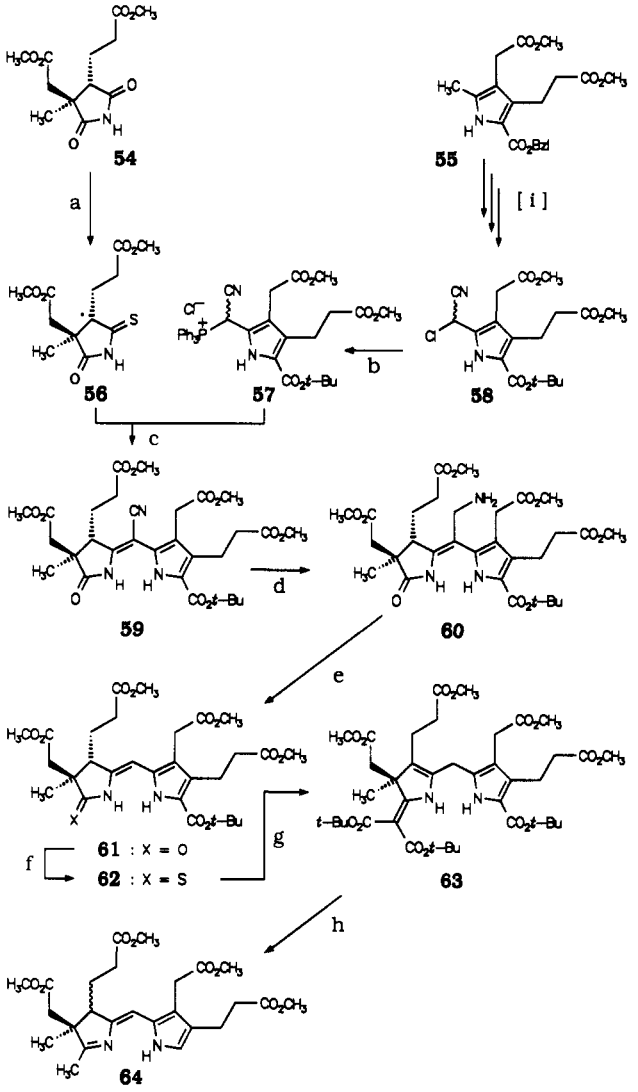


[a] (a) TsOH, CH_2Cl_2, room temperature, 1.75 h. (b) (1) H_2, Pd/C, MeOH; (2) Br_2, TFA; (3) OH^-/H_2O. (c) (1) TFA, $HC(OMe)_3$; (2) $(Me)_3O^+BF_4^-$. [i] Turner, S. P. D.; Block, M. H.; Sheng, Z.-C.; Zimmermann, S. C.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1985**, 583.

is one of the main difficulties in synthesizing these types of structure and therefore presents an interesting challenge. Furthermore, factor I (**14**) should be available in an isotopically labeled form for biosynthetic studies, whereas the unusual biological activity of bonellin (**12**) makes it an attractive synthetic target. To date the problems involved in concerning these structures have been solved by total synthesis. Battersby et al. were able to synthesize factor I (**14**)[42] by following the model synthesis described in Scheme 1.

For this reason only a rough outline of the total synthesis of factor I (**14**) is presented here, details can be taken from Schemes 4–6. A "southern" part **53** (Scheme 4) of the target structure is prepared in several reaction steps from the monopyrrolic building blocks **48** and **50**. The aldehyde function of the dipyrromethene **53** ensures that linkage with the "northern" AB part **64** (Scheme 5) occurs, whereas the methoxyimine function at the other end enables the photochemical cyclization to take place, yielding the chlorin chromophore. The "northern" AB part **64** of factor I (**14**) is constructed from the optically active succinimide **54** and the monopyrrole **55**. The optically active imide building block **54** can be obtained by ozonolytic degradation of cobyrinic acid heptamethyl ester, the product of the methanolysis of vitamin B_{12}. The imide **54** is converted into its thioimide **56** (see Scheme 17) and then connected with the pyrrole **57** by thio-Wittig reaction to yield the bicyclic lactam **59**. In addition to the sulfide contraction, the thio-Wittig reaction of thioimides, which was investigated by Gossauer et al.[43] during the course of bile pigment syntheses, is a valuable

Scheme 5. A–B Dimeric Building Block for the Total Synthesis of Factor I Octamethyl Ester (67)[a]

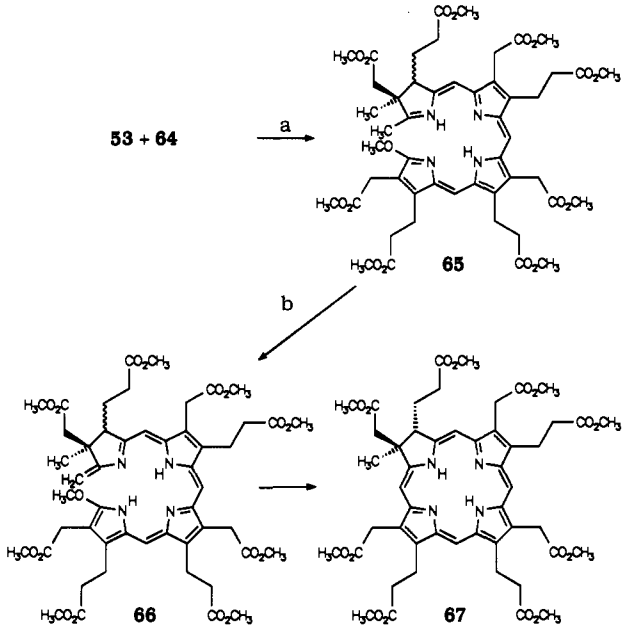


[a] (a) Lawesson's reagent (see also Scheme 17) [for preparation of **54** see: Eschenmoser, A. *Pure Appl. Chem. Suppl.* **1971**, *2*, 69 (23th Int. Congress Pure Appl. Chem., Boston). Löliger, P. Darstellung eines die Ringe B und C umfassenden Zwischenproduktes zur Synthese von Vitamin B_{12} (Preparation of an Intermediate for the Synthesis of Vitamin B_{12} which Contains Rings B and C), Dissertation, ETH Zürich (Eschenmoser, A.), 1968]. (b) PPh_3. (c) Base, toluene, reflux. (d) Raney-Ni, MeOH, H_2O, HOAc. (e) Δ, 1,2-bis(Methylamino)ethane, anisole. (f) Lawesson's reagent. (g) (1) $BrCH(CO_2t\text{-}Bu)_2$, DBU; (2) DBU, PPh_3, reflux. (h) TFA, labile **64** was immediately condensed with **53** to give **65**. [i] Turner, S. P. D.; Block, M. H.; Sheng, Z.-C.; Zimmermann, S. C.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1985**, 583.

tool for connecting unsaturated pyrrole rings with partially reduced pyrrole structures.

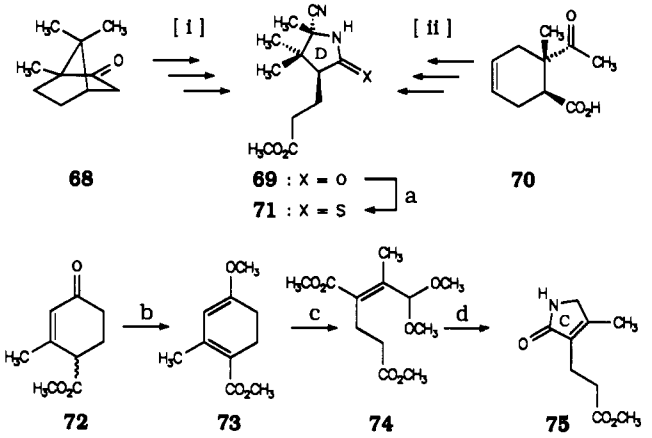
A disadvantage of the thio-Wittig reaction in the present synthesis is that the cyano group, which is necessary to stabilize the ylide, requires additional reaction steps for its removal. A missing methyl group, which has to form the "western" methine bridge, is introduced into the bicyclic lactam **59** by sulfide contraction, which also results in the *tert*-butyl ester group in the pyrrolic position being lost. The "northern" molecular part **64** is now ready for condensation with the "southern" bicycle **53** (Scheme 6). The newly formed linear tetrapyrrole **65** can be cyclized photochemically, as in the model series, via the enamine tautomer **66** to give the factor I octamethyl ester (**67**).

Scheme 6. Final Steps in the Total Synthesis of Factor I Octamethyl Ester (67)[a]



[a] (a) TFA. (b) $h\nu$ (vis), THF, TFA, i-Pr_2NEt.

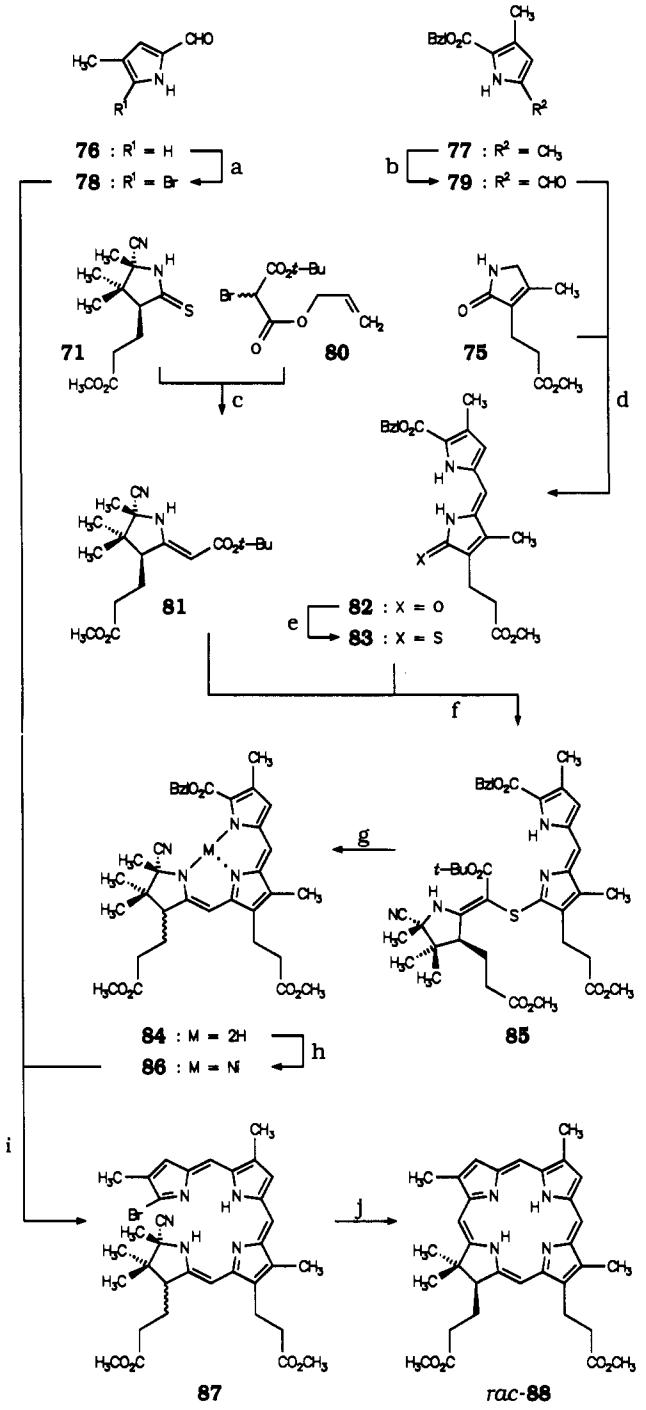
Scheme 7. Synthesis of Building Blocks for Rings C and D of Bonellin (12)[a]



[a] (a) Lawesson's reagent, THF, reflux, 30 min. (b) $HC(OMe)_3$, TsOH, benzene, reflux, 2.5 h. (c) (1) O_3/O_2, MeOH, CH_2Cl_2, −80 °C; (2) Me_2S, room temperature, 3 h; (3) $HC(OMe)_3$, TsOH, room temperature, 12 h. (d) (1) Raney-Ni, H_2, MeOH, room temperature, 4.5 h; (2) $HClO_4$ (60%), $MeCN/H_2O$, room temperature, 2.5 h; (3) NH_3/NH_4Cl, MeOH, room temperature, 4.5 h; (4) AcOH, reflux, 5.5 h. [i] Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519; **1971**, *25*, 283. [ii] Eschenmoser, A.; Winter, C. E. *Science* **1977**, *196*, 1410. Eschenmoser, A. *Naturwissenschaften* **1974**, *61*, 1913. Eschenmoser, A. *Pure Appl. Chem.* **1971**, *2*, 69 (23th Int. Congress Pure Appl. Chem., Boston. Dubs, P. Beiträge zur Synthese von Vitamin B_{12} (Contributions to the Synthesis of Vitamin B_{12}), Dissertation, ETH Zürich (Eschenmoser, A.) **1969**.

Since ring D of bonellin (**12**) is constitutionally and configurationally identical to ring C of vitamin B_{12} it was decided to use the lactam **69** as the starting material for the synthesis of bonellin. Lactam **69** is a building block used in the syntheses of vitamin B_{12} by Woodward[44] and Eschenmoser.[45] In principle, the synthetic pathway used to prepare the model chlorin **47**[36] (see Scheme 3), could be applied to synthesize bonellin (**12**).[46] The lactam **69**, which is available from (+)-camphor **68**[44] or from the enantiomerically pure cyclohexene derivative **70**,[45] is converted into its thio analogue **71**. The ring C building block **75** is obtained in a few reaction steps from Hagemann's ester **72** (see Scheme 7).

Scheme 8. Total Synthesis of Bonellin Dimethyl Ester (*rac*-88)[a]



[a] (a) Br_2, CH_2Cl_2/py, −45 °C. (b) (1) $Pb(OAc)_4$, $CHCl_3$, reflux, 210 h; (2) HCl/H_2O, room temperature, 6 h. (c) (1) DBU, MeCN, 0 °C, 20 min; (2) $P(OEt)_3$, 80 °C, 2 h; (3) piperidine, $[(Ph_3P)_4Pd]$, THF, room temperature, 2 h. (d) 2-(*tert*-Butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine, benzene, reflux, 10 h. (e) Lawesson's reagent, THF, reflux, 30 min. (f) (1) NBS, CH_2Cl_2, room temperature, 20 min; (2) DBU, MeCN, room temperature, 20 min. (g) $P(CH_2CH_2CN)_3$/TFA, benzene, reflux, 25 min. (h) $Ni(OAc)_2{\cdot}4H_2O$/NaOAc, CH_2Cl_2, room temperature, 1 h. (i) (1) Pd/C, H_2, MeOH, room temperature, 1 h; (2) TsOH, $CHCl_3$, reflux, 15 min. (j) (1) $Zn(OAc)_2$/KO*t*-Bu, *t*-BuOH, reflux, 1 h; (2) CH_2N_2, Et_2O, room temperature, 30 min.

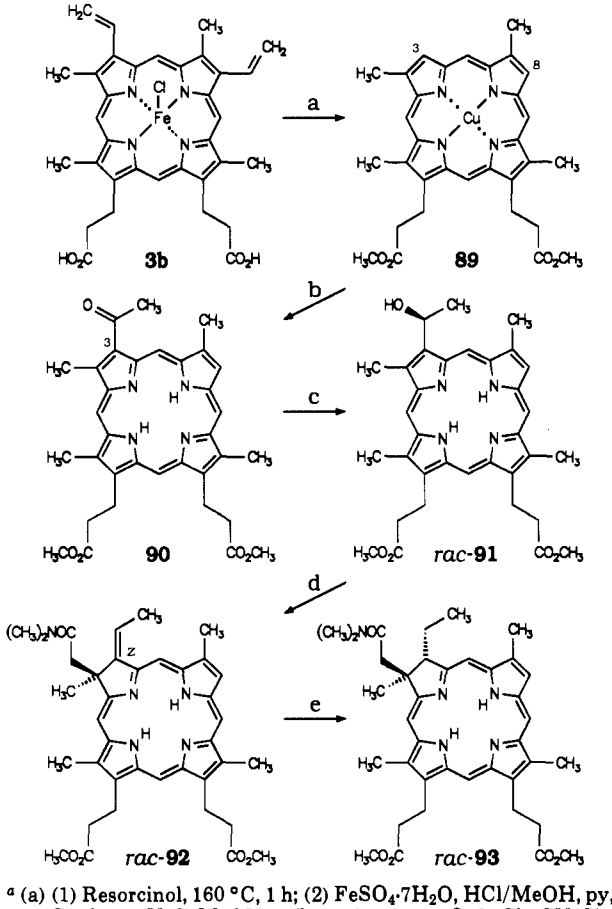
The thiolactam **71** and the ring C building block **75**, together with the monopyrroles **78** and **79**, and the selectively cleavable malonic ester **80**, form the linear tetrapyrrole **87** as described for the model chlorin **47**

(Scheme 8). In the last synthetic step the tetrapyrrole **87** is cyclized in the presence of zinc(II), which acts as a template, to give bonellin dimethyl ester (*rac*-**88**). However, in order to achieve good yields in the synthesis of the natural product, it is necessary to change some of the protecting groups used in the model synthesis. The selectively cleavable allylic ester group in the brominated malonic acid ester **80** can be removed very gently by nucleophiles in the presence of Pd(0). The natural tricycle **86** possesses a readily removable benzyl ester group instead of an ethyl ester, as in the model series. Although enantiomerically pure thiolactam **71** is used and all of the synthetic intermediates in the synthesis of bonellin are enantiomerically pure, in the final reaction step racemization does occur at the center of chirality, which is substituted by the propionic acid side chain, to give racemic bonellin dimethyl ester (*rac*-**88**). In the preceding reaction steps it was only possible for epimerization to occur, since the additional cyano-substituted center of chirality does not change its configuration but is removed in the final cyclization process leading to bonellin.

3. Partial Synthesis of Chlorins

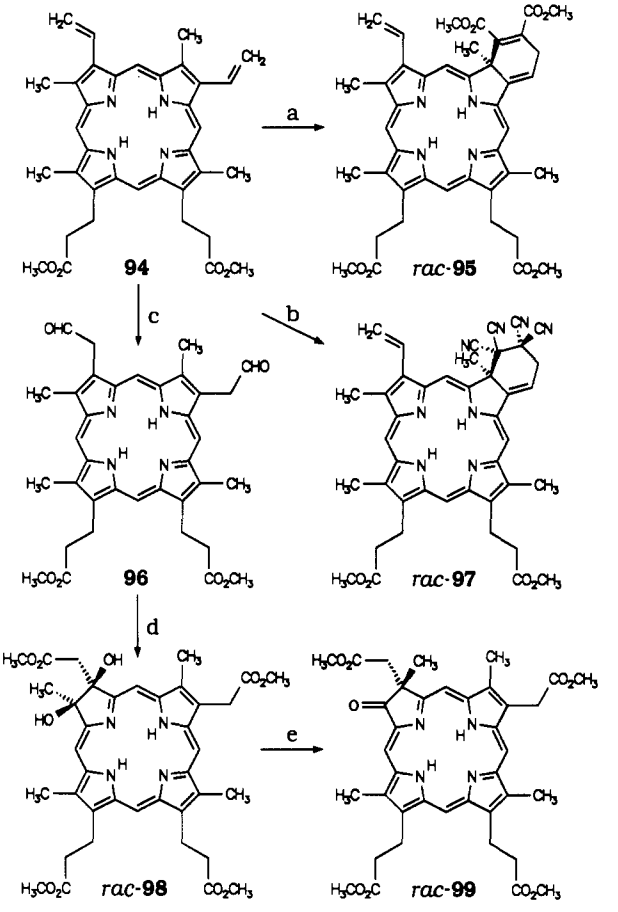
As has already been seen, one of the main difficulties in the total synthesis of model and naturally occurring chlorins and, as will be shown later, in the synthesis of other hydroporphyrins is constructing the geminally dialkylated moiety in the saturated pyrrole rings. In a synthetic study it was found that this moiety can be conveniently generated by Claisen rearrangement of readily available hydroxyalkylporphyrins (Scheme 9).[47] (Hydroxyalkyl)porphyrins like *rac*-**91** can be obtained in a few simple reaction steps from the readily available red blood pigment hemin hydrochloride (**3b**). Friedel–Crafts acylation of copper(II) deuteroporphyrin dimethyl ester (**89**) produces two isomeric acyl derivatives, of which only the 3-acyl constitution isomer **90** is shown in the formula Scheme 9. Both isomers can be separated on a preparative scale by means of medium-pressure liquid chromatography (MPLC). Upon reaction with *N*,*N*-dimethylacetamide dimethyl acetal, the hydroxyalkylporphyrin rac-**91** is converted into the chlorin *rac*-**92**. The *Z*-configuration of the exocyclic double bond in the product, which is readily detectable by the intramolecular ^{1}H nuclear Overhauser effect (NOE), provides evidence of the expected stereoselective course of the rearrangement. Catalytic hydrogenation of the exocyclic double bond in *rac*-**92** yields the chlorin *rac*-**93**, with a geminally dialkylated structural part and *trans* arrangement of the alkyl residues. To a large extent, the substitution pattern and the stereochemical arrangement match those of the naturally occurring chlorins. Since methods are available for the synthesis of enantiomerically pure porphyrins[47e,f] with function-

Scheme 9. Partial Synthesis of Chlorins from Hemin (3b) via Claisen Rearrangement[a]



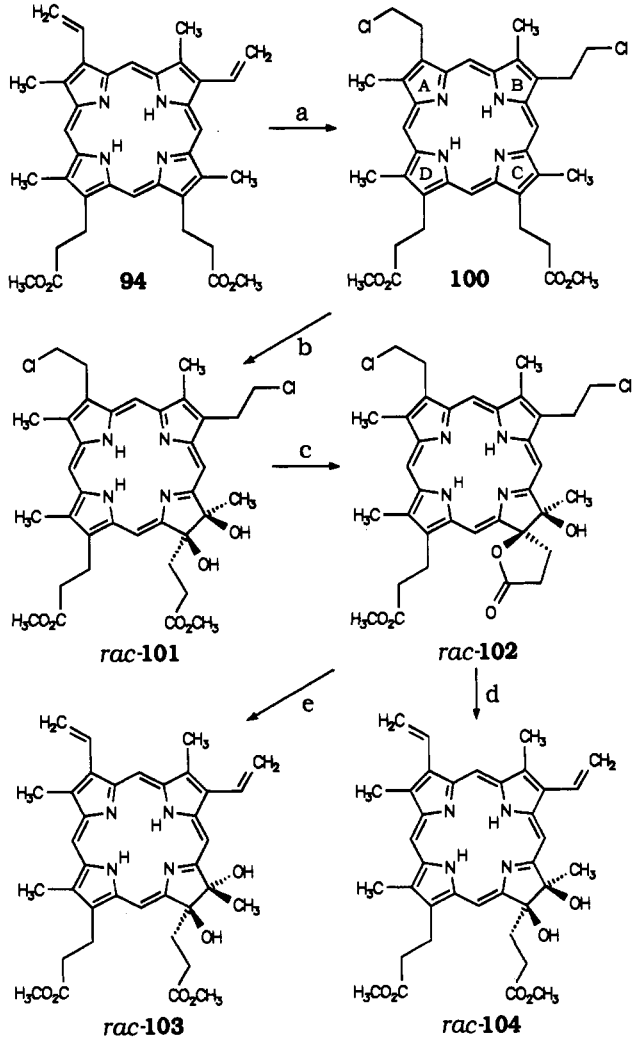
[a] (a) (1) Resorcinol, 160 °C, 1 h; (2) $FeSO_4 \cdot 7H_2O$, HCl/MeOH, py, 4 h; (3) $Cu(OAc)_2 \cdot H_2O$, MeOH, reflux, 1 h. (b) Ac_2O, $SnCl_4$, CH_2Cl_2, −20 °C, 1 h (3- and 8-regioisomers, chromatographic separation, only the 3-isomer is shown). (c) $NaBH_4$, MeOH/CH_2Cl_2, −20 °C, 20 min. (d) *N*,*N*-dimethylacetamide dimethyl acetal, o-xylene, reflux, 1.5 h. (e) $Pd(OAc)_2$, THF/H_2O (4/1), $(EtO)_3SiH$, room temperature, 30 min.

Scheme 10. Partial Synthesis of Chlorins from Protoporphyrin IX Dimethyl Ester (94) via Diels–Alder Reactions or Pinacol Rearrangement[a]



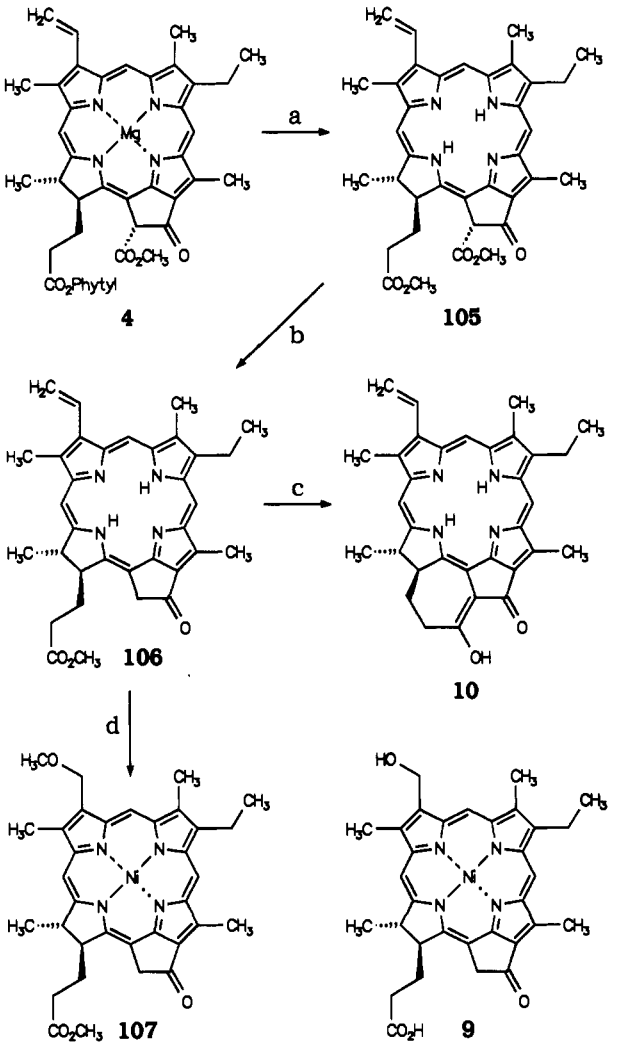
[a] (a) Dimethyl acetylenedicarboxylate, toluene, reflux, 5 days. (b) Tetracyanoethylene, $CHCl_3$, reflux, 30 min. (c) $Tl(NO_3)_3$, MeOH. (d) (1) Jones oxidation; (2) esterification; (3) OsO_4, CH_2Cl_2/py, room temperature, 24 h. (e) $FSO_3H/H_2SO_4/SO_3$.

Scheme 11. Partial Synthesis of Porphyrin *d rac*-103 or *rac*-104 (Heme *d rac*-13)[a]



[a] (a) (1) $Tl(NO_3)_3$, MeOH; (2) $NaBH_4$; (3) PhCOCl, DMF. (b) OsO_4, py, CH_2Cl_2, 25 °C, 26 h, MeOH, H_2S. (c) NaOAc, MeOH, reflux, 30 min. (d) (1) KOH, py, reflux, 6 h; (2) 10% HCl; (3) CH_2N_2, MeOH. (e) (1) epimerization on silica gel; (2) conditions as for d.

Scheme 12. Partial Syntheses of Cyclopheophorbide (10) and Dimethyl Tunichlorin (107) from Chlorophyll *a* (4)[a]



[a] (a) (1) H_2SO_4, MeOH/$CHCl_3$ (1/1), room temperature, 5 min; (2) 3% H_2SO_4, MeOH, 22 °C, 22 h. (b) Collidine, 165 °C, 100 min. (c) (1) $[(Me)_3Si]_2NNa$, benzene, THF, room temperature, 2.5 min; (2) NaH_2PO_4, H_2O, CH_2Cl_2, 0 °C. (d) (1) OsO_4, $NaIO_4$, dioxane/H_2O (1/1), 20 °C, 4 h; (2) $NaBH_4$, MeOH, 20 °C, 1 min; (3) $Ni(OAc)_2$, MeOH, $CHCl_3$, 70 °C, 3 h; (4) TsOH, MeOH, 40 °C, 10 min.

alized hydroxyalkyl substituents, which contain the center of chirality, this concept should open up a route to the enantiomerically pure natural hydroporphyrins.

In numerous synthetic studies[10,48,49,50] chlorins have been obtained from the completely unsaturated porphyrins by reactions that attack the periphery of the porphyrin chromophore. For instance, the geminally dialkylated chlorins *rac*-**95** and *rac*-**97** can be formed by Diels–Alder reactions on protoporphyrin IX dimethyl ester (**94**, Scheme 10). However, the substitution patterns of the products obtained bear little resemblance to the arrangement of residues which was found in naturally occurring chlorins. Geminally dialkylated structural elements that consist of a methyl group and an acetic acid side chain and that correspond to the natural arrangement have been introduced into the porphyrin **96**. The bishydroxylation of a peripheral double bond of **96** yields the diol *rac*-**98**, which on pinacol rearrangement is transformed into the geminally dialkylated chlorin *rac*-**99**. A major disadvantage of this procedure is the lack of regioselectivity during bishydroxylation, which can take place on each of the four pyrrole rings of the macrotetracycle. The subsequent pinacol rearrangement can also occur in two directions, leading to additional constitutional isomers. Appropriate partially synthetic approaches exist for preparing naturally occurring heme *d* (**13**) (Scheme 11) from protoporphyrin IX dimethyl ester (**94**), and for cyclopheophorbide (**10**) and tunichlorin (**9**) from chlorophyll *a* (**4**, Scheme 12). Porphyrin *d*, the metal-free ligand system of heme *d*, was synthesized from **94** by Chang et al.[51]

Before bishydroxylation of ring C of **94** is carried out, the vinyl groups have to be protected. This is achieved by converting them into chloroethyl residues. Subsequent bishydroxylation yields the four possible constitutional isomers as expected. The desired isomer *rac*-**101** is present in the mixture in 22% yield along with 26% ring D isomer, 6.8% ring A isomer and 6.8% ring B isomer. In the presence of sodium acetate the dihydroxyporphyrin *rac*-**101** forms the spirolactone structure *rac*-**102**, which can be transformed into either of the stereoisomeric porphyrins *rac*-**103** or *rac*-**104** depending on the reaction conditions chosen. Section II.A made reference to the difficulty in determining

the stereochemistry of natural heme *d*, so that both stereoisomers formed may be of interest.

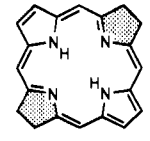
A common intermediate in the partial synthesis of cyclopheophorbide (**10**)[19] and dimethyltunichlorin (**107**)[17] is methylpheophorbide (**106**), which can be obtained from chlorophyll *a* (**4**) by removal of the central magnesium ion, transesterification and decarbomethoxylation (Scheme 12). Dieckmann condensation converts the intermediate **106** into the cyclopheophorbide **10**. Cyclopheophorbide **10** is completely enolized in solution and in the crystalline state. It is also worth noting that **10** exhibits no fluorescence, in contrast to other chlorophyll derivatives. To produce dimethyltunichlorin (**107**), the vinyl group of **106** is cleaved to yield the hydroxymethyl residue. This is followed by complexation with nickel(II) and methylation. Conversely, naturally occurring tunichlorin (**9**) can be converted into dimethyltunichlorin (**107**).

III. Bacteriochlorins

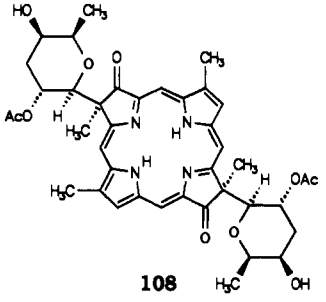
The bacteriochlorin structural type **5** is formally derived from the porphyrin by saturation of two peripheral double bonds in opposite pyrrole rings. The term bacteriochlorin originates from the bacteriochlorophylls, which are widespread as pigments in bacterial photosynthesis[8-10] (Chart 4). The only representative of this class of compounds that is not involved in bacterial photosynthesis, is the recently discovered tolyporphin (**108**).[52] The unusual tolyporphin was isolated from the Pacific cyanophyte *Tolypothrix nodosa* by Moore et al.[52] The substitution pattern, especially the tetrahydrofuran residues of the bacteriochlorin, is unique among the naturally occurring porphinoids. The constitutional and relative configuration of **108** were elucidated by classical spectroscopic methods, with ^{1}H NMR spectroscopy naturally playing the most important part. It was shown that tolyporphin (**108**) eliminates the multidrug resistance (MDR) in a vinblastin-resistant subline of the human ovarian adenocarcinoma line. Tolyporphin potentiates the cytotoxicity of adriamycin and vinblastin in these cell lines at doses as low as 1 μg/mL.

Methods for the total synthesis have yet to be developed for bacteriochlorins. The only method for obtaining mixtures of constitutionally isomeric bacteriochlorins along with other hydroporphyrins has been bishydroxylation of highly symmetric porphyrins, followed by pinacol rearrangement (see Scheme 10).[50e,50g,53] The structure of one of these geminally dialkylated bacteriochlorins derived by partial synthesis was investigated in detail by means of single X-ray diffraction, in order to provide a simple model for the naturally occurring bacteriochlorins of the bacterial photosynthetic membrane.[53e]

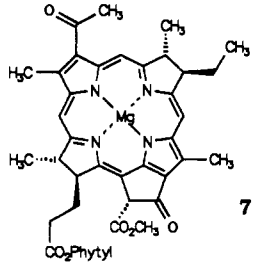
Chart 4. Naturally Occurring Bacteriochlorins



5
Bacteriochlorin



108
Tolyporphin



7 Bacteriochlorophyll a

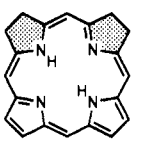
IV. Isobacteriochlorins

A. Discovery of New Naturally Occurring Isobacteriochlorins

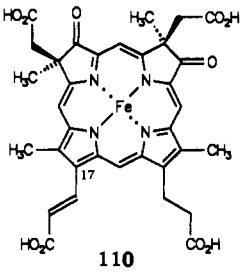
Isobacteriochlorins (**109**, Chart 5) with two adjacent saturated pyrrole rings are the constitutional isomers of bacteriochlorins, in which two opposite rings are partially reduced. In 1973 the first naturally occurring isobacteriochlorin, iron-containing siroheme (**111**), was isolated by Siegel et al.[54] from a sulfite reductase of *Escherichia coli*. Later it was also discovered in sulfite and nitrite reductases of numerous bacteria and plants.[55]

The complete structural elucidation of **111** by means of spectroscopic methods and biogenetic considerations was not accomplished until Battersby et al.[56] and Byhkovsky et al.[57] were able to isolate factor II (sirohydrochlorin) (**112**) from bacteria producing vitamin B_{12}. Factor II (**112**) is the metal-free isobacteriochlorin chromophore of siroheme. The reduced forms of factor II (**112**) and of the subsequently discovered factor III (**113**) were identified, together with factor I (**14**), as the first links in the biosynthetic chain from uroporphyrinogen III (**153**) to vitamin B_{12} (**8**) (see Scheme 22).[58,11-13] The vitamin B_{12} biosynthesis will be dealt with in more detail in a latter section. Factor III (**113**) differs from factor II (**112**) by virtue of an additional methyl group in the methine position 20.

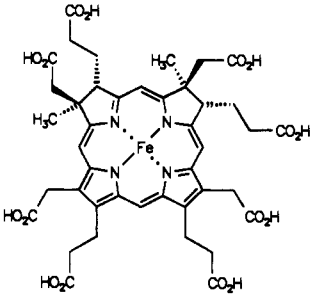
Chart 5. Naturally Occurring Isobacteriochlorins



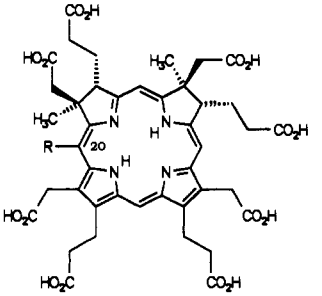
109
Isobacteriochlorin



110
Heme d_1

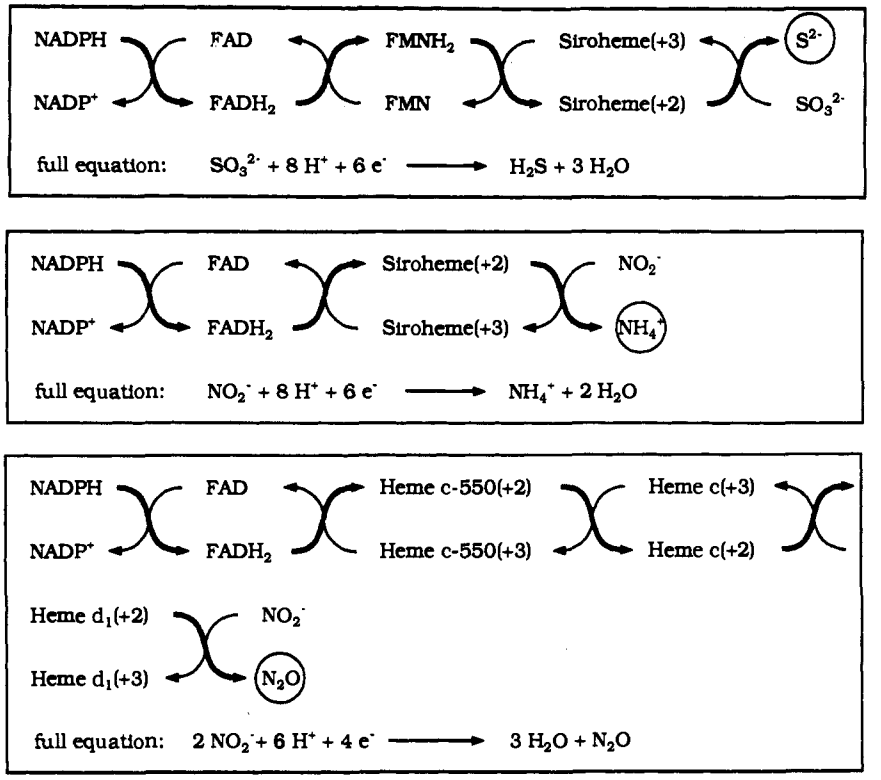


111
Siroheme



112 : R = H Factor II
113 : R = CH_3 Factor III

Scheme 13. The Biological Functions of Heme d_1 (110) and Siroheme (111)



Heme d_1 (**110** or *ent*-**110**), which was isolated by Timkovich et al.[59] and Chang et al.,[60] occurs as one of two cofactors in the reductase cytochrome cd_1.[61]

Cytochrome cd_1 participates in the reduction of nitrite to nitrous oxide (N_2O) in chemoautotrophic bacteria, such as *Pseudomonas aeruginosa*, *Paracoccus denitrificans*, and *Thiobacillus denitrificans*.[62] From recent investigations it seems very likely that cytochrome cd_1 mediates the nitrite reduction to nitric oxide (NO) and that a second enzyme produces N_2O from NO.[62h-j] A structure was originally proposed for heme d_1 on the basis of UV/vis, MS, IR, and NMR spectroscopic data on the metal-free, esterified macrocyclic framework.[59] The original structural formula was revised on the basis of synthetic studies[60] and a new interpretation of spectroscopic data,[63] leading to a dioxoisobacteriochlorin structural formula with unknown configuration and rather uncertain position of the acrylic acid double bond. In a partial synthesis[64] (see Scheme 19) the dioxoisobacteriochlorin chromophore of heme d_1 was obtained from protoporphyrin IX. The configurations of stereoisomeric intermediates in the synthesis were tentatively assigned on the basis of their different chromatographic behavior. The proposed *cis* intermediate then leads to heme d_1 with *cis* configuration. In another partial synthesis[65] (see Scheme 20) the constitution and the relative configuration of the final porphyrin d_1 was established by a crystal structure analysis.[65,66] The synthetic porphyrin d_1 with *cis* configuration and 17-acrylic acid side chain corresponds to heme d_1. This finding has unambiguously confirmed the constitution and relative configuration of heme d_1 (**110**). Both cofactors, siroheme (**111**)[55] and heme d_1 (**110**),[62] play an important role in the sulfur and nitrogen metabolisms of numerous organisms (Scheme 13). It can be assumed that the global cycles of nitrogen and sulfur are decisively influenced by these organisms.

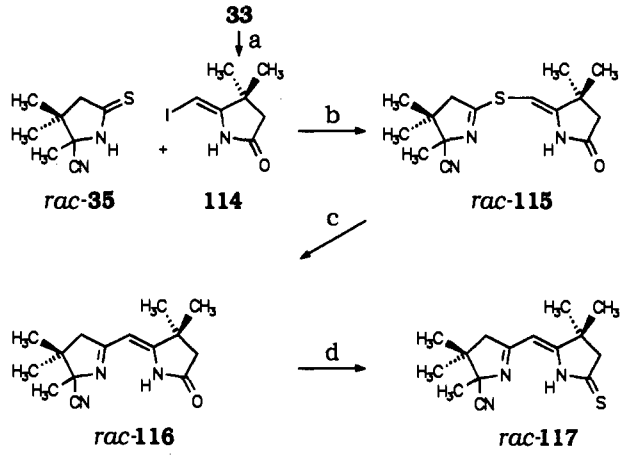
B. Synthesis of Isobacteriochlorins

1. Total Synthesis of Model Compounds

All of the naturally occurring isobacteriochlorins contain the geminally dialkylated structural parts in the saturated pyrrole rings, which require special approaches for their synthesis. Until the discovery of siroheme (**111**) and sirohydrochlorin (**112**), this structural element was only known from the vitamin B_{12} structure (**8**). Using the synthetic potential, which was invented during numerous syntheses of model corrins[7,38,67] and of vitamin B_{12},[7,45] Eschenmoser et al.[40,68] developed the first total syntheses of model isobacteriochlorins (Schemes 14–16). The thiolactam *rac*-**35** and the iodo enamide **114** (see Scheme 2), which is formed on iodination of the enamide **33**, were linked with each other by the sulfide contraction procedure to yield the bicycle *rac*-**116**.[38,67i] As mentioned above, the sulfide contraction was developed especially for the coupling of saturated five-membered geminally dialkylated lactams during the course of corrin syntheses. *rac*-**116** possesses the geminally dialkylated structures in adjacent pyrrole rings characteristic of isobacteriochlorins.

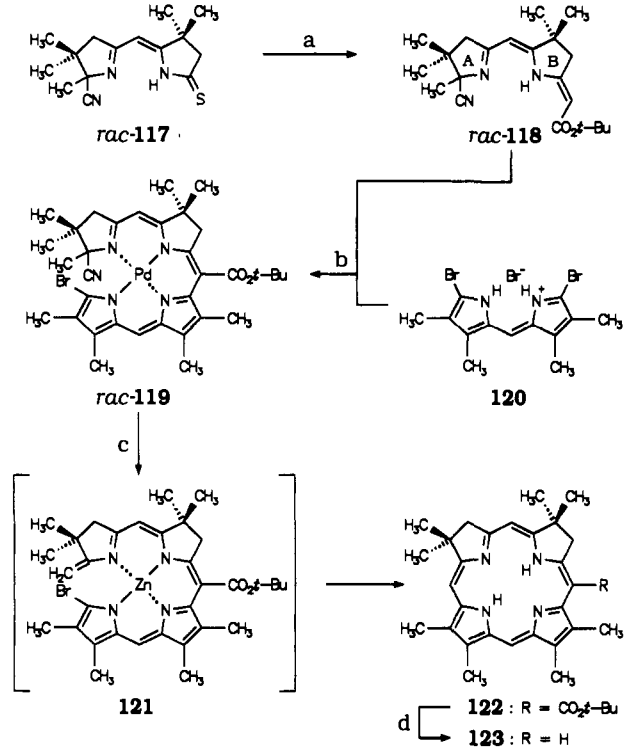
After formation of the thiolactam *rac*-**117** the thiolactam function enables the carbon atom to be introduced by an ester condensation, which later on will form the "eastern" methine bridge of the isobacteriochlorin. The AB-component *rac*-**118** is condensed with the dibromopyrromethene **120**[69] in the presence of a base and palladium(II), which exerts a decisive template effect during the formation of the seco-complex *rac*-**119** (Scheme 15). The palladium is easily removed from the linear tetracycle *rac*-**119** with potassium cyanide. Removal of the palladium from the macrocyclic isobacteriochlorin is no longer possible. In the next step, the seco compound is cyclized via the intermediate **121**

Scheme 14. Geminally Dimethylated Dimeric Building Blocks for Syntheses of Different Hydroporphyrins (See Also Scheme 2)[a]



[a] (a) I_2, K_2CO_3, Et_2O, room temperature (for **33** and *rac*-**35** see Scheme 2). (b) KO*t*-Bu, HO*t*-Bu, benzene, 20 °C, 3 h. (c) $(EtO)_3P$, xylene, 130 °C, 20 h. (d) P_2S_5, toluene/4-Me-py (20/1), 130 °C, 4 h.

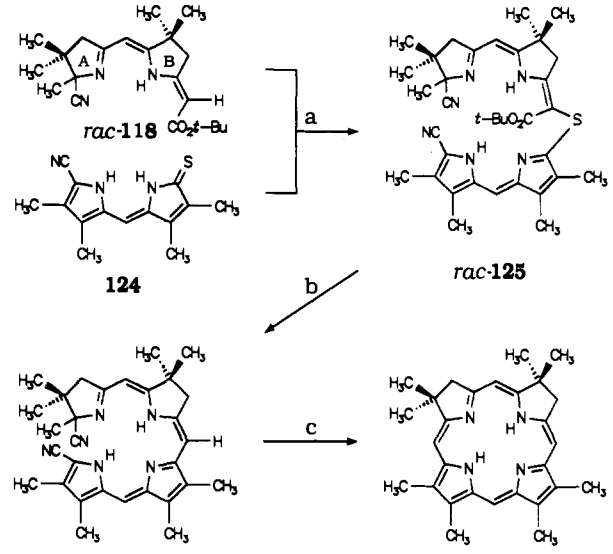
Scheme 15. Total Synthesis of a Model Isobacteriochlorin by the Palladium Template Approach[a]



[a] (a) (1) $(Me)_3O^+BF_4^-$, DBU, CH_2Cl_2, room temperature; (2) $H_2C{=}C(OLi)Ot$-Bu, THF, −78 °C to room temperature. (b) $Pd(OAc)_2{\cdot}(DBU)_2$, MeCN, 80 °C. (c) (1) KCN, MeOH, room temperature; (2) $Zn(ClO_4)_2{\cdot}(MeCN)_x$; (3) KO*t*-Bu, HO*t*-Bu, 80 °C; (4) 10% HCl/H_2O. (d) (1) CF_3CO_2H, room temperature; (2) glutaric acid, 105 °C.

to the isobacteriochlorin **122**, with zinc(II) in the presence of base now providing the template effect. The zinc(II) is lost during the acidic treatment that follows. Acidic cleavage of the *tert*-butoxycarbonyl group, which has served to keep the enamine double bond of *rac*-**118** in the exocyclic position, completes the isobacteriochlorin synthesis. A similar concept has made it possible to synthesize a symmetric, geminally dimethylated isobacteriochlorin.[70]

Scheme 16. Total Synthesis of a Model Isobacteriochlorin by the Sulfide Contraction Approach[a]



[a] (a) $(PhCOO)_2$, $CHCl_3$, room temperature. (b) CF_3CO_2H, $(NCCH_2CH_2)_3P$, sulfolane, 110 °C, 30 min. (c) (1) $Zn(OAc)_2$, DBU, sulfolane, 140 °C (no O_2); (2) CF_3CO_2H.

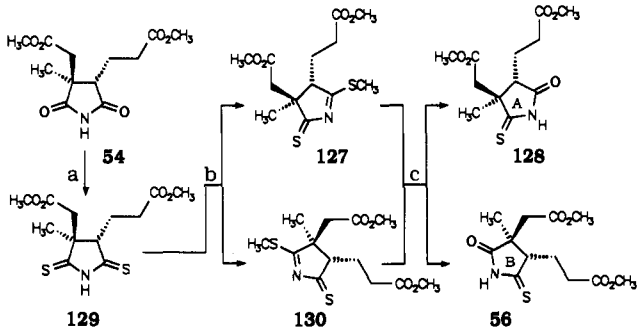
In a modified synthetic approach[40] the isobacteriochlorin **123** was obtained from the "corrinoid" AB-bicycle *rac*-**118** and the thiolactam (**124**, Scheme 16). The key step in this synthesis is the linking of the two molecular parts according to the sulfide contraction procedure. The sulfur-bridged tetracycle *rac*-**125**, which is formed in the first reaction step, can be transformed into the C–C-connected tetracycle *rac*-**126** under acidic conditions. The advantage of this procedure is that the *tert*-butoxycarbonyl group is removed during the course of the sulfide contraction. As shown in the preceding synthesis, *rac*-**126** is cyclized under the template influence of zinc(II) to yield the isobacteriochlorin **123**. The synthetic concepts developed for the model should be transferable to the synthesis of natural sirohydrochlorin, if the corresponding "corrinoid" building blocks from vitamin B_{12} synthesis are used. Total and partial syntheses of model isobacteriochlorins have also been developed in other laboratories and many of the synthesized products contain geminally dialkylated structural parts.[35b,35g,71] One of these concepts has been successfully applied to the synthesis of sirohydrochlorin[71h,j] (see section IV.B.2).

2. Synthesis of Naturally Occurring Isobacteriochlorins

In the light of investigations into the biosynthesis of vitamin B_{12} (**8**), Battersby et al.[72] have performed a total synthesis of factor II (sirohydrochlorin, **112**).

The geminally dialkylated building blocks[72b,c] for rings A and B of sirohydrochlorin are obtained as in the factor I synthesis (see Scheme 5) from cobyrinic acid heptamethyl ester by ozonolytic degradation. The succinimide **54** formed is treated with Lawesson's reagent to yield the dithiosuccinimide **129**. Methylation of **129** leads to a mixture of the constitutionally isomeric thioimino esters **127** and **130**, which can be hydrolyzed to yield the corresponding monothiosuccinimide con-

Scheme 17. Geminally Dialkylated Building Blocks for Syntheses of Factor I (14) and Sirohydrochlorin (Factor II, 112) (See Also Schemes 4–6)[a]



[a] (a) Lawesson's reagent (see also a of Scheme 5). (b) $HC(OMe)_3$, TFA. (c) Aqueous acid, separation of regioisomers.

stitutional isomers, **128** and **56** (Scheme 17). After chromatographic separation, the constitution isomer **128** is used as a building block for ring A of sirohydrochlorin whereas the other isomer **56** is useful as a ring B building block.

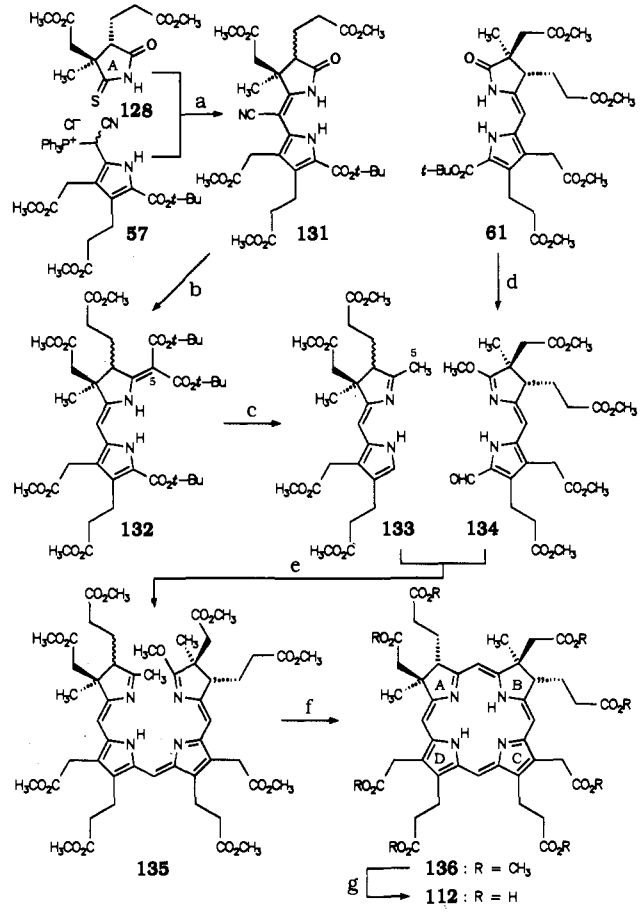
The synthetic concept to construct the macrotetracycle **112** from two molecular components in "north–south direction" has the advantage that one and the same pyrrole building block **57** can be used to form rings C and D of **112** (Scheme 18). Furthermore, the "eastern" BC half **61** for factor II (**112**) is identical to the previously used "northern" AB part of factor I (**14**, see Scheme 5). Formylation and formation of an imino ester function prepares the BC component **61** for the condensation steps with the AD dimer. Thio-Wittig reaction of the pyrrole **57** and the A-monothiosuccinimide **128** yield the bicyclic AD-lactam **131**. Removal of the cyano group, introduction of the carbon atom 5 by sulfide contraction, and subsequent cleavage of the *tert*-butoxycarbonyl residues lead to the complete "western" AD component **133**. Both parts of the molecule, **133** and **134**, undergo acid-catalyzed condensation to yield the *seco*-isobacteriochlorin **135**. Photochemical cyclization, as in the synthesis of factor I, and hydrolysis of the ester groups complete the total synthesis of factor II (sirohydrochlorin, **112**).

Partially synthetic routes to the other naturally occurring isobacteriochlorin, heme d_1 (**110**), were developed by Chang et al.[64] and Montforts et al.[65] The syntheses begin with protoporphyrin or hematoporphyrin, both derivatives of the readily available red blood pigment heme **3b**. As mentioned in section IV.A, both synthetic pathways also served to elucidate the structural formula of heme d_1 (**110**). In the synthesis of Chang et al.[63] the vinyl residues of protoporphyrin IX dimethyl ester (**94**) were transformed into acetic acid side chains (Scheme 19).

Osmium tetroxide bishydroxylates the porphyrin **137** to give the four possible diol constitutional isomers. The ring C,D diols, which were formed in a total yield of 35% can be converted back into the educt **137**. The constitutional isomer *rac*-**138** has no preparative use, since the second bishydroxylation, which is required for the product of the pinacol rearrangement of *rac*-**138**, tends to occur at ring D and not at the ring B position, as desired.

The dihydroxychlorin *rac*-**139** undergoes pinacol rearrangement to yield the geminally dialkylated chlorin

Scheme 18. Total Synthesis of Sirohydrochlorin (Factor II, 112) (See Also Schemes 4–6)[a]

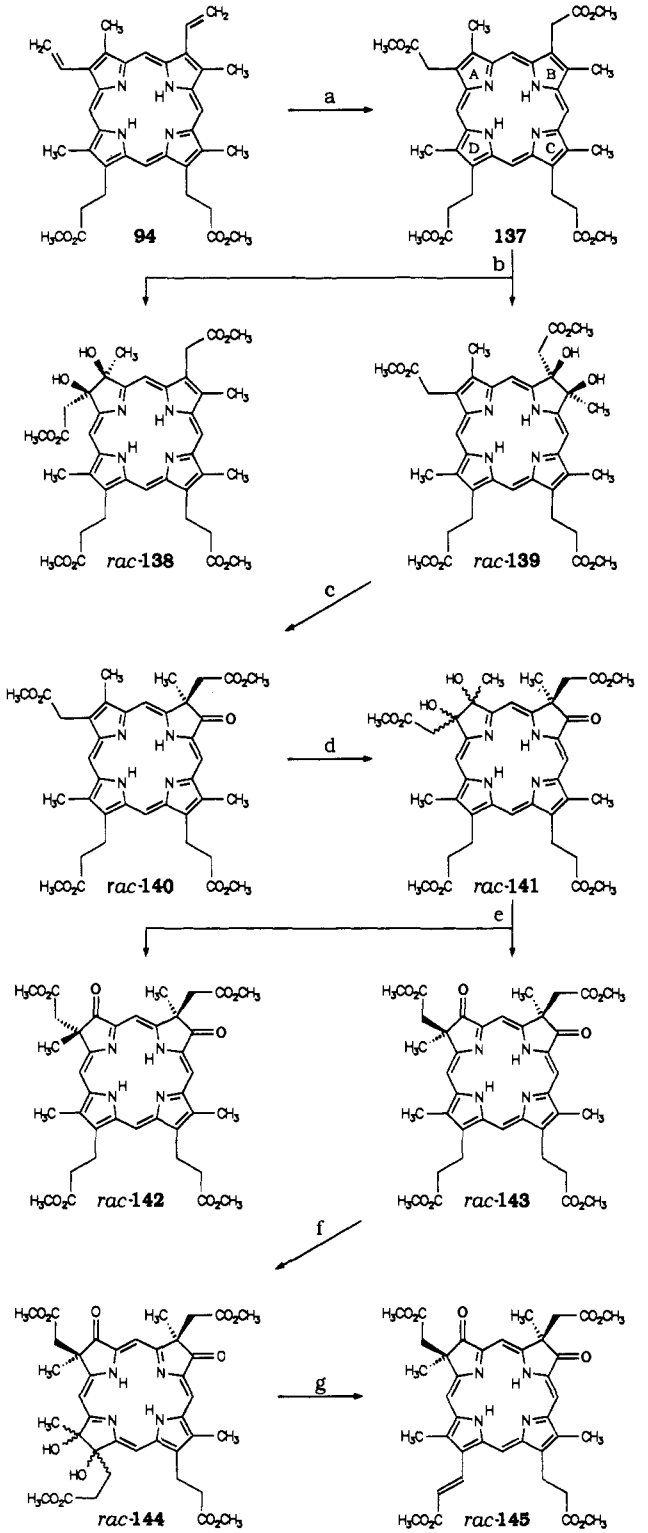


[a] (a) KO*t*-Bu, toluene, reflux. (b) (1) H_2, Raney-Ni, MeOH, H_2O, MsOH; (2) MsCl, DMAP; (3) Δ, 1,2-bis(ethylamino)ethane, anisole; (4) Lawesson's reagent; (5) $BrCH(CO_2t\text{-}Bu)_2$, DBU; (6) PPh_3, DBU, toluene, reflux. (c) TFA, labile **133** was condensed immediately with **134**. (d) (1) TFA, $HC(OMe)_3$; (2) $(Me)_3O^+BF_4^-$, *i*-Pr_2NEt. (2) $(Me)_3O^+BF_4^-$, *i*-Pr_2NEt. (e) TFA/MeOH (2/3). (f) *hν* (vis), TFA, *i*-Pr_2NEt, THF, MeOH, 3–4 days. (g) Hydrolysis.

rac-**140**. Repetition of the bishydroxylation gives the isobacteriochlorin *rac*-**141** in 18% yield, together with the unwanted ring C and ring D constitutional isomers in 27% yield. Pinacol rearrangement of *rac*-**141** leads to a diastereomeric mixture of the *syn*- and *anti*-dioxoisobacteriochlorins (*rac*-**142** and *rac*-**143**, respectively). In this case, the partial synthesis of porphyrin d_1 (*rac*-**145**) is completed by selective hydroxylation of ring D and subsequent removal of water to produce the acrylic acid side chain at position 17.

The synthesis performed by Montforts et al.[65] also leads to porphyrin d_1 (*rac*-**145**), the metal free ligand of heme d_1, (Scheme 20). The key step in this synthesis is a stereoselective 2-fold amide acetal Claisen rearrangement of the diastereomerically pure hematoporphyrin dimethyl ester (*rac*-**146**). This provides a simple method of stereoselectively generating the characteristic geminally dialkylated structure with a *syn* configuration. Claisen rearrangement of the diastereomeric hematoporphyrin yields the *anti*-isobacteriochlorin. The hydrolysis of the amide groups and cleavage of the newly formed exocyclic double bonds can be achieved very easily with the more stable zinc complex of *rac*-**147**, if both reactions are coupled with each other. Iodolactonization accompanied by hydrolysis of the amide groups and substitution of the iodine yields the

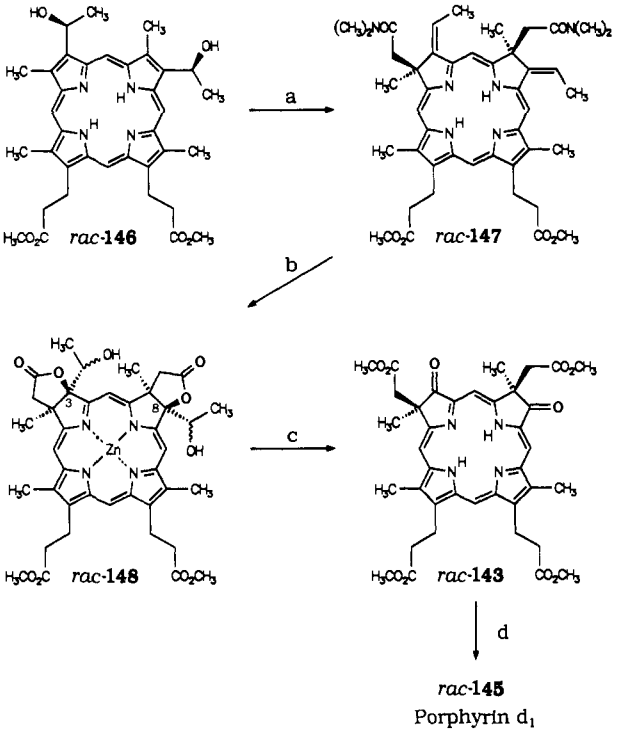
Scheme 19. Partial Synthesis of Porphyrin d_1 (*rac*-145) (Heme d_1 *rac*-110): Pinacol Rearrangement Approach[a]



[a] (a) (1) $Tl(NO_3)_3$, MeOH; (2) Jones oxidation, esterification. (b) (1) OsO_4, py, CH_2Cl_2, 25 °C, 24 h, quenched by H_2S (formation of four regioisomeric diols, ring C, D diols can be transformed back into **137** by HI, H_3PO_2, HOAc). (c) FSO_3H/H_2SO_4/fuming H_2SO_4 (10/10/1). (d) (1) $Zn(OAc)_2$, $CHCl_3$/MeOH; (2) OsO_4, py, CH_2Cl_2, H_2S; (3) HCl/H_2O. (e) H_2SO_4 (pinacol rearrangement). (f) OsO_4, py, CH_2Cl_2, H_2S. (g) (1) HCl/H_2O, reflux, 5 min; (2) H_2SO_4, MeOH, reflux, 5 min; 25 °C, 12 h.

nonisolated hydroxylactone *rac*-148. A retroaldol-type fragmentation of the 3 and 8 residues also occurs when the lactone *rac*-148 is hydrolyzed. Spontaneous oxidation, followed by removal of metal and reesterification yield the crystalline dioxoisobacteriochlorin *rac*-143. The synthesis of the metal-free chromophore porphyrin d_1 (*rac*-145) of heme d_1 (110) is completed by the regioselective introduction of a double bond into the 17 propionic acid residue according to Chang's procedure[64b,73] (see Scheme 19). The assignment of the constitution and relative configuration is based on two crystal structure analyses of *rac*-145[65] and of the nickel complex of *rac*-143.[66]

Scheme 20. Partial Synthesis of Porphyrin d_1 (*rac*-145) (Heme d_1 *rac*-110): Claisen Rearrangement Approach[a]



[a] (a) *N,N*-Dimethylacetamide dimethyl acetal, *o*-xylene, reflux, 2.5 h [separation of *rac*-146 from a mixture of hematoporphyrin-IX dimethyl ester diastereomers by HPLC: μ-Bondapak C-18, MeOH/aq $Bu_4N^+H_2PO_4$ [2.5 mM] (8/2) pH 2 (see: Cadby, P. A.; Dimitriadis, E.; Grant, H. G.; Ward, D.; Forbes, J. J. *J. Chromatogr.* **1982**, *231*, 273)]. (b) (1) Zn(II) acetyl acetonate, $CHCl_3$, reflux, 3.5 h; (2) I_2, THF/H_2O (1/1), 25 °C, 5 h; (3) $Na_2S_2O_3$, H_2O. (c) (1) KOH, H_2O, MeOH, 65 °C, 22 h; (2) aqueous acid pH 1–2, 65 °C, 30 min; (3) CH_2N_2, Et_2O, MeOH, room temperature, 2 h. (d) (1) OsO_4, py, CH_2Cl_2, 25 °C, 72 h, quenched by H_2S; (2) HCl/H_2O, dioxane, 70 °C, 7 min; (3) H_2SO_4, MeOH, 65 °C, 5 min; 25 °C, 18 h.

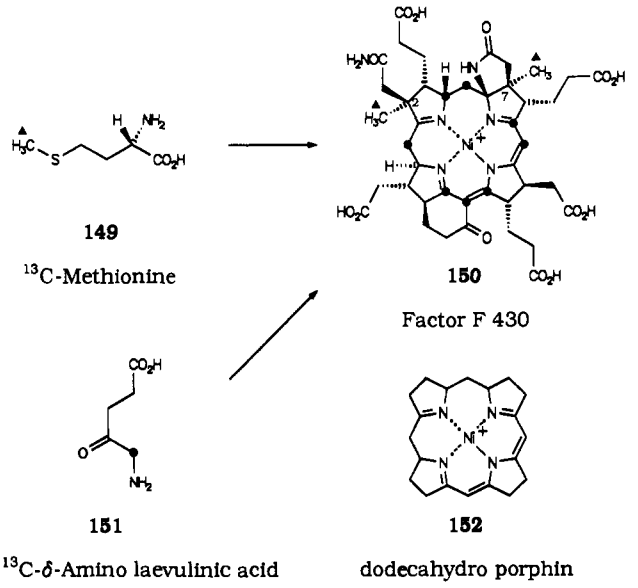
V. Other Highly Saturated Hydroporphinoid Structures

A. Discovery of New Naturally Occurring Hydroporphinoid Structures

As mentioned in the introduction, the investigation of the biosynthesis of vitamin B_{12}[11-13] has brought several new hydroporphinoid structures to light and stimulated the synthesis of these structural types. The discovery,[74] structural elucidation,[75] chemistry,[7,76] and biology[77] of factor F 430 (150) in the laboratories of Wolfe, Thauer, Eschenmoser, Pfaltz, and Jaun has been an important source of additional impetus for the study of the chemistry of highly reduced porphyrins.

The nickel-containing factor F 430 (150) provides an example of nature exploiting the reactivity of organo-

Scheme 21. Structure and Structure Elucidation of the Naturally Occurring Dodecahydroporphyrin Factor F 430 (150)



149 ^{13}C-Methionine

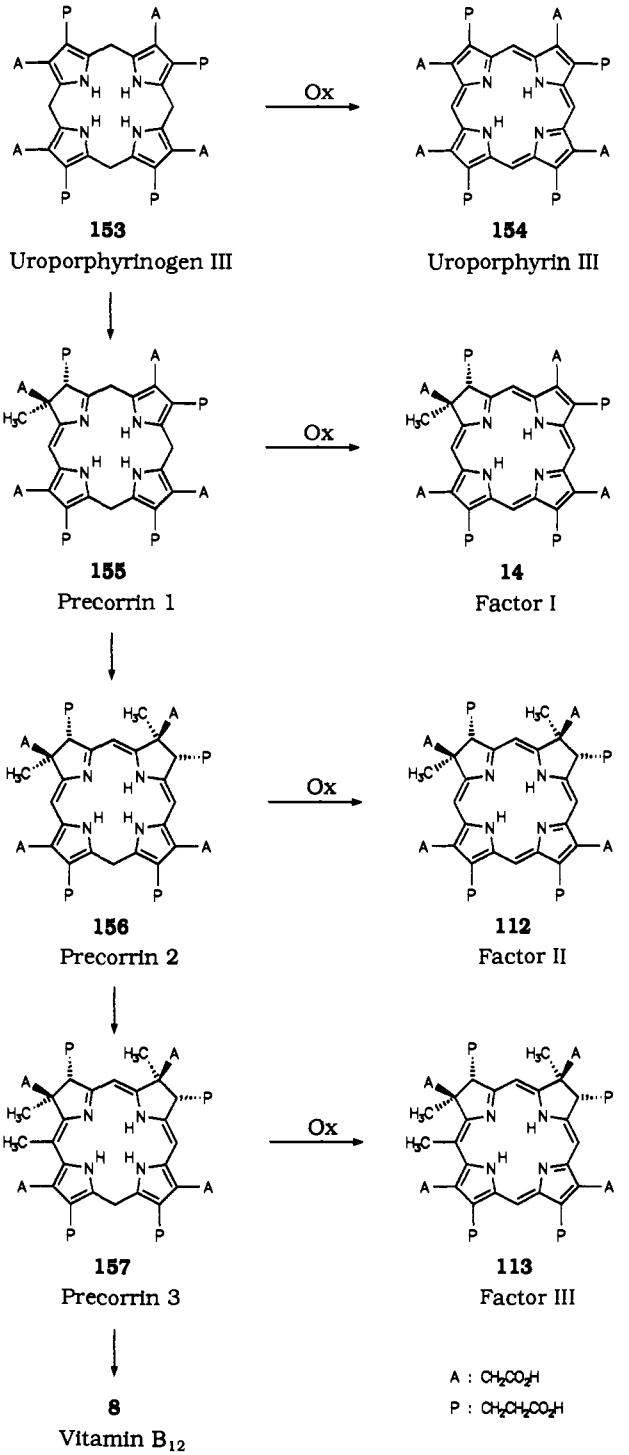
150 Factor F 430

151 ^{13}C-δ-Amino laevulinic acid

152 dodecahydro porphin

metallic compounds, as is the case with vitamin B_{12}. Factor F 430 plays a key role as a cofactor for the coenzyme M reductase of primitive methanogenic bacteria in the formation of methane from 2-(methylthio)ethanesulfonate.[78] The structural elucidation of factor F 430 (**150**) is based on a combination of classical spectroscopic methods, biosynthetic studies with ^{13}C-labeled biosynthetic precursors,[75a] and chemical degradation.[75b] From the biosynthetic investigations it should be emphasized that the peripheral methyl groups in positions 2 and 7 stem from ^{13}C-methionine (**149**), and that δ-aminolevulinic acid (**151**), which is ^{13}C-labeled in position 5, produces an isotope pattern typical for all porphyrins that have been biosynthetically derived from uroporphyrinogen III (**153**) (see Scheme 21). The isotopic distribution can be readily identified by ^{13}C NMR spectroscopy. Detailed investigations into the precise function of factor F 430 are currently in progress. Previous investigations indicate that the conformationally flexible dodecahydroporphyrin ligand of factor F 430 influences the redox properties and reactivity of the central nickel atom depending on the conformation of the ligand.[7,8,75e] Factors I–III (**14**, **112**, and **113**) have been isolated from bacteria producing vitamin B_{12}. Their reduced forms, the precorrins 1–3 (**155**–**157**), have been identified as actual intermediates in the biosynthesis of vitamin B_{12}[11–13,79] (Scheme 22). All the precorrins are produced from uroporphyrinogen III (**153**) by consecutive methylation steps with *S*-adenosyl methionine. The oxidation level of uroporphyrinogen III (**153**), which is a hexahydroporphyrin, is retained in the different precorrins. Factors I–III (**14**, **122**, and **113**) are stable oxidation products of the precorrins and are formed during the isolation process. The biosynthetic pathway leading from the precorrins 1–3 (**155**–**157**) to vitamin B_{12} (**8**) contains more precorrins, which have all so far been identified as representatives of the "true" corrin type with the characteristic direct link between rings A and D in the chromophore. For this reason the structures will not be presented here.

Scheme 22. Hydroporphinoid Intermediates in the Biosynthesis of Vitamin B_{12} (8)

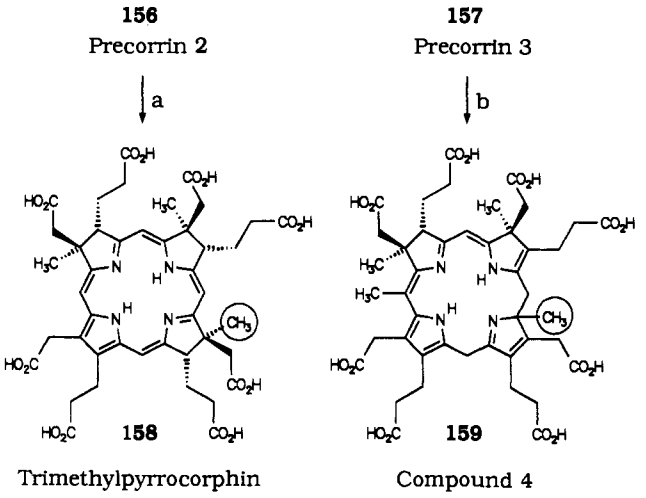


B. Synthesis of Model Compounds

Two issues have strongly influenced the synthesis of highly saturated hydroporphinoid structures. The first is concerned with the problem of how nature produces the corrin chromophore of vitamin B_{12} from precorrin 3 (**157**) by methylation and ring contraction.[7,11–13]

This not only raises the question as to how vitamin B_{12} is formed biosynthetically or biomimetically, but also that of whether the corrin structure and its corresponding hydroporphinoid precursors could possibly have a prebiotic origin.[17,67d] Various hydroporphinoid structures have been synthesized in an attempt to provide the answers. Extensive investigations into

Scheme 23. Enzymatically Formed Type III Hexahydroxyporphinoid Structures[a]

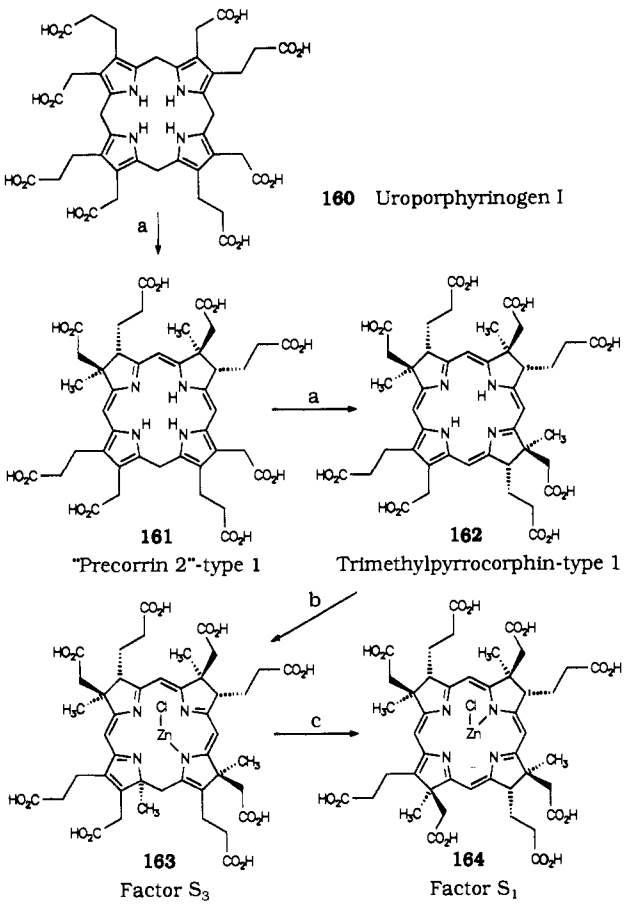


[a] (a) Uroporphyrinogen III methylase (M-1), *S*-adenosyl methionine (SAM). (b) Methyltransferase (cbiF), SAM.

this topic have been described in detail by Eschenmoser.[7] Treatment here will therefore be restricted to the description of a few important synthetic studies. The synthetic investigations are closely related to the second issue, namely how to determine the structure and function of factor F 430 (**150**). For this purpose, numerous nickel-containing hydroporphinoid compounds were prepared[7] and analyzed by X-ray diffraction in terms of their structure–function relationships. In the search for highly methylated hydroporphinoid intermediates that follow on from precorrin 3 (**157**) it has only been possible to isolate and identify corrinoid strucutres as precursors for vitamin B_{12}.[11-13,79,89] However, Scott et al.[13,80] were able to identify, clone, and overexpress methylation enzymes by using molecular biological methods. This provides the enzymes from various bacteria that produce siroheme (**111**) and vitamin B_{12} (**8**) in sufficient amounts for further methylation experiments. The experiments show that the enzymes are not very specific and accept substrates other than those of the biosynthetic chain. This opens up the possibility of using methylation enzymes for the synthesis of methylated hydroporphyrins.

The uroporphyrinogen III methylase (M1) from *Escherichia coli*, which was overexpressed and therefore available in sufficient amounts, methylates uroporphyrinogen III (**153**) in the presence of *S*-adenosyl methionine (SAM) on the biosynthetic pathway to siroheme (**111**). On prolonged incubation trimethylpyrrocorphine (**158**) is formed by overmethylation.[13,81] The product of the methylation does not act as an intermediate in the biosynthesis of vitamin B_{12}. The so-called compound 4 (**159**, Scheme 23) is also an overmethylated product of precorrin 3 **157**, which is formed with an overexpressed methyltransferase (cbi F) from *Salmonella typhimurum*.[82] Compound 4 (**159**) is closely related to factor S_3 (**163**)[83] (see Scheme 24). Although uroporphyrinogen I (**160**), a constitutional isomer of uroporphyrinogen III (**153**), plays no direct role in porphyrin biosynthesis, this unnatural substrate is methylated in the presence of SAM by the methyl transferases of some bacteria. A constitutional type I precorrin 2 (**161**) is obtained by methylation of uroporphyrinogen I (**160**) with the methylase M1 or *S*-adenosyl

Scheme 24. Enzymatically Formed Type I Hexahydroxyporphinoid Structures[a]

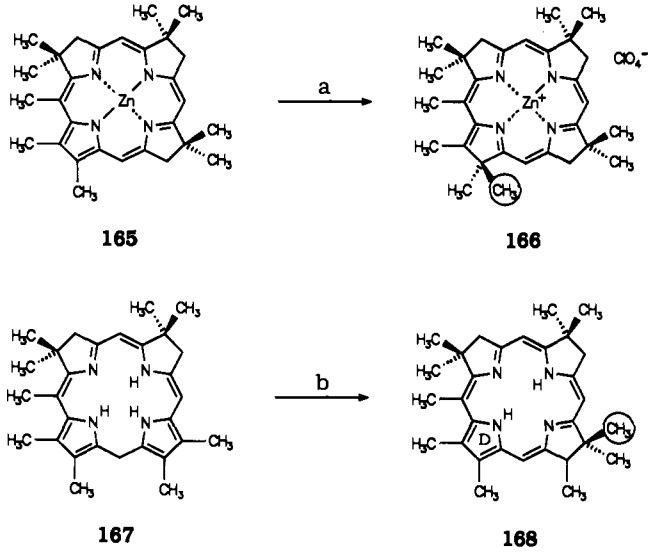


[a] (a) M-1, SAM or *S*-adenosyl methionine uroporphyrinogen III methyltransferase (SUMT), SAM. (b) cbiF, SAM. (c) [1,5] sigmatropic methyl shift.

methionine uroporphyrinogen III methyl transferase (SUMT) from *Propionibacterium shermanii* and overexpressed in *Paracoccus denitrificans* (Scheme 24).[13,82] The methyltransferase M1 is able to methylate the unnatural precorrin **161** once more to give the trimethylpyrrocorphin-type I (**162**). Previously the zinc-containing factors S_3 (**163**) and S_1 (**164**)[83] were isolated from *Propionibacterium shermanii*. Metal-free factor S_3 is also obtained by methylation of the trimethylpyrrocorphin-type I (**162**) with the methyltransferase (cbi F) from *Salmonella typhimorum*. [1,5]sigmatrophic rearrangement of the 16 methyl group to position 17 converts factor S_3 (**163**) into factor S_1 (**164**) with its so-called corphin chromophore.

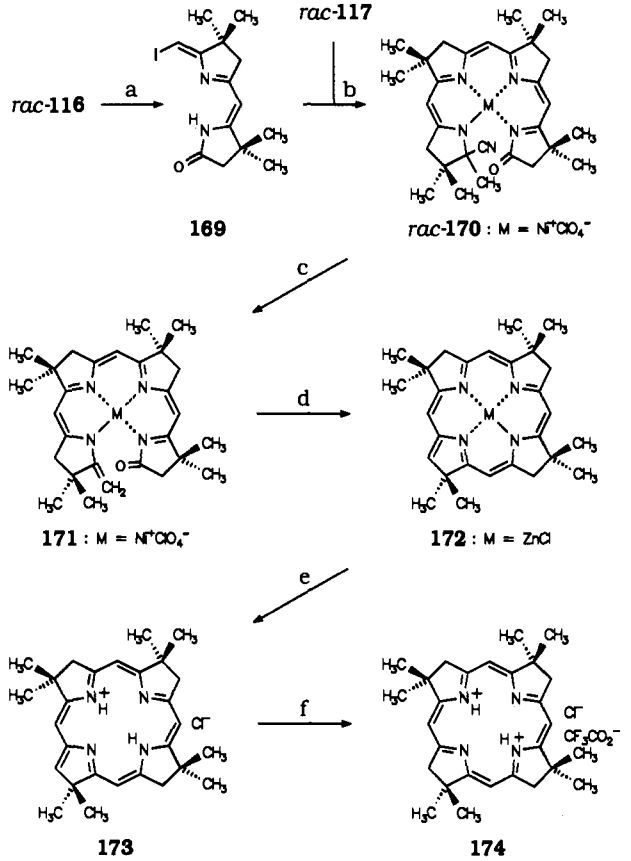
The enzymatic methylations correspond with biomimetic investigations on the structural types of the zinc D-pyrrocorphinate (**165**) and the metal-free dipyrrolic pyrrocorphin tautomer **167**, which were performed by Eschenmoser et al.[7,84] (Scheme 25). From this and other experiments it was concluded that the tetrapyrrolic porphyrinogen structures can be transformed by methylation reactions into the thermodynamically less stable, tautomeric, but similarly hexahydroporphinoid corphin type structures. The methyl groups then fix the corphin chromophore. Zinc(II)-pyrrocorphinate (**165**) and other metal(II)-pyrrocorphinates were C-methylated at the periphery to give the corresponding corphinates **166**. The dipyrrolic pyrrocorphin tautomer **167**, which corresponds to the natural precorrin 3 (**157**),

Scheme 25. Possible Biomimetic Methylation of Hexahydroporphyrins[a]



[a] (a) (1) MeI, 85 °C, 15 min; treatment with benzene + 1% aqueous $NaClO_4$. (b) MeI/MeCN (1/4), 60 °C.

Scheme 26. Total Synthesis of a Model Hexahydroporphyrin of Corphin Type[a]

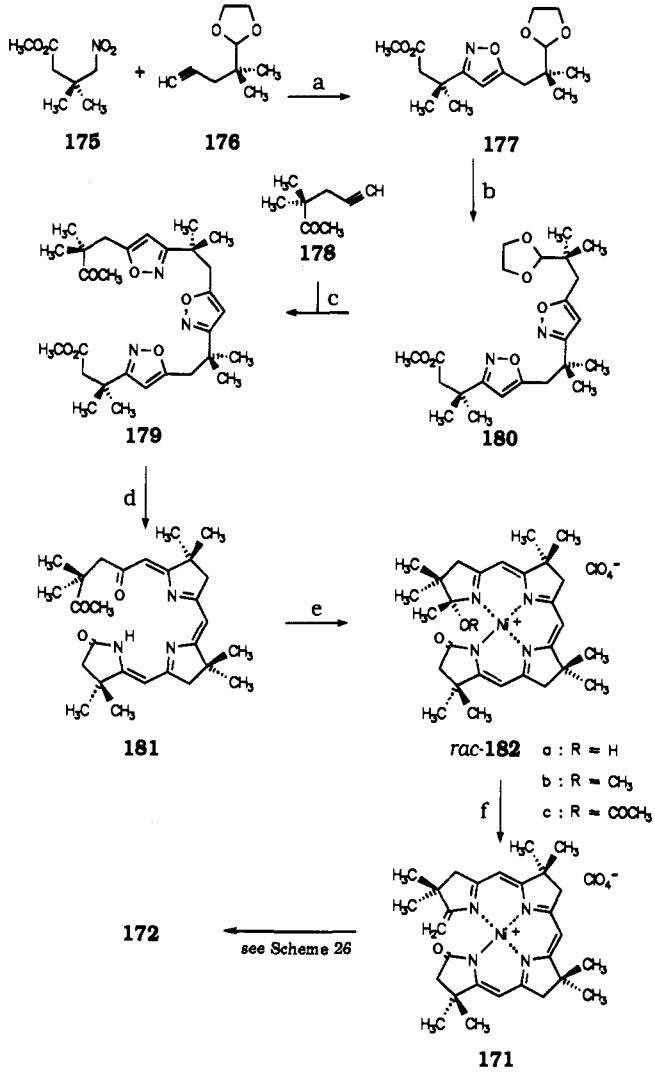


[a] (a) *N*-iodosuccinimide, benzene, HO*t*-Bu, room temperature, 30 min (for *rac*-116 see Scheme 14). (b) (1) DBU, MeCN, room temperature; (2) $Ni(ClO_4)_2$ or $Zn(ClO_4)_2$, PPh_3, 50 °C, 2 h (for *rac*-117 see Scheme 14). (c) KO*t*-Bu, HO*t*-Bu, 80 °C, 1.5 h. (d) (1) KCN, MeOH, room temperature, 10 min; (2) $Zn(ClO_4)_2 \cdot 6H_2O$; (3) $Et_3O^+BF_4^-$, Et*Ni*-Pr_2, CH_2Cl_2, room temperature, 19 h. (e) HCl/H_2O, room temperature, 1 h. (f) CF_3CO_2H.

is also biomimetically methylated to form the D-pyrrocorphin **168**.

Eschenmoser et al.[75e,78c,84,85] have devised numerous syntheses of corphins in order to investigate the problem

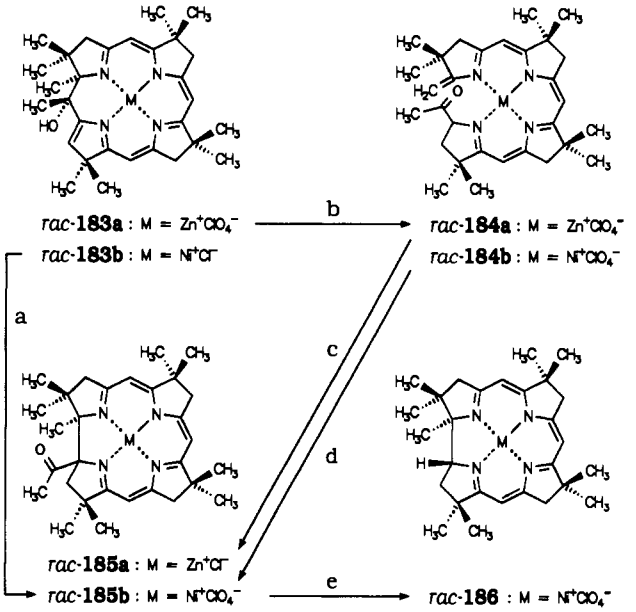
Scheme 27. Total Synthesis of a Corphin: Isoxazole Approach[a]



[a] (a) PhNCO, NEt_3, benzene, 50 °C, 24 h. (b) (1) 10% HCl, THF, room temperature, 6.5 h; (2) $H_2NOH \cdot HCl$, py, room temperature, 5 h; (3) NBS, DMF, 0 °C, Et_3N + **176**, room temperature, 24 h. (c) (1) 10% HCl, THF, room temperature; (2) $H_2NOH \cdot HCl$, Py, room temperature, 5 h; (3) NBS, DMF, 0 °C, Et_3N + **178**, room temperature, 24 h. (d) (1) H_2, Raney-Ni, MeOH, pH 7; (2) Et_3N, $CHCl_3$, room temperature, 24 h. (e) (1) NaOMe, MeOH, MeCN, $Ni(ClO_4)_2 \cdot 6H_2O$, room temperature, 30 min; (2) NH_4OAc, MeOH, room temperature, 19 h (crude mixture of *rac*-**182a–c**). (f) *t*-BuOK, *t*-BuOH, 65 °C, 1.5 h.

of corrin formation from corphinoid precursors and to examine the structure–function relationships of hydroporphinoid metal complexes. Most of the syntheses are based on a synthetic concept which was developed to prepare the prototypic octamethylcorphin **173**.[85j,k] Sulfide contraction tranforms the "corrinoid" components *rac*-**116** and *rac*-**117** (see Scheme 14) into the nickel(II) secocorphinate *rac*-**170** (Scheme 26). Base-induced elimination of the cyano group liberates an enamine double bond, which can be used to cyclize **171** to **172**. To obtain the metal-free corphin **173**, the secocorphin must first undergo decomplexation. Zinc(II) can be readily removed from the cyclized ligand **172**, but not nickel(II). The metal-free corphin **173** is obtained as its hydrochloride and can be protonated under strongly acidic conditions to yield the centrosymmetric tetraaza[16]annulene system.

Scheme 28. Possible Biomimetic and Prebiotic Formation of Corrins from Hexahydroporphyrins[a]



[a] (a) Melting, 240 °C, 5 min. (b) $h\nu$ (vis), CH_2Cl_2, CF_3CO_2H trace, room temperature or melting, 215 °C, 70 s. (c) $h\nu$ (vis), benzene, 40 °C. (d) AcOH/Et_3N (4/1), 100 °C. (e) 2 N KOH, 70 °C.

Stevens et al.[86] have developed a unique approach for the synthesis of corphins[86] and corrins.[86c] The basic methodology of this approach involves the construction of the triisoxazole **179** from the subunits **175**, **176**, and **178** by consecutive 1.3 and dipolar cycloaddition reactions (Scheme 27). Nitrile oxide moieties generated in situ in the building blocks **175** and **177** are added to the terminal acetylenic parts of **176** and **178**. The triisoxazole **179** serves as a latent synthon for the three vinylogous amidine substructures present in the secocorphinoid and corphinoid macrocycles. Hydrogenolysis of the three isoxazole nuclei in **179**, followed by exposure to a trace of base, produces the desired conjugated structure **181**. In the next step nickel and the required nitrogen are incorporated to yield a mixture of the precorphin complexes *rac*-**182a–b**, which on treatment with a base are transformed into the known secocorphin **171**. The synthesis of corphins, e.g. **172**, from **171** follows established routes (see Scheme 26).

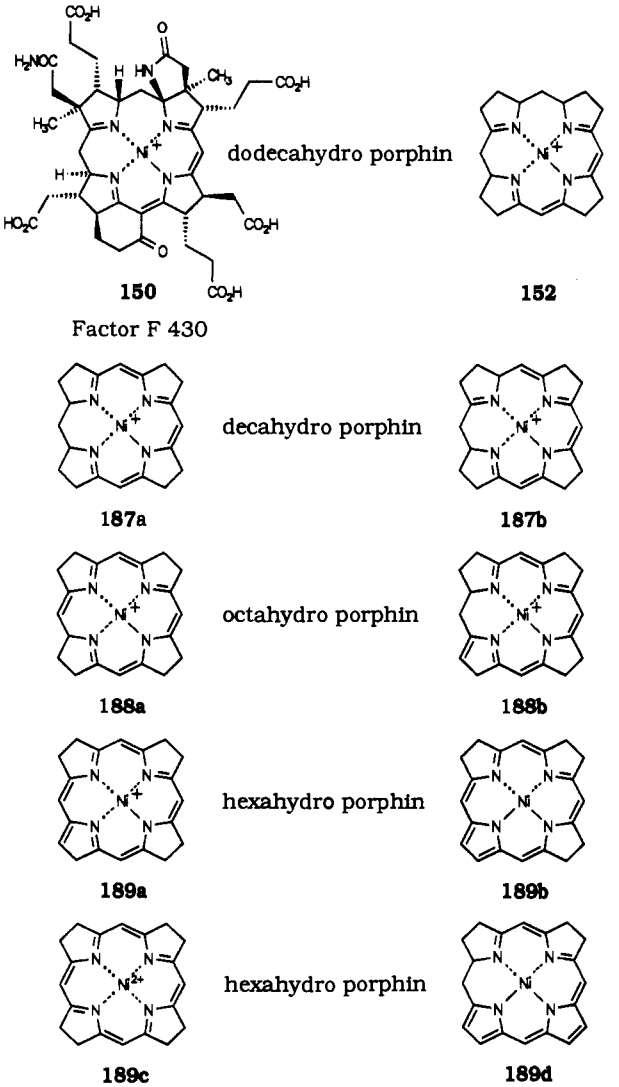
The direct coupling of rings A and D is an essential structural element of the corrins. Important information on the origin of the corrin structure is supplied by the diversity of cyclization reactions with which they can be formed.[7] The spectrum of ring closure reactions[7] ranges from the photochemical A–D cycloisomerization, a key step in the synthesis of vitamin B_{12}, to the acid-catalyzed dehydrobilin cyclizations,[87] which yield the corroles and octadehydrocorrins. Chemistry has so far been unable to ascertain how rings A and D are coupled during the biosynthesis of vitamin B_{12} in nature. In section V.A. it was shown that highly reduced hydroprophinoid structures play an important role as intermediates on the pathway to the corrin structure. Eschenmoser et al.[7,85f,85g] have shown in synthetic studies that corrins can be formed from hydroporphyrins in a biomimetic mode. On heating, the nickel-containing dihydrocorphinol *rac*-**183b** is easily converted into the corrin *rac*-**185b**. The acyl group in the corrin *rac*-**185b** which stems from the 20 methylene bridge, is removed in a retroaldol type fragmentation to yield the 19 unsubstituted corrin *rac*-**186** (Scheme 28).

The removal of the acyl residue as acetic acid, in particular, corresponds very closely to the vitamin B_{12} biosynthesis. In isotope labeling experiments it has been shown[88] that the methylated 20 methine position of precorrin 3 (**157**) (see Scheme 22) is lost as acetic acid in the course of the vitamin B_{12} biosynthesis. Moreover, Blanche et al.[89] have recently identified a precorrin 4, which bears an acyl residue in position 1 and which is a biosynthetic precursor for vitamin B_{12}. The dihydrocorphinol–corrin rearragnement can occur in a concerted or stepwise manner. The stepwise process is observed when the zinc(II) corphinate (*rac*-**183a**) is heated for a short time or is photochemically opened in the presence of acid to yield the secocorrin (*rac*-**184a**). The zinc(II) secocorrin (*rac*-**184a**) undergoes photochemical cyclization and the nickel(II) secocorrin (*rac*-**184b**) undergoes acid-catalyzed ring closure to give the corresponding corrins *rac*-**185a** and **185b**, respectively.

VI. Summary

The Chart 6 shows the nickel-containing frameworks of all the highly reduced hydroporphins synthesized[75e]

Chart 6. Naturally Occurring Factor F 430 and Chromophores of the Highly Saturated Hydroporphinoid Structures Synthesized to Date



to date. The tautomeric hexahydroporphins **189a–d** have the same oxidation level as uroporphyrinogen III (**153**), the key building block in the biosynthesis of all currently known, naturally occurring porphinoid structures. They can be formed under controlled experimental conditions from the porphyrinogens by tautomerization. The chemistry of natural hydroporphinoid compounds and their importance for the biosynthesis of vitamin B_{12} were discussed in section V. Naturally occurring chlorins, bacteriochlorins and isobacteriochlorins, which have oxidation levels in between the hexahydroporphins and the completely unsaturated porphins, were dealt with in the sections II–IV. The upper limit in the spectrum of hydroporphinoid structures, which are characterized by different oxidation levels, is currently represented by the dodecahydroporphin chromophore **152** of factor F 430 (**150**). It remains to be seen whether nature has been able to produce more highly reduced porphyrins or the missing links in the spectrum of hydroporphinoid structures, octahydroporphin (188) and decahydroporphin (187).

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