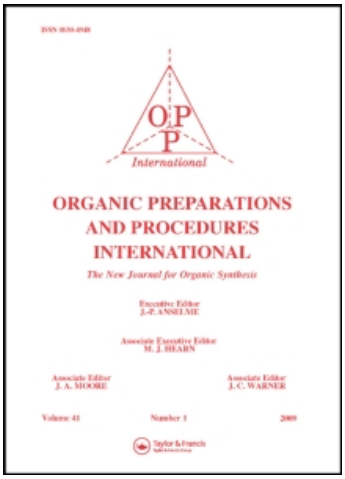

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DIPYRRINONES-CONSTITUENTS OF THE PIGMENTS OF LIFE. A REVIEW

Stefan E. Boiadjiev[a]; David A. Lightner[a]
[a] Department of Chemistry, University of Nevada, Reno, Reno, Nevada, USA

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Stefan E. Boiadjiev and David A. Lightner*

Department of Chemistry, University of Nevada, Reno
Reno, Nevada 89557-0020, USA
e-mail: lightner@scs.unr.edu

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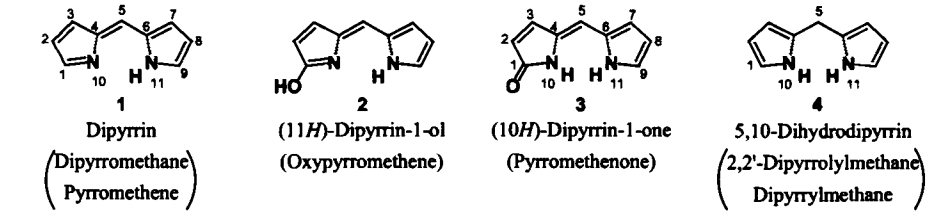
INTRODUCTION

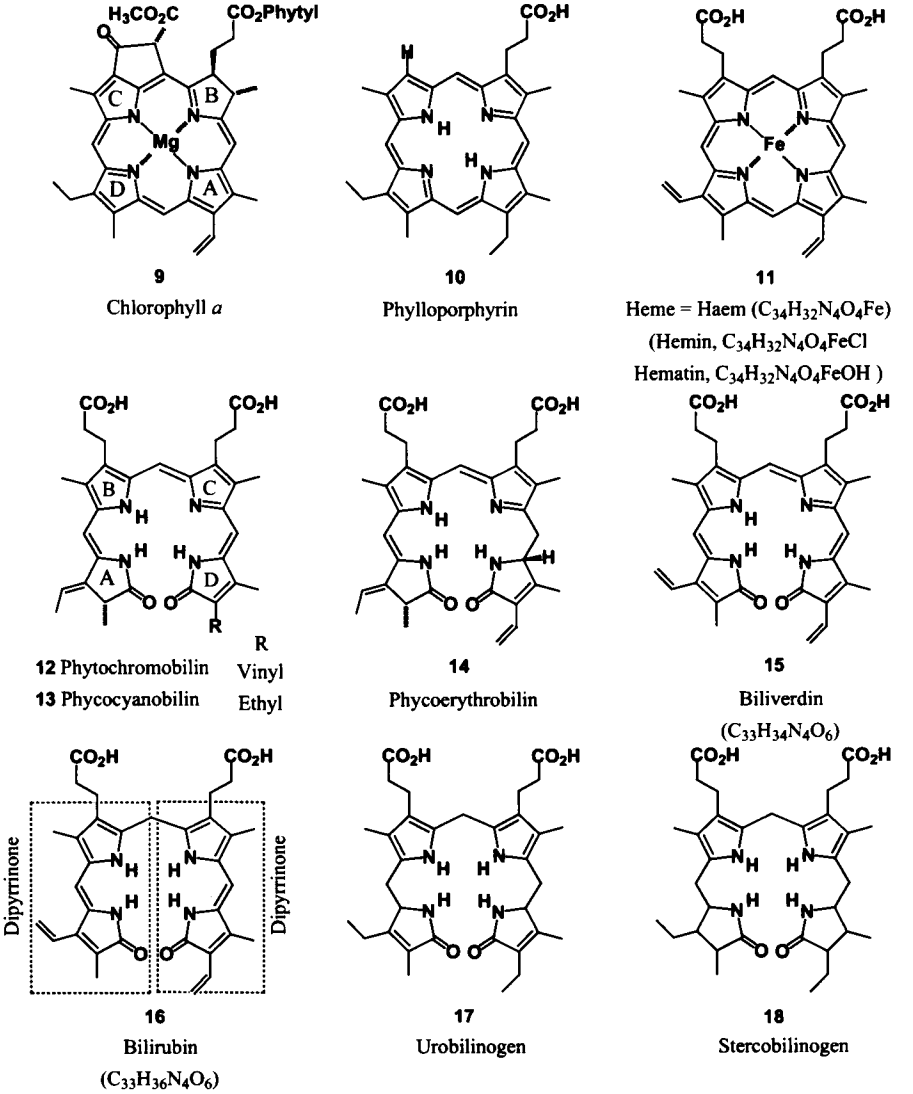
The systematic name of the most unsaturated system (*Fig. 1*) arising from two pyrrole rings conjoined by one carbon atom is 2-[(2*H*)-pyrrol-2-ylidenemethyl]pyrrole; however, the trivial name dipyrrin (**1**) implies that N(11) is saturated and is recommended by IUPAC.[1] With a hydroxyl substituent at C(1), the dipyrrin becomes a dipyrrin-1-ol (**2**), the lactim tautomer favored by Hans Fischer (the "father" of pyrrole chemistry and 1930 Nobel Prize in chemistry awardee) that is now known to be less stable than the lactam form (**3**), a dipyrrinone (formerly pyrromethenone, or as Fischer preferred: oxypyrromethene). The designation (10*H*) specifies the lactam form. Further saturation of dipyrrin **1** at C(4)-C(5) leads to the well known dipyrrylmethane skeleton **4**, whose C(1) hydroxylated derivative, now known to be the more stable 4,5-dihydrodipyrrinone tautomer **6**, was important historically as the first dipyrrinone. Its isomer **7** and tetrahydrodipyrrinone **8** are found in the literature, and as core components of natural products.



Dipyrroles Relevant to this Review and their Nomenclature

Fig. 1

Dipyrrin and dipyrrinone units are structural elements in tetrapyrrolic compounds (*Fig. 2*) called pigments of life: chlorophyll-*a* (**9**) and its degradation product, phylloporphyrin (**10**), heme (**11**) and its catabolite bile pigments biliverdin (**15**) and bilirubin (**16**). Dihydro derivatives



9 Chlorophyll *a*

10 Phylloporphyrin

11 Heme = Haem ($C_{34}H_{32}N_4O_4Fe$)
(Hemin, $C_{34}H_{32}N_4O_4FeCl$
Hematin, $C_{34}H_{32}N_4O_4FeOH$)

12 Phytochromobilin — R = Vinyl
13 Phycocyanobilin — R = Ethyl

14 Phycoerythrobilin

15 Biliverdin ($C_{33}H_{34}N_4O_6$)

16 Bilirubin ($C_{33}H_{36}N_4O_6$)

17 Urobilinogen

18 Stercobilinogen

Monocyclic and "Linear" Tetrapyrroles Containing the Dipyrrole Units of *Figure 1*. All but 10 are Natural Products.

Fig. 2

6 and **7** maybe recognized in higher plants biliproteins such as phytochrome which contains phytochromobilin (**12**), the algal antenna pigment phycocyanobilin (**13**) and phycoerythrobilin (**14**); whereas, dihydro derivative **6** and tetrahydro- **8** are found in nature in the bilirubin metabolites urobilinogen (**17**) and stercobilinogen (**18**).

In the present review, various syntheses leading to dipyrrinones **3** are discussed. Although indispensable for porphyrins, dipyrrin **1** and hydrogenated systems **4-8** are not included herein. Many dipyrrinone (**3**) syntheses are intimately connected to the structure proofs and syntheses of higher, *e. g.* tetrapyrrolic systems, and often a specific substitution pattern on **3** was introduced in order to gain insight into their physicochemical properties – so important for understanding the function of naturally-occurring oligopyrroles.[2] However, both facets of such research fall out of the scope of this review. Instead, we focus mainly on the story of dipyrrinones with skeleton **3** (or **2**) and their historically related dihydro analogs **5** and **6**. Our literature sources on the structure and synthesis of dipyrrinones cover 1912 - 2006.

I. EARLY HISTORY OF DIPYRRINONES

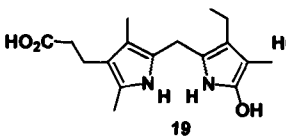
Bilirubinic acid and its dehydro analog, xanthobilirubinic acid (**19** and **20** of *Fig. 3*), the first known dipyrrinones, were isolated following degradation of bilirubin (**16**). Their structures were characterized in 1914, long before those of bilirubin or its metabolic precursors, biliverdin (**15**) and heme (**11**), over a long, confusing and contentious history. What would be relatively straightforward structure proofs today were confounded by an inability to separate reaction product mixtures cleanly, which proved to befuddle, and by a lack of reference compounds of proven structure. Structure proof in the late 1800s and especially the early 1900s relied on degradation of complex structures to smaller components (which were identified typically by synthesis), followed by a reconstruction of the puzzle from its component pieces by applying logic and intuition. Total syntheses of complex molecules followed later.

In the late 1800s investigators of heme (haem), chlorophyll, bilirubins and biliverdins (*Fig. 2*) were concerned mainly with isolation (procedures) from diverse sources, purification and peripheral nibbling at structure. Early attempts at structure analysis involved degradation and were complicated by impure samples and product mixtures. Two main degradation procedures stand out: (1) reductive cleavage using hydriodic acid (HI) and PH_4I in acetic acid and (2) oxidation using dichromate or chromic acid in acetic acid. In the first, macrocyclic tetrapyrroles such as hemin (Hämin = Fe(III) heme chloride, *Fig. 2*, under **11**),[3] Hämatoporphyrin (hematoporphyrin, a heme porphyrin with $-CH=CH_2$ converted to $-CH(OH)CH_3$,[4,5] or isolated from urine), "Acethämin",[3,6] β-Hämin[6] and phylloporphyrins[7,8] (from chlorophyll) yielded a liquid monopyrrole named "Hämopyrrol", based on its source. Unsuspected at the time perhaps, but suspected subsequently to be a mixture of various alkylated pyrroles,[9] some identified as phyllopyrrole, 2,4-dimethyl-3-ethylpyrrole, isohemopyrrole, etc, "Hämopyrrol" was shown[10] to be a mixture of hemopyrrole (**21**), kryptopyrrole (**22**), phyllopyrrole (**23**) and opsopyrrole (**24**)[9,10] – see *Fig. 3*. "Hämopyrrol" analyzed for $C_8H_{13}N$ – a molecular formula that fits both the hemopyrrole (**21**) and kryptopyrrole (**22**) of *Fig. 3* as well as other regioisomers and constitutional isomers.

In the second degradation method, oxidation of hematin (Hämatin = Fe(III) heme hydroxide, *Fig. 2*, under **11**) yielded the imide (**26**) and anhydride, $C_8H_9NO_4$ and $C_8H_8O_5$

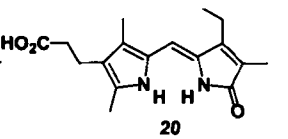
respectively, of what was named (based on its origin) "tribasic Hämatinsäure" ($C_8H_{10}O_6$).[11,12] The imide was the primary product, as much as 50% of hematin.[11] At the time, the chemical structures were incompletely characterized, but these solids were probably pure. It was known that the tribasic acid was easily converted to the anhydride, and the latter was converted to the imide (**26**) using alcoholic ammonia at 100-110°C; and both imide and anhydride could be hydrolyzed to the acid.[11-15] Under similar oxidation conditions, biliverdin (**15**)[16] was converted to $C_8H_9NO_4$, again named after its source as "Biliverdinsäure" (**26**). Bilirubin (**16**) was also observed to give "Biliverdinsäure" (**26**) upon oxidation with $K_2Cr_2O_7$ in acetic acid.[12] It was soon recognized that "Biliverdinsäure" was identical with the imide of "Hämatincarbonsäure", thus establishing a structural link between the pigments of blood (heme, **11**) and bile (biliverdin (**15**) and bilirubin (**16**)).

"Biliverdinsäure", upon heating at 125-130°C in alcoholic ammonia was observed to give the imide $C_7H_9NO_2$, apparently *via* decarboxylation, shown to be methylethylmaleimide



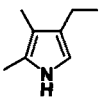
19

Bilirubinic acid (Fischer's late 1913 Bilirubinsäure) $C_{17}H_{24}N_2O_3$

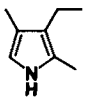


20

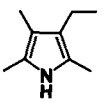
Xanthobilirubinic acid (Fischer 1913) $C_{17}H_{22}N_2O_3$



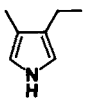
21 Hemopyrrole (Piloty's 1911 Phonopyrrol) $C_8H_{13}N$, mp 39°C



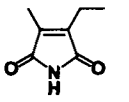
22 Kryptopyrrole (Piloty's 1911 Isophonopyrrol) $C_8H_{13}N$



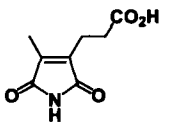
23 Phyllopyrrole $C_9H_{15}N$



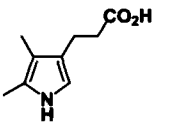
24 Opsopyrrole $C_7H_{11}N$



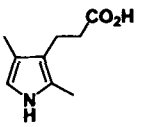
25 Methylethyl-maleimide $C_7H_9NO_2$, mp 67°C



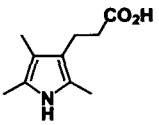
26 Hematinic acid Imide (Hämatinsäure, Biliverdinsäure)



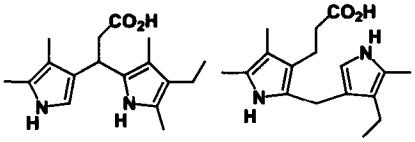
27 Hemopyrrole carboxylic acid (Phonopyrrolcarbon-säure) $C_9H_{13}NO_2$



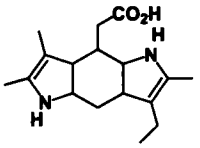
28 Kryptopyrrole carboxylic acid (Isophonopyrrolcarbon-säure) $C_9H_{13}NO_2$



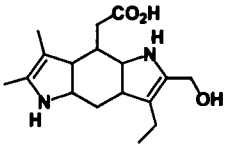
29 Phyllopyrrole carboxylic acid (Phyllopyrrolcarbon-säure) $C_{10}H_{15}NO_2$



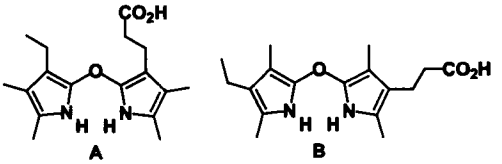
30 Hematopyrrolidinic acid (Piloty's 1910 Hämato-pyrrolidinsäure) $C_{17}H_{24}N_2O_2$



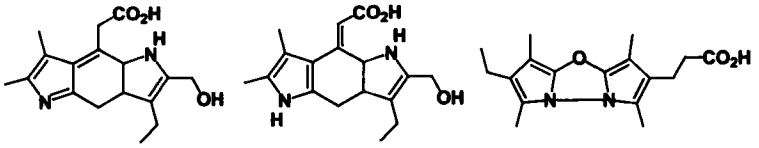
31 Hematopyrrolidinic acid (Piloty's 1912 revised Hämatopyrrolidinsäure) $C_{17}H_{26}N_2O_2$



32 Bilinic acid (Piloty's 1912 Bilinsäure) $C_{17}H_{26}N_2O_3$



33 Bilirubinic acid (Fischer's early1912 (**A**) and late 1912 (**B**) Bilirubinsäure) $C_{17}H_{24}N_2O_3$



34 Dehydrobilinic acid (Piloty's 1912 Dehydrobilinsäure) $C_{17}H_{22}N_2O_3$

35 Xanthobilirubinic acid (Fischer's late 1912 Xanthobilirubinsäure) $C_{17}H_{22}N_2O_3$

The First Published Dipyrrinones (19 and 20) and the Mono- and Dipyrroles of Historical Importance to Elucidating Dipyrrinone and Tetrapyrrole Structures

Fig. 3

(**25**, *Fig. 3*).[17] From the structure of methylethylmaleimide, one might infer several structures for "Biliverdinsäure", what we now know as hematinic acid (**26**, *Fig. 3*): the corresponding structure with an α-methylacetic acid group replacing propionic, or a structure with one ethyl and one acetic acid group. The two imides, $C_7H_9NO_2$ (methylethylmaleimide, **25**) and $C_8H_9NO_4$ (hematinic acid imide, **26**), were of early importance to the interwoven structure elucidations of heme (**11**), biliverdin (**15**) and bilirubin (**16**). They were also the essential molecular building blocks used in reconstructing and elucidating the first dipyrrinone structures.

Many of the early investigators of hemes, chlorophylls and bile pigments did not pursue investigations of their structures, except L. Marchlewski in Cracow (Krakau), who continued studies of chlorophylls into the mid-1930s and William Küster in Stuttgart, whose prolific and pioneering structural studies of hemes, bilirubin and biliverdin extended from the late 1800s into the late 1920s – and who with remarkable insight published an essentially correct structure of hemin in 1912,[18] and apparently retracted it.[19]

Yet, despite Küster's considerable and fundamental contributions, others who commenced structural studies in the early 1900s are credited with the conclusive advances to our

understanding of structure: Richard M.Willstätter, who from 1905-1916 investigated the structure of plant pigments, especially chlorophyll and was awarded the Nobel Prize in chemistry in 1915; and Hans Fischer, who from 1911 until his death in March 1945 investigated and elucidated the structures of bilirubin, biliverdin, and heme. For the last and its relation with chlorophyll, Fischer was awarded the Nobel Prize in chemistry in 1930. Had Oskar Piloty not perished in 1915 in WWI, who in a brief career as professor of inorganic chemistry in Munich investigated the structure of heme and bilirubin from 1908 until his death, he might have been more highly recognized.

It was the unknown chemical structure of the coloring matter of blood that attracted investigators such as Küster, Willstätter, Piloty and Fischer. The first *dipyrrinone* isolation and structure elucidation came from the work of the latter two. Piloty's attempts to solve the structure of hematin (*Fig. 2*, under **11**), published between 1909 and 1914 led him to (1) note the analogy in the constitution of the blood pigment and bilirubin (**16**), (2) comment on the formation of the latter from the former in the liver, and (3) isolate of the first dipyrrinone by degradation of the latter.[20] Piloty's work thus intersected with the independent investigations of Hans Fischer, published from 1912 forward on the chemical structures of bile pigments.[21] And it led to controversy.

In 1909 Piloty reported his investigations on the structure of the coloring matter of blood[22] by a series of transformations: hemin ($C_{34}H_{32}N_4O_4FeCl$) ⟹ hematoporphyrin ($C_{34}H_{38}N_4O_8$) ⟹ desoxyhematoporphyrin ($C_{34}H_{38}N_4O_5$) ⟹ Hämopyrrol ($C_8H_{13}N$) + Hämopyrrol-carbonsäure ($C_9H_{13}NO_2$) + Hämatopyrrolidinsäure ($C_{17}H_{28}N_2O_2$ or $C_{17}H_{24}N_2O_2$).[23] The last reaction, from treatment with HI in hot acetic acid, followed by HI-PH_3 (reaction of Nencki and Zaleski[3]) thus gave not only the expected Hämopyrrol but also two new acids. Reaction of Hämopyrrol with HNO_2 gave methylethylmaleimide ($C_7H_9NO_2$) (**25**, *Fig. 3*) and its monoxime ($C_7H_{10}N_2O_2$); whereas similar reaction of "Hämopyrrolcarbonsäure" gave hematinic acid (**26**, *Fig. 3*) and its monoxime. The second new acid, "Hämatopyrrolidinsäure", an entirely new discovery, also gave hematinic acid upon treatment with MnO_2 in H_2SO_4,[22] and it gave Hämopyrrolcarbonsäure,[23] Hämopyrrole,[24] 2,3-dimethylpyrrole[24] and acetic acid[24] upon fusion of the Zn complex with molten KOH. These data might have been sufficient to formulate possible structures for the $C_{17}H_{24}N_2O_2$ "Hämatopyrrolidinsäure" (**30**) as the first dipyrrin, which is what Piloty[24] did in 1910 (*Fig. 3*), but not before having determined that the $C_9H_{13}NO_2$ "Hämopyrrolcarbonsäure"[22,23] described in 1909 from reduction of hematoporphyrin with Zn did not, upon loss of CO_2, give "Hämopyrrol". Rather, it gave an isomer for which Piloty adopted the name "Phonopyrrol" and to which he assigned the structure of the hemopyrrole (**21**) of *Fig. 3*.[24] Accordingly, Piloty adopted the name "Phonopyrrolcarbonsäure" for the acid and assigned it the structure of the hemopyrrole carboxylic acid (**27**) shown in *Fig. 3*.[24] This left him to assign to "Hämopyrrol" the structure of kryptopyrrole (**22**), and to "Hämopyrrolcarbonsäure" – the structure of the kryptopyrrole carboxylic acid (**28**) shown in *Fig. 3*.[24] Apparently, the structure assign-

ments of "Hämopyrrol" and "Hämopyrrolcarbonsäure" had been under consideration by Piloty,[25] inasmuch as he had carefully purified the "Hämopyrrol" from hematoporphyrin by distillation to afford a solid with mp 39°C (a mp identical to that of the hemopyrrole (**21**) of *Fig. 3*). This upon reaction with HNO_2 gave methylethylmaleimide oxime (mp 206°C), which converted to methylethylmaleimide (**25**) upon treatment with boiling dilute H_2SO_4. Piloty knew that the HNO_2 oxidation replaced a pyrrole α-alkyl (CH_3) with an oxime (=NOH) and the pyrrole α-H by a carbonyl (=O), thus leading to the two regioisomeric $C_7H_{10}N_2O_2$ oximes.[25] And he thus concluded[25] that (1) "Hämopyrrol" had either the hemopyrrole (**21**) or kryptopyrrole (**22**) structure shown in *Fig. 3* and (2) Hämopyrrolcarbonsäure had either the hemopyrrole carboxylic acid (**27**) or kryptopyrrole carboxylic acid (**28**) structure (*Fig. 3*). Although unable to determine which was which at that time,[25] he shortly thereafter concluded in 1910 that Hämatopyrrolidinsäure consists of one molecule of "Phonopyrrolcarbonsäure" (hemopyrrole carboxylic acid, **27**) and one molecule of "Phonopyrrol" (hemopyrrole, **21**), both of which can arise from the postulated (**30**) "Hämatopyrrolidinsäure" structures[24] (*Fig. 3*) by scission / reduction of an α-pyrrole C–C bond. These structures led Piloty to further postulate structures for hemin and hematoporphyrin,[24] later disproved, but the structures of hematopyrrolidine carboxylic acid greatly influenced Piloty's choice of structure (**31**) assignment in 1912 when from bilirubin (**16**) he isolated the first dipyrrinone – work that intersected with Hans Fischer's entry into pyrrole chemistry.

In 1912 Piloty and Thannhauser[20] reported on the treatment of bilirubin with HI in glacial acetic acid on a boiling water bath, then with HI-PH_3 from which was isolated a colorless product that analyzed for $C_{17}H_{26}N_2O_3$ by combustion and had a molecular weight of 299-347, as determined by boiling point elevation (ebulioscopy). It was shown to be a monobasic acid by its neutralization equivalent (NE = 306). This previously unknown crystalline substance, mp 187°C, was named "Bilinsäure" by the authors, or "bilinic acid" (**32**). It was isolated along with a second product, a new monopyrrole carboxylic acid, named "Isophonopyrrolcarbonsäure" ($C_9H_{13}NO_2$, mp 126-127°C) and assigned to it the structure of kryptopyrrole carboxylic acid (**28**) shown in *Fig. 3*, consistent with the earlier assignment of "Phonopyrrolcarbonsäure" to the structure of hemopyrrole carboxylic acid,[20,24,25] (**27**) in *Fig. 3*. However, it was the bilinic acid structure that proved to cause problems.

Piloty's assignment of structure to bilinic acid followed from several experimental results and their interpretation. Bilinic acid did not produce hemopyrrole upon fusion with KOH, but when oxidized with CrO_3 in dilute H_2SO_4 at 50-60°C, or with HNO_2 in warm, dilute H_2SO_4, gave equal amounts of the known methylethylmaleimide (**25**) and hematinic acid (*Fig. 3*).[20] These results suggested the presence of two intact pyrrole rings in bilinic acid, with β-substituents corresponding to those of the two imides, but with neither pyrrole component being represented by hemopyrrole. Remarkably, in the same work, Piloty re-evaluated his 1910 structure of "Hämatopyrrolidinsäure" (for which two molecular formulas, $C_{17}H_{28}N_2O_2$ and $C_{17}H_{24}N_2O_2$, were calculated from combustion analysis of picrates)[24] in favor of $C_{17}H_{26}N_2O_2$, the

average value, and in 1912 he gave a revised tricyclic structure for the compound (**31**, *Fig. 3*). Apparently strongly influenced by this structure, in early 1912 Piloty[20] proposed a structure (**32**, *Fig. 3*) for bilinic acid that appeared to be consistent with the various data. By mid-1912 he had determined that bilinic acid, upon treatment with 0.1 N $KMnO_4$ at 7°C yielded a strongly yellow product that he and Thannhauser named dehydrobilinic acid, and (recognizing that the substance must have conjugated double bonds) proposed two structures (**34**, *Fig. 3*).[26]

At nearly the same time as Piloty's reported degradation of bilirubin,[24] Fischer entered the bile pigment arena by addressing the structure of bilirubin and its relationship to urinary and fecal pigments (urobilinogen (**17**), urobilin, stercobilin).[27] Applying similar reductive degradation, Fischer and Röse[21] reported that bilirubin (**16**), when reacted with HI in acetic acid, warmed on a boiling water bath then treated with PH_4I, afforded a new acid that they named "Bilirubinsäure" (or bilirubinic acid, **33**). This substance, like Piloty's bilinic acid (**32**), had mp 187°C, a molecular weight 301-359 (from boiling point elevation measurements) and a neutralization equivalent NE = 307-311 – thus confirming a monobasic acid. The molecular formula from combustion analysis and MW ($C_{17}H_{24}N_2O_3$) differed from bilinic acid, however by two hydrogens. Like bilinic acid (**32**), bilirubinic acid (**33**) gave (nearly equal quantities of) methylethylmaleimide (**25**) and hematinic acid from oxidation with PbO_2 in H_2SO_4 or CrO_3-H_2SO_4.[21] It proved to be surprisingly resistant to reductive cleavage in hot HI-P and even in 70% H_2SO_4. Although equivocating about the location of the methyl groups at the α-pyrrole sites, on 20 May 1912, five days before Piloty and Thannhauser's article[20] on bilinic acid (**32**) was received in the editorial office of *Justus Liebig's Annalen der Chemie*, Fischer's article[21] on bilirubinic acid (**33**) was received in the editorial office of the *Berichte der Deutschen chemischen Gesellschaft*, a paper in which he and Röse proposed an oxygen-bridged dipyrrole structure for bilirubinic acid (**33A**, *Fig. 3*). The proposed structure fit with the molecular formula, the isolated oxidation products and the apparent resistance toward HI. Fischer considered alternative structures, *e. g.* with a carbon rather than an oxygen bridge and an alcohol group, but he believed that the latter would be reactive toward HI, whereas, bilirubinic acid showed a resistance reminiscent of diphenyl ether. In 1912 Fischer and Röse[28] recognized that their bilirubinic acid and Piloty's bilinic acid were probably the same material, that the evidence was insufficient to determine which structure was correct, but that Piloty's structure could not be correct due to the sensitivity of its hydroxyl group in **32** to HI, *inter alia*.

In the same year (1912) Fischer and Röse reapplied the reductive cleavage method (HI-acetic acid on a boiling water bath, followed by addition of PH_4I) to both bilirubin (**16**) and bilirubinic acid (**19**), with an improved work-up involving separation from inorganic acids by vacuum distillation then washing the residue with aq. Na_2CO_3 to separate organic acids from neutral or basic material.[29] The separated materials were treated with picric acid, and the crystalline complexes were isolated and fractionally crystallized. From the "basic" reaction products was isolated kryptopyrrole (**22**, *Fig. 3*) (picrate mp 136-137°C), and from the carbonate-soluble

fraction was isolated an isomeric "Phonopyrrolcarbonsäure" (picrate mp 156°C) thought to be kryptopyrrole carboxylic acid (*Fig. 3*). Those findings led to a revised structure (**33B**, *Fig. 3*) for bilirubinic acid. And Fischer[29] considered that the evidence refuted the Piloty structure. Fischer, like Piloty and bilinic acid, found that his bilirubinic acid could be oxidized to a new yellow compound by heating in methanolic sodium methoxide at 220-230°C (autoclave) and for which he and Röse proposed the name "Xanthobilinsäure" and the structure **35** of *Fig. 3*.[29] They noted the similarity between their xanthobilirubinic acid (**35**) and Piloty and Thannhauser's dehydrobilinic acid (**34**), indicating that it was not unlikely that they were the same substance.

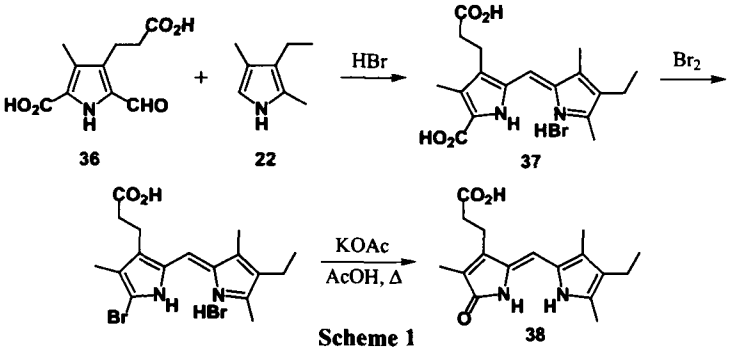
The intersection of Piloty's[30] and Fischer's[31] studies of the bilirubin-derived dipyrroles led to commentaries (received by the journals on 27 February 1913[30] and 28 April 1913[31], respectively) from each in which they agreed that bilinic acid (**32**) and bilirubinic acid (**33**) were probably identical, that dehydrobilinic acid (**34**) and xanthobilirubinic acid (**35**) were probably the same, and that by virtue of the dates received by the journals, Piloty's "Bilinsäure" (**32**) should be called "Bilirubinsäure" and that Fischer was satisfied to accept the name "Dehydrobilinsäure" (**34**) in place of "Xanthobilinsäure". The latter was apparently short lived.

In 1914 Piloty joined WWI and was killed on the Western front in 1915. In 1914 Fischer and Röse published corrected structures for bilirubinic acid (**19**) and xanthobilirubinic acid (**20** in *Fig. 3*).[32] These structures remain correct today, except that bilirubinic acid is known to be in the lactam rather than the lactim (hydroxypyrrole) tautomeric form. Thus Fischer had discarded[32] the oxygen-bridged dipyrrole structures **33**, **35** when he learned in 1913 that oxidation of bilirubinic acid (**19**) with HNO_2 gave methylethylmaleimide (**25**), hematinic acid and the "oxime" of "Phonopyrrolcarbonsäure" instead of the oxime of "Isophonopyrrolcarbonsäure" (where the two possible "oximes" are based on hematinic acid mono-oxime with one C=O replaced by C=NOH). Since it had been shown earlier that hemopyrrole (**21**) and kryptopyrrole (**22**) gave two isomeric mono-oximes of methylethylmaleimide, with the C=NOH group regiospecifically replacing the α-CH_3, it was assumed by Fischer that reaction of bilirubinic acid structure **33B** (*Fig. 3*) should give the mono-oxime of "Isophonopyrrolcarbonsäure" rather than that from "Phonopyrrolcarbonsäure". This puzzle was solved when Fischer showed that phyllopyrrole carboxylic acid (**29**, *Fig. 3*) gave exclusively the same mono-oxime as "Phonopyrrolcarbonsäure", thereby revealing that the β-propionic acid directed oximation at the adjacent α-pyrrole site while converting the α'-site to a carbonyl. This finding suggested to Fischer that the pyrrole acid of bilirubinic acid (**19**) was actually tetra-alkyl substituted and not trisubstituted, a conclusion that indicated a carbon and not an oxygen bridge between the pyrrole rings, hence structure **19** of *Fig. 3*. Xanthobilirubinic acid would thus have structure **20**. In 1914 Fischer then speculated on the structure of bilirubin (**16**) and hemin,[32] as it later turned out, incorrectly. The structures of bilirubinic (**19**) and xanthobilirubinic (**20**) acids were reconfirmed by Fischer some 17-18 years later by logical chemical syntheses,[33] but the structure of bilirubin was still uncharacterized and was not recognized[34] until 1933 and not conclusively proved (by

total synthesis)[35] until 1941 – a monumental achievement rivaling Fischer's Nobel Prize work on the structure of heme (**11**).

II. ORIGINS OF MODERN DIPYRRINONE SYNTHESIS

Hans Fischer pioneered the research on linear oligopyrroles, in particular, on dipyrrinones. His work on their total synthesis culminating in structure determination of hemin (1930 Nobel prize) and bilirubin (concluded in 1941) was extensively reviewed in his famous 3-book series that covered research until late 1930s and is still used today as a starting point in syntheses involving pyrroles.[36] The Fischer dipyrrinone syntheses first developed as an acid-catalyzed condensation of α-formylpyrroles such as **36** with α-unsubstituted alkylpyrroles (similar to **22** in *Scheme 1*) to afford dipyrrinones such as **38**.[33] By varying the pyrrole β-substituents on **22** and **36**, a myriad of dipyrrins (**37**) could be realized and converted to dipyrrinones. By judiciously choosing the location of the propionic acid, a variety of dipyrrinones would be prepared and compared by then available physical methods to those products obtained from resorcinol fusion of bilirubin (**16**), or by reductive degradation of hemin (*Fig. 2*, under **11**).

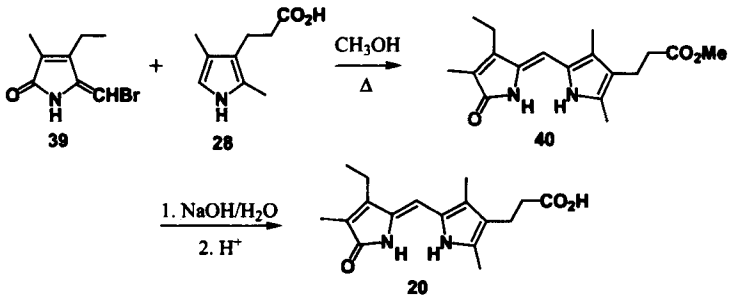


Scheme 1

The applicability and success of the route of *Scheme 1* depends on how easily the dipyrrin hydrobromide compounds such as **37** precipitate after a very rapid and smooth condensation. When pure, they are stable. However, prolonged contact with strongly acidic reaction medium leads to deterioration of the product. When the dipyrrin salt does not crystallize rapidly, it becomes difficult to isolate the desired compounds in subsequent manipulative or separation procedures, even where spectroscopy reveals that a considerable amount of red-purple dipyrrin has been formed. These difficulties are perhaps due to oligomerization, especially if a free pyrrole α-position is present. The decarboxylative bromination (above) is also often capricious, and the 9-CH_3 group of **37** may be reactive. Although still of value in porphyrin chemistry,[37] (for an ingenious use of a dipyrrin intermediate, see Woodward's chlorophyll total synthesis[38]) the dipyrrin route to dipyrrinones was completely abandoned after base-catalyzed condensation of 3-pyrrolin-2-ones[39] with α-pyrrole aldehydes was discovered.[40]

Dipyrrinone **38** has an unnatural location of the propionic acid and ethyl groups. When these two groups are interchanged, the resulting structure corresponds to that found in natural tetrapyrroles **9** and **11-18**. One of the structural parts of mesobilirubin-IXα (meso indicates saturation of vinyl in bilirubin (**16**) to ethyl, total synthesis accomplished in 1937 by W. Siedel[41]) is xanthobilirubinic acid (XBR, **20**, a bright yellow compound, whereas bilirubinic acid (structure **19** in *Fig. 3*), which is saturated at C(4)-C(5), is colorless). XBR was synthesized in 1931 as above, using silver acetate[42] at the last stage of *Scheme 1*.

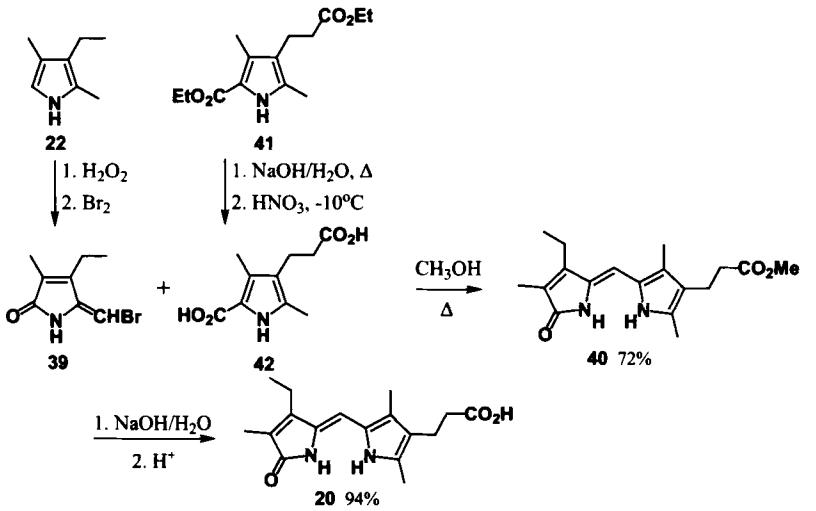
XBR (**20**) is a key model compound, mimicking half of bilirubin. A myriad of its derivatives and analogs have been described.[2] They have long served as structurally simpler models for understanding the stereochemistry, chemical properties and photochemistry of bilirubin, the yellow neurotoxic pigment of jaundice. Bacause **20** and its methyl ester (**40**) are archetypical components of biologically important linear tetrapyrroles, their total syntheses have been reported more than once, with increasing detail. In 1933 Fischer reported an alternative synthesis (to that of *Scheme 1*), preparing XBR by condensation of 5-bromo-3-ethyl-2-formyl-4-methylpyrrole (difficultly prepared) and opsopyrrole carboxylic acid (3-methyl-4-pyrrolepropionic acid).[43] Substitution of bromine at C(1) at dipyrrin stage was achieved by reaction with sodium methoxide under pressure at 180°C with concomitant C(9) methylation.[43] Fischer also synthesized XBR in 1932 by condensation of 5-bromomethylene-4-ethyl-3-methyl-3-pyrrolin-2-one (**39**) with 3-(2-carboxyethyl)-2,4-dimethyl-1*H*-pyrrole (**28**, Kryptopyrrole carboxylic acid), *Scheme 2*. This last method of synthesis is the method of choice today.[44,45]



Scheme 2

Despite the successful route of *Scheme 2*, it was encumbered by an early difficult synthesis of **28** that required a long sequence of reactions involving (toxic) liquid HCN or (carcinogenic) chloromethyl methyl ether. Also oxidation of kryptopyrrole (2,4-dimethyl-3-ethylpyrrole, **22**) followed by bromination to give **39** proved to give erratic yields and required further fine tuning.[44] About 30 years ago, Grunewald and coworkers reported and characterized these two intermediates spectroscopically and published a significant improvement in the condensation step (67% yield of **40**) and in the bromination step leading to pyrrolinone **39**, and provided, in addition, a shorter and more efficient route to pyrrole **28** (*Scheme 2*).[46] They found it

convenient to synthesize **28** from a pyrrole diethyl ester (**41**), that was readily available from 2,4-pentanedione, ethyl acrylate and ethyl acetoacetate. Double saponification of **41** and decarboxylation of the corresponding pyrrole-2-carboxylic acid (**42**) yielded α-free pyrrole **28**.

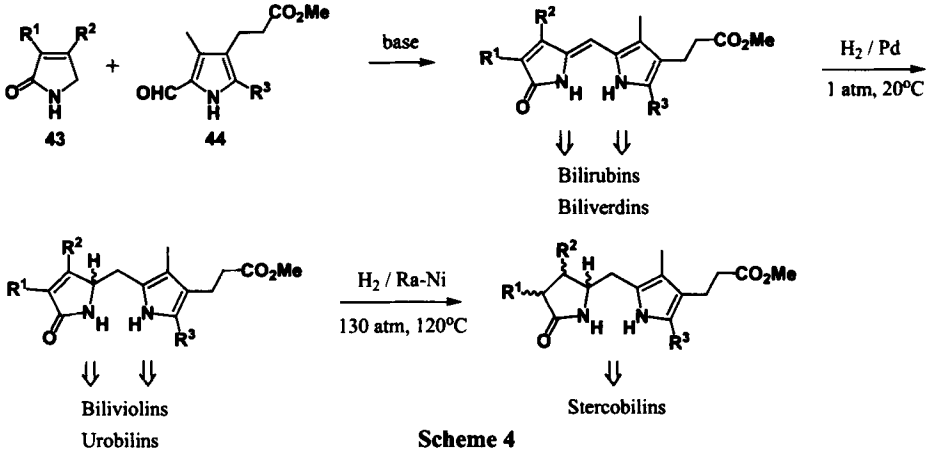


Scheme 3

Subsequently, in 1984, it was shown that the isolation of air- and light-sensitive **28** was not necessary, that the diacid **42** of *Scheme 3* could be used directly in the condensation. It was obtained by saponification of ethyl 3,5-dimethyl-4-(2-ethoxycarbonylethyl)-pyrrole-2-carboxylate (**41**), whose improved synthesis was also described.[47] Careful optimization[48] at each step on the way to **22** and **41** was published in 1990. In particular, after numerous tests of reaction conditions, oxidation and bromination of **22** gave a combined 56% yield of pure bromomethylene-pyrrolinone **39** on a large scale, and diester **41** was readily prepared in 55% yield from ethyl 4-acetyl-5-oxohexanoate (obtained *via* Michael addition of 2,4-pentanedione to ethyl acrylate, 96%) and nitrosated ethyl acetoacetate. More recent syntheses of **41** report that the ethyl acetoacetate can be replaced by diethyl amino- or oximinomalonate with even better yields.[49] The condensation step alone, involving three processes in one pot: selective decarboxylation of the diacid (**42**), electrophilic reaction with **39** and reesterification of the propionic acid, gave a satisfactory 72% yield of **40** on a 10 g scale.[48]

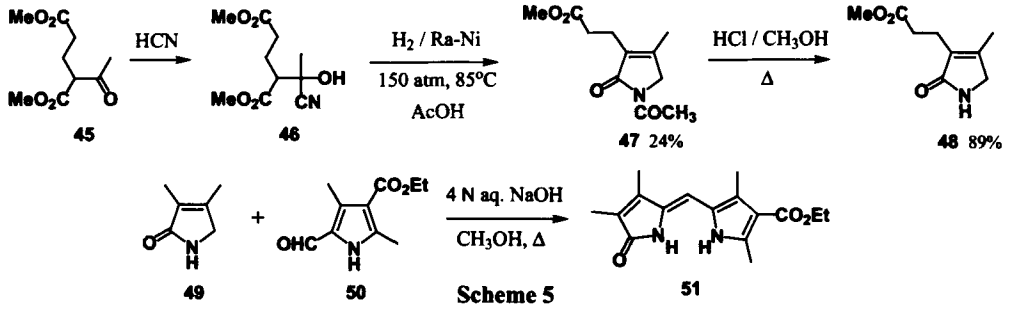
In 1942 Hans Plieninger found that 3-pyrrolin-2-ones (such as **43** but still referred to as hydroxypyrroles) react with aldehydes in alkaline medium by a vinylogous amide deprotonation followed by aldol condensation and dehydration.[40] Natural photoreceptors related to the bile pigments such as phycobilins in cyanobacteria and some algae had been discovered to function as accessory photosynthetic pigments, and phytochrome in green plants responsible for triggering morphological changes,[50] and this rekindled synthetic efforts toward total synthesis of linear tetrapyrroles during 1970s-1980s. Some of the convergent syntheses, reviewed briefly by Albert Gossauer[51] in 1983, greatly benefitted from the base-catalyzed condensation of a 3-

pyrrolin-2-one (**43**) with α-formyl pyrroles (**44**) as illustrated in *Scheme 4*. The formyl pyrroles of *Scheme 4* are readily available by variety of methods (even classical), however, the choice of R^1 and R^2 in pyrrolinones **43** was limited in earlier work.



Scheme 4

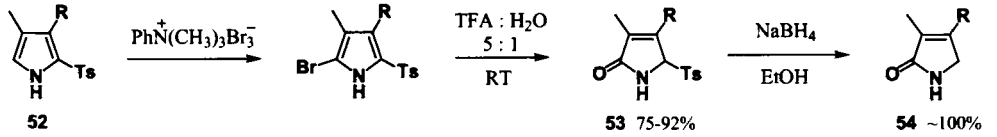
Until 1956, oxidation of α,α'-free pyrroles, similar to **24**, by hydrogen peroxide[52, 53] was problematic when the β,β'-substituents were different because a mixture of isomeric pyrrolinones was generated. Plieninger developed an efficient although inconvenient and potentially hazardous way to obtain pyrrolinones with different β,β'-substituents, as shown in *Scheme 5*.[54] Thus, α-acetylglutaric acid dimethyl ester (**45**) reacted with liquid HCN to give a cyanohydrin (**46**), which was hydrogenated over Raney-nickel catalyst at high pressure and temperature



Scheme 5

to yield an N-acetylpyrrolinone (**47**). Acid-catalyzed saponification led to a valuable pyrrolinone (**48**). Much higher yields were reported from α-methyl- and α-ethyl ethyl acetoacetates leading to 3-methyl (**49**) and 3-ethyl analogs of **48**, respectively. Symmetric **49** was condensed with ethyl 2,4-dimethyl-5-formylpyrrole-3-carboxylate (**50**) in the presence of methanolic-aqueous NaOH (100°C, several minutes) to afford dipyrrinone **51**.[54a] 3-Pyrrolin-2-ones (**43**) could also be accessed by less popular methods, for instance, a modification of the Paal-Knorr synthesis,[55] condensation of an acetaminoketone with cyanoacetate,[56] or by H_2O_2 oxidation of α-formyl-α'-free pyrroles with concomitant loss of formyl group.[57]

Almost 40 years after Plieninger's work, Katsuhiko Inomata and Hideki Kinoshita described an easy and versatile synthesis of 3-pyrrolin-2-ones (**54**) from α-tosyl pyrroles (**52**) in 1993 (*Scheme 6*).[58] Their method takes advantage of then readily available starting α-tosyl pyrroles, which are usually prepared efficiently by a Barton-Zard pyrrole synthesis *via* nitroalkenes[59] using the van Leusen (*p*-tolylsulfonyl)methylisocyanide (TosMIC) chemistry.[60]

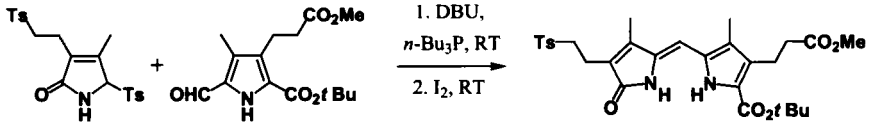


52 **53** 75-92% **54** ~100%

R = CH_2CH_3, CH_2CH_2Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$
Ts = -$SO_2C_6H_4$-*p*CH_3

Scheme 6

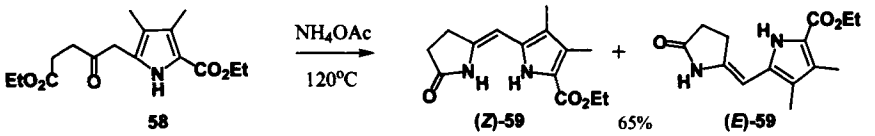
Inspired perhaps by easily-conducted detosylation of **53** by sodium borohydride in ethanol, the authors examined the reactivity of 5-tosylpyrrolinones (**53**) with various nucleophiles and found a facile displacement of tosyl, not only by simple nucleophiles but also by activated methylene compounds with good leaving groups. The last reaction type led to development of a new Wittig-like reaction between 5-tosyl-3-pyrrolin-2-ones such as **55** and aromatic aldehydes including pyrrole aldehydes (*Scheme 7*).[61]



55 **56** **Scheme 7** **57** 73%

The crude condensation product (**57**) consisted of both (4*E*)- and (4*Z*)-dipyrrinones, with the kinetically favored (4*E*) being the dominant product, consistent with reactions of phosphonium ylides. Iodine-promoted isomerization shifted a Z ⇄ *E* equilibrium between the two product isomers toward thermodynamically preferred (4*Z*)-**57**, which was isolated in 73% yield. The 5-tosyl group of **55** is necessary to produce a Wittig-type intermediate with tri-*n*-butylphosphine (Ph_3P did not react), and a strong non-nucleophilic amine like diazabicyclo[5.4.0]undec-7-ene (DBU) is the base of choice. Even from this first communication[61] it was clear that the mild method outlined in *Scheme 7* allows for sensitive groups to reside on the peripheral substituents, and that their potential variations are great since both **55** and **56** have retrosynthetic roots in precursors generated from TosMIC or alkyl isocyanoacetates.[59, 60]

Stereoisomerically homogeneous 2,3-dihydrodipyrrinones (**7**) are not easily available by hydrogenation of **3** (*Fig. 1*). An alternative cyclization of a judiciously-constructed 2-pyrrolyl side chain in **58** to a lactam ring was employed in 1976 using ammonium acetate at high temperature,[62] as is shown for a 2,3-unsubstituted model **59** in *Scheme 8*.

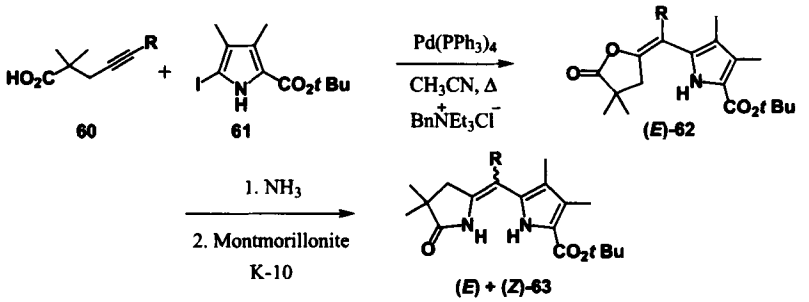


58 (Z)-59 (E)-59

Scheme 8

The structures of both diastereomers (*Z*)-**59** and (*E*)-**59** were determined by X-ray crystallography[62] and complemented an earlier X-ray analysis of 2,3,8-triethyl-7,9-dimethyl-(10*H*)-dipyrrin-1-one,[63] as well as the finding in 1975 by Heinz Falk that photochemical isomerization of (4*Z*)-2,3-dimethyl-(10*H*)-dipyrrin-1-one led to its separable (4*E*)-diastereomer.[64]

The cyclization approach evolved greatly in the following decade in work by Alan Battersby on vitamin B_{12} biosynthesis and by Franz-Peter Montforts on less common natural hydroporphyrins (for comprehensive reviews see ref. 65). This methodology was augmented in 2005 by Peter Jacobi who developed the reaction sequence shown in *Scheme 9* and involving



60 61 (E)-62 (E) + (Z)-63

Scheme 9

Pd(0)-catalyzed coupling-cyclization of alkyne acids **60** with iodopyrrole **61**.[66] Enelactones **62** were converted to 2,3-dihydrodipyrrinones **63** by aminolysis and cyclodehydration. Although precursors **63** are valuable compounds in their own right, they were ultimately carried on to 1-methyl-2,3-dihydrodipyrrin useful for chlorin macrocycle construction.

As indicated above, the syntheses of dipyrrinones span more than 70 years, and the collection of known structures is still growing. A compilation of some dipyrrinones synthesized by the strategies outlined above is presented in the following sections organized by the type of decisive step.

III. FORMATION OF THE DIPYRRINONE FRAMEWORK

1. Acid-catalyzed Condensation

Selected examples[36] of dipyrrinones prepared by acid-catalyzed condensation, as shown in *Scheme 1*, followed by reaction with sodium methoxide or potassium (or silver) acetate and hydrolysis are presented in *Table 1*.

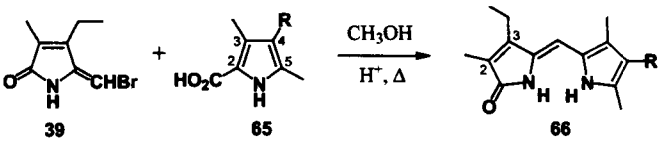
Table 1. Dipyrrinones Synthesized from Dipyrrins

X	R^1	R^2	R^3	R^4	R^5	Reference
Br (CH_3O)	CH_3	CH_2CH_3	CH_3	CH_2CH_3	CH_3	67, 68
CH_3O	CH_3	CH_2CH_3	CH_2CH_3	CH_3	H	69
CH_3O	CH_3	CH_2CH_3	CH_2CH_3	CH_3	CO_2H	69
Br	CH_3	$(CH_2)_2CH_3$	CH_3	$(CH_2)_2CH_3$	CH_3	70
Br	CH_3	Br	CH_3	$COCH_3$	CH_3	71
Br	$(CH_2)_2CO_2H$	CH_3	CH_3	H	CH_3	72
Br	$(CH_2)_2CO_2H$	CH_3	CH_3	$COCH_3$	CH_3	72
Br	CH_3	$(CH_2)_2CO_2H$	CH_3	CH_2CH_3	CH_3	33
Br	CH_3	CH_2CH_3	$(CH_2)_2CO_2H$	CH_3	CH_3	42
Br	CH_2CH_3	CH_3	$(CH_2)_2CO_2H$	CH_3	CH_3	42
Br (CH_3O)	CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2H$ (CH_3)	H	43, 73, 74
Br	CH_2CH_3	CH_3	CH_3	$(CH_2)_2CO_2H$ (CH_3)	H	43, 73
Br (CH_3O)	CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2H$ (CH_3)	CH_3	42, 43, 68
Br	CH_2CH_3	CH_3	CH_3	$(CH_2)_2CO_2H$ (CH_3)	CH_3	42, 43
Br	CH_3	$(CH_2)_2CO_2H$ (CH_3)	CH_3	$(CH_2)_2CO_2H$ (CH_3)	CH_3	68, 71

In the methodology of *Scheme 1*, with an electron-donor α-substituent, 2-methoxy-3-methoxycarbonyl-4-methylpyrrole exhibits good nucleophilic capability at C(5) and reacts under HBr catalysis with a pyrrole aldehyde to give isolatable lactim ether of **3** (*Fig. 1*), which on heating is hydrolyzed (a close parallel to the entries of *Table 1*) to 9-benzyloxycarbonyl-3,8-dimethyl-7-ethyl-2-methoxycarbonyl-(10*H*)-dipyrrin-1-one.[75] Electron-donor activation can be from an easily deprotectable *tert*-butyldimethylsilyloxy group as in **64**, and condensation can be carried out with a Lewis acid in mild conditions as illustrated in *Scheme 10*.[76]

64 **56** **Scheme 10**

Acid-catalyzed condensation of bromomethylene pyrrolinone **39** (*Scheme 2*) with a variety of 3,5-dimethylpyrrole-2-carboxylic acids (**65**, *Table 2*) has been used extensively for syntheses of bilirubin analogs utilized in studies of stereochemistry and metabolism. Stemming from the bilirubin constitutional structure, the C(3) and C(5) substituents of **65** are kept invariant



39 65 66

Table 2. Dipyrrinones Synthesized by Acid Catalyzed Condensation

R	Yield (%)	Reference
H	70	81, 82
CH_3 (7-H)	56	82
CH_3 (9-H)	25	81
CH_2CH_3	64	47, 83, 84
$(CH_2)_2CH_3$	72	85
(*S*)-$CH(CH_3)CH_2CH_3$	71	86
(*S*)-$CH(CH_3)CH_2CH_2F$	59	87
CO_2Me	20	88
$(CH_2)_2CO_2Me$	71	44, 45, 46, 48
$(CH_2)_2CO_2Me$, 11N-Me	65	89
$(CH_2)_2SO_3Na$	59	90
$(CH_2)_nCO_2Me$ n = 1, 3, 4, 5	72, 70, 77, 70	88
$CH_2CH(CH_3)CO_2Me$	55	91
(*R*)-$CH_2CH(CH_3)CO_2Me$	70	92
$CH_2CH(R)CO_2Me$ R = CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, Ph, CH_2Ph	63, 48, 80, 58, 67	93
$CH_2CH(XCH_3)CO_2Me$ X = O, S	49, 64	94
CH_2CHFCO_2Me	74	95
$CH_2C(CH_3)_2CO_2H$ (Me)	72	96
(*S*)-$CH(CH_3)CH_2CO_2Me$	50	97
(*S*)-$CH(CH_3)(CH_2)_nCO_2Me$ n = 2, 3, 4, 5	52, 48, 53, 37	98
($\alpha S,\beta S$)-$CH(CH_3)CH(CH_3)CO_2Me$	51	99
($\alpha R,\beta S$)-$CH(CH_3)CH(CH_3)CO_2Me$	35	99
(*S*)-$CH(CH_3)(CH_2)_2SCH_3$	54	100
o-$C_6H_4CO_2Me$ (H)	(94)	101, 102
m-$C_6H_4CO_2Me$ (H)	75, (98)	102
p-$C_6H_4CO_2H$ (*i*-Bu)	81, (58)	102

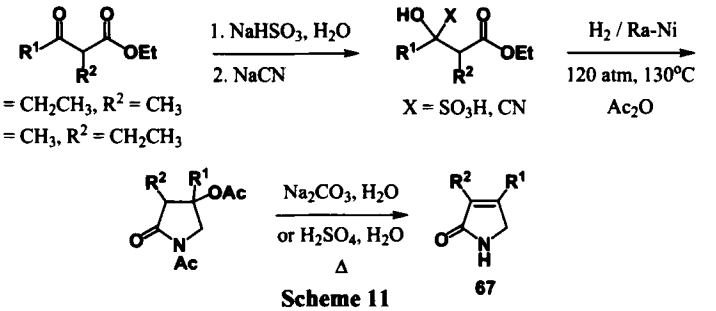
to give C(9)-methyl dipyrrinones, which are readily self-coupled to symmetric biliverdins in the presence of an oxidant.[77,78] Reaction of **39** with **65** (*Table 2*) is not applicable to pyrrole acids containing a second electron-withdrawing group such as an ester, aldehyde, acrylate or even a CF_3 group. In such cases base-catalyzed condensation (*Scheme 5*) or Wittig-type reaction (*Scheme 7*) are the methods of choice. The resulting dipyrrinones **66** differ in the nature of R groups of the pyrrole ring, but the lactam ring is typically 2-methyl-3-ethyl substituted, *Table 2*, although the substitution pattern could in principle be different. However, to the best of our knowledge, other 5-bromomethylene pyrrolinones analogous to **39** have appeared only sporadically in the literature after Hans Fischer.[36] For example, 5-bromomethylene-4-ethoxycarbonyl-3-methyl-3-pyrrolin-2-one reacted with 3,4-dimethylpyrrole to give 3-ethoxycarbonyl-2,7,8-trimethyl-(10*H*)-dipyrrin-1-one (76%).[79] Similarly, 2-(2-acetoxyethyl)-3,8-diethyl-7,9-dimethyl-(10*H*)-dipyrrin-1-one and its 2-*n*-propyl analog have been synthesized via bromomethylene derivatives from H_2O_2 oxidation / bromination sequence on the appropriate α-unsubstituted-α'-methylpyrroles.[80]

In the scheme of *Table 2*, pseudo-xanthobilirubinic acid methyl ester has been synthesized by reaction of **39** with 3-(2-carboxyethyl)-4,5-dimethylpyrrole-2-carboxylic acid.[84] An aldimine formed from α-formyl pyrrole and ethylamine has been condensed with 4-ethyl-3-methyl-3-pyrrolin-2-one in refluxing acetic acid to give a dipyrrinone with both propionic and C(9)-carboxylic acid esters preserved, but the yield is ~50%, which is lower than that from base-catalyzed condensation (see *Table 3*).[103]

2. Base-catalyzed Aldol Condensation

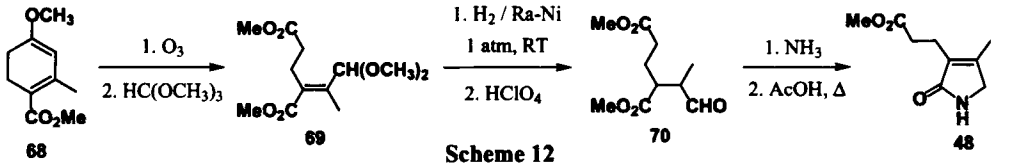
A 3-pyrrolin-2-one heterocycle (**43**) may participate, after vinylogous deprotonation, in an aldol condensation[54,104] with a variety of carbonyl partners, including 2-formylpyrroles (*Scheme 5*). The reaction readily affords a completely conjugated (10*H*)-dipyrrin-1-one framework, a driving force for the dehydration. This type of condensation is presently the most often used reaction for syntheses of dipyrrinones (*Schemes 4* and *5*). Except for the necessary reactive centers: C(5)-CH_2 on the pyrrolinone ring (**43**) and α-formyl on the pyrrole component (such as **44** and **50**), the remaining five positions (and even the nitrogens) can bear alkyl or carbalkoxy groups, thus providing unmatched flexibility for substituent manipulations – before or after the condensation. Starting materials such as those shown in *Scheme 4* are accessible by one of many available synthetic options, thereby increasing the number of routes to dipyrrinones *via* aldol condensation. The requisite 3-pyrrolin-2-ones, when symmetrically substituted at C(3) and C(4), are obtained simply by oxidation of the corresponding pyrroles with H_2O_2 in pyridine[79] as reported, for example, for pyrrole and 1-methylpyrrole[105] and for 3,4-diethylpyrrole.[106] When necessary, unsymmetric 3-pyrrolin-2-ones are often prepared through cyanohydrins (**46**). Improving on his cyanohydrin synthesis[54a] Plieninger prepared[54b] key building

blocks such as 4-ethyl-3-methyl-3-pyrrolin-2-one (**67**, *Scheme 11*), and 3-(2'-carboxyethyl)-4-methyl-3-pyrrolin-2-one (corresponding to **48**). And as discovered later, employing a bisulfite adduct intermediate (*Scheme 11*) avoided the need for large amounts of anhydrous HCN.[107, 108]



Scheme 11

Substantial improvement over the high pressure and temperature hydrogenation of cyanohydrins (**46**) was made by Montforts during his bonellin total synthesis.[109] His approach to the important pyrrolinone **48** was based on selective ozonolysis of dienol ether **68**, producing acetal and propionate chains on a double bond in **69**. After hydrogenation (Raney-Ni, RT, 1 atm), the deprotected aldehyde and ester functions in **70** enabled incorporation of nitrogen as a half-amidal, which was thermally dehydrated and isomerized to pyrrolinone **48**, *Scheme 12*.[109]



68 **69** **70** **48**

Scheme 12

Even more options exist for the preparation of α-formyl pyrroles. To mention a few: Vilsmeier-Haack formylation is widely used on α-H pyrroles as exemplified in the synthesis of 2-formylpyrrole[110] and 2-formyl-1-methylpyrrole;[105] treatment of an α-H or α-*tert*-butoxycarbonyl pyrrole with triethyl (or trimethyl) orthoformate in TFA cleanly formylates[111] the ring; oxidation of an α-methyl to α-formyl group using ceric ammonium nitrate[112] is a recently-developed alternative to the use of lead (IV) tetraacetate as oxidant.[113] Regioselective (up to 4:1)[38,114] Vilsmeier formylation of α,α'-H pyrroles, such as opsopyrrole methyl carboxylate (a propionate analog of **24**), provided the intermediate aldehyde for synthesis of neoxanthobilirubinic acid (9-H XBR).[114]

Selected examples of dipyrrinones synthesized by aldol condensation carried out in typical conditions are presented in *Table 3*.

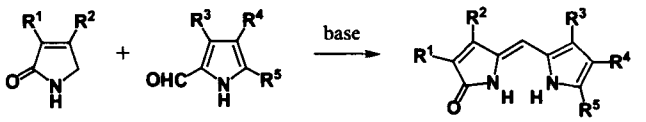


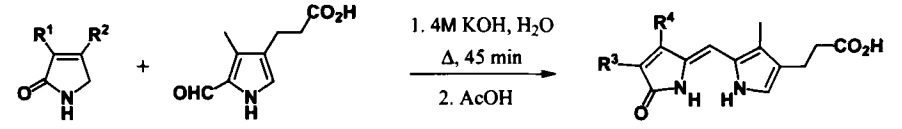
Table 3. Dipyrrinones Synthesized by Base-Catalyzed Condensation

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	H	H	H	H	22	105
(10N-CH_3) H	H	H	H	H	26	105
(11N-CH_3) H	H	H	H	H	25	105
(10,11N,N-diCH_3) H	H	H	H	H	29	105
(10,11N,N-CH_2-) H	H	H	H	H	30	115
CH_3	H	H	H	H	(*E*)+(*Z*) 62	83
CH_3	CH_3	H	H	H	70	64
(10N-CH_3) CH_3	CH_3	H	H	H	(*E*)+(*Z*) 69	116
(11N-CH_3) CH_3	CH_3	H	H	H	67	83
(10,11N,N-diCH_3) CH_3	CH_3	H	H	H	(*E*)+(*Z*) 85	116
CH_3	CH_2CH_3	H	H	H	60	81
CH_2CH_3	CH_2CH_3	H	H	H	66	106
(11N-CH_3) CH_3	CH_2CH_3	H	H	H	85	81
H	H	CH_3	CH_2CH_3	CH_3	59	82
CH_2CH_3	CH_2CH_3	H	H	CH_3	47	82
CH_3	CH_3	CH_3	CH_3	H	91	117,118
(10,11N,N-$(CH_2)_n$) CH_3 n=1,2,3	CH_3	CH_3	CH_3	H	20, 17, 10	119
CH_2CH_3	CH_2CH_3	CH_3	CH_3	H	68	120
CH_2CH_3	CH_2CH_3	CH_2CH_3	CH_2CH_3	H	70	106
(11N-CH_3) CH_3	CH_2CH_3	CH_3	CH_3	H	68	121
(11N-CH_2OBn) CH_3	CH_2CH_3	CH_3	CH_3	H	77	122
CH_3	CH_3	CH_3	H	CH_3	46	123
CH_3	CH_3	CH_3	$(CH_2)_2CO_2H$ (Me)	H	90	124
CH_2CH_3	CH_3	CH_3	$(CH_2)_2CO_2H$	H	44	114
CH_2CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2H$ (Me)	H	88	124
CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2H$	H	93	114
$(CH_2)_2NHCO_2Bn$	CH_3	CH_3	$(CH_2)_2CO_2H$	H	54	125
CH_3	$(CH_2)_2NHCO_2Bn$	CH_3	$(CH_2)_2CO_2H$	H	36	125
$CH{=}CH_2$	CH_3	CH_3	$(CH_2)_2CO_2H$ (Me)	H	36	103, 126
CH_3	$CH{=}CH_2$	CH_3	$(CH_2)_2CO_2H$ (Me)	H	49	103, 126
CH_3	CH_2CH_3	CH_3	$(CH_2)_nCO_2H$ n = 1, 3	H	79, 82	127
CH_3	CH_3	H	H	CHO	60	128a
(10N-CH_3) CH_3	CH_3	H	H	CHO	39	128b

Table 3. Continued...

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
(11N-CH_3) CH_3	CH_3	H	H	CHO	63	128a
(10,11N,N-diCH_3) CH_3	CH_3	H	H	CHO	36	128b
CH_3	CH_3	CH_3	CO_2Et	H	20	120
CH_3	CH_3	H	CH_3	CO_2H	86	123
CH_2CH_3	CH_3	CH_3	H	CO_2H	90	129
$(CH_2)_2CO_2Me$	CH_3	CH_3	H	CO_2t-Bu	89	130
H	CH_3	CH_3	$(CH_2)_2CO_2Me$	CO_2t-Bu	61	131
CH_3	CH_3	CH_3	CH_2CH_3	CH_3	54	78
$CH=CH_2$	CH_3	CH_3	CH_2CH_3	CH_3	27	82
CH_2CH_3	CH_2CH_3	CH_3	CH_2CH_3	CH_3	53	82, 132
CH_2CH_3	CH_2CH_3	CH_2CH_3	CH_2CH_3	CH_3	26	106
CH_3	CH_3	CH_3	CO_2Et	CH_3		54a
CH_3	CH_3	CH_2CH_3	CH_3	CO_2Et	90	114
CH_3	CH_3	CH_3	CH_3	CO_2H (Me)	69	133, 134
CH_3	CH_3	CH_3	CH_3	CO_2t-Bu	88	135, 136
CH_2CH_3	CH_3	CH_3	CH_3	CO_2H (Me)	80	133
CH_2CH_3	CH_3	CH_3	CH_3	CO_2t-Bu	87	135
CH_3	CH_2CH_3	CH_3	CH_3	CO_2t-Bu	84	135
CH_3	CH_3	CH_2CH_3	CH_2CH_3	CO_2H	88	137
CH_2CH_3	CH_3	CH_2CH_3	CH_2CH_3	CO_2H	78	138
CH_3	CH_3	$CH_2C(CH_3)_3$	CH_3	CO_2H	87	139
$(CH_2)_2CO_2H$ (Me)	CH_3	CH_2CH_3	CH_3	CO_2H	84	133
$(CH_2)_2CO_2Me$	CH_3	CH_3	CH_3	CO_2t-Bu	70	140
CH_3	CH_3	CH_3	$(CH_2)_2CO_2H$	CO_2H	84	141
CH_3	CH_3	CH_3	$(CH_2)_3CO_2H$	CO_2H	69	142
CH_2CH_3	CH_3	CH_3	$(CH_2)_2CO_2H$	CO_2H	75	143
CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2H$	CO_2H	94	143
CH_3	CH_3	CH_3	$(CH_2)_2CO_2H$	CO_2t-Bu	70	144
CH_2CH_3	CH_3	CH_3	$(CH_2)_2CO_2Me$	CO_2t-Bu	68, 92	108, 145
CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2Me$	CO_2t-Bu	93	108
CH_3	CH_2CH_3	CH_3	$(CH_2)_nCO_2H$ n=2, 5	CO_2H	85, 92	127, 146
$CH(OH)CH_3$	CH_3	CH_3	$(CH_2)_2CO_2Me$	CO_2t-Bu	25	131
$CH(S(CH_2)_2S)CH_3$	CH_3	CH_3	$(CH_2)_2CO_2Me$	CO_2t-Bu	58	131
$(CH_2)_2OH$	CH_3	CH_3	$(CH_2)_2CO_2Me$	CO_2t-Bu CO_2R *	78	107
$(CH_2)_2OH$	CH_3	CH_3	$(CH_2)_2CO_2R$*	*R**=α-methyl-fenchyl	75	147
CH_3	$(CH_2)_2OH$	CH_3	$(CH_2)_2CO_2Me$	CO_2t-Bu	66	148

Most of the condensation products in *Table 3* were obtained by heating the reactants in 4 M aqueous KOH (or NaOH) with or without CH_3OH (or C_2H_5OH) cosolvent for several minutes to several hours, which indicates that the dipyrrinone skeleton is incredibly robust toward alkali. In some instances, the harshly alkaline conditions of this reaction are incompatible with sensitive functionality, such as leaving groups needed for introduction of a vinyl substituent on side chains. However, as shown in *Scheme 13*, one can take advantage of this fact by conducting the condensation with simultaneous elimination of, *e. g.* trimethylamine.[103,126]

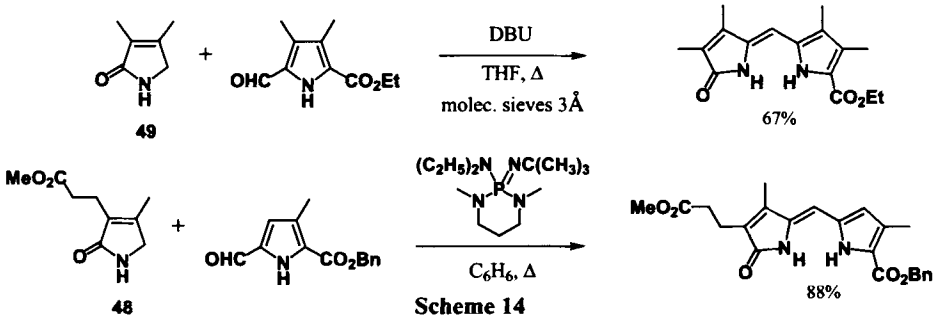


$R^1 = CH_3$, $R^2 = (CH_2)_2N^+(CH_3)_3I^-$
$R^1 = (CH_2)_2N^+(CH_3)_3I^-$, $R^2 = CH_3$

$R^3 = CH_3$, $R^4 = CH{=}CH_2$
$R^3 = CH{=}CH_2$, $R^4 = CH_3$

Scheme 13

Reaction at ambient temperature preserves a *tert*-butyl ester on the pyrrole[108,135,145,149] C(9)-position (R^5 in *Table 3*) but an aliphatic side chain ester is always saponified, with reesterification by diazomethane often being part of the isolation procedure. However, diazomethane can also react with the dipyrrinone lactam group to give a lactim ether,[143] which is usually an unreported side product. Saponification has been avoided in condensations using titanium tetrachloride - pyridine.[107] Alkoxides such as sodium methoxide[108] or potassium *tert*-butoxide[117] under anhydrous conditions have been found to be inferior to methanolic-aqueous KOH. Strong organic bases such as DBU[117] and 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-1,3,2λ⁵-diazaphosphinan[109] have been used more recently, *Scheme 14*.

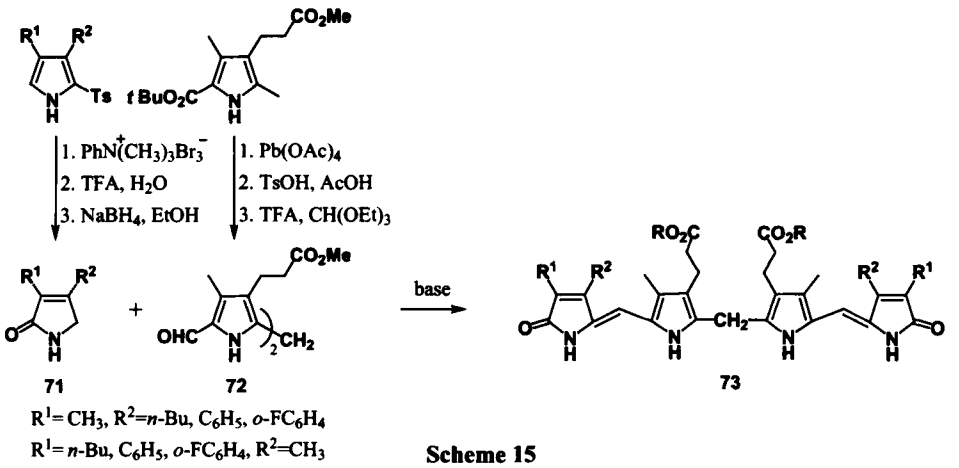


Scheme 14

Condensation of pyrrolinones with 5-bromo-2-(dialkylamino)methylene-2*H*-pyrroles[150] (masked formylpyrroles) in the presence of sodium methoxide in DMSO afforded various 9-bromodipyrrinones in one step.[151]

Piperidine in DMF or alcohols has also been used as a base to synthesize benzodipyrrinones,[152] dipyrrinone analogs with oxindole components,[153] and bilirubin analogs (*Scheme 15*) – the last by double condensation.[154] But with piperidine there is the potential to convert a propionate ester into the corresponding amide. A rarely applied possibility to construct a linear bilirubin-like tetrapyrrole (**73**) is the "1 + 2 + 1" approach[155] where double condensation of

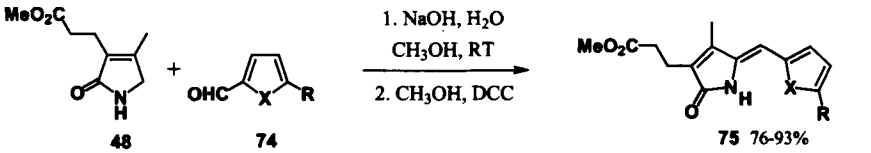
(outer, **71**) pyrrolinone with bifunctional di(5-formyl-2-pyrryl)methane (core, **72**) synthon is carried out, *Scheme 15*. This strategy has been used in the syntheses of carboxyrubin,[156] 10-oxobilirubin,[157] acetylene expanded bilirubins,[158] and various end-ring modified mesobilirubins.[154a,159]



Scheme 15

When the starting formylpyrrole contains a neighboring ester group then, presumably after the condensation to the dipyrrinone, an intramolecular cyclization occurs to afford highly fluorescent pyrrolo[3,2-f]indolizine-4,6-diones – or, depending on the location of formyl and ester moieties, the result is [2,3-f] or [3,4-f] ring fusion.[160,161] The products originate from an attack of a deprotonated lactam nitrogen on a proximally positioned ester carbonyl carbon when the dipyrrinone adopts an *s-anti*-conformation. Such a conformation is accessible at high temperatures, whereas, the preferred conformation of a (4*Z*)-(10*H*)-dipyrrin-1-one is *s-syn* as shown in *Schemes 13* and *14*.

Dipyrrinone-like structures (**75**) with the pyrrole nitrogen (N11) replaced by oxygen or sulfur have been synthesized[140,162] using typical conditions for base-catalyzed condensations involving 2-furaldehyde or 2-formylthiophene (**74**), *Scheme 16*.



Scheme 16

3. Wittig-type Reaction

The reaction provided in *Scheme 7* between a 5-tosyl-3-pyrrolin-2-one (**76**) and an α-formylpyrrole (**77**) in the presence of tri-*n*-butylphosphine and DBU (or *tert*-BuOK) has great potential in dipyrrinone syntheses for two main reasons: (i) very mild reaction conditions that are compatible with multiple functional groups on the dipyrrinone (**78**) periphery, *e. g.* entry 12 of

Table 4 has all pyrrole positions functionalized; and (ii) relatively easy synthetic routes to tosylpyrrolinones (**76**)[58-60,163-165] which can have C(3)-R^1 and C(4)-R^2 substituents of choice. In addition, the reaction directly provides (4*E*)-dipyrrinones that were available previously only by photochemical equilibration of (4*Z*)-diastereomers (**78**). One limitation of this condensation is the necessity to have an electron-withdrawing group, usually an ester on the second α-carbon of the pyrrole component (**77**), *i. e.* when R^3, R^4 and R^5 in *Table 4* (entry one) are all alkyls, the reaction fails. The dipyrrinones synthesized so far by this novel procedure are presented in *Table 4*.

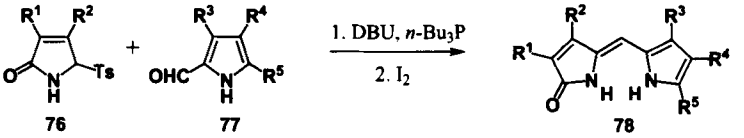
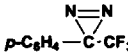
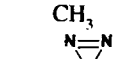


Table 4. Dipyrrinones Synthesized by Wittig-type Reactions

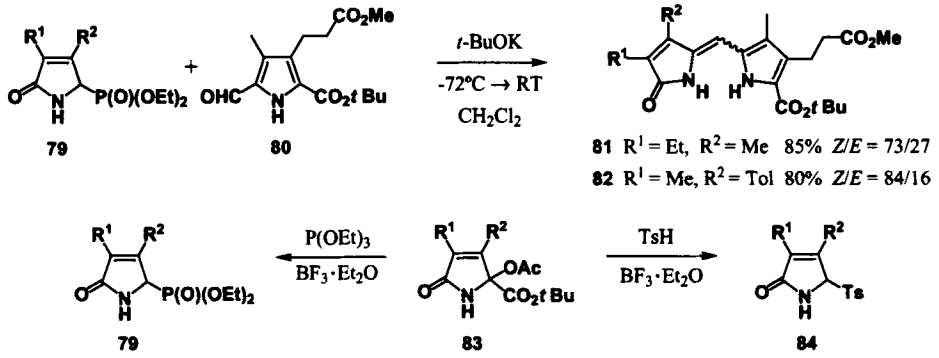
R^1*	R^2*	R^3	R^4*	R^5	Yield (%)	Ref.
CH_3	CH_2CH_3	CH_3	CH_2CH_3	CH_3	6 (*Z*)	166
CH_3	CH_2CH_3	CH_2CH_3	CH_3	CO_2Et	56 (*E*), 6 (*Z*)	166
CH_3	CH_2CH_3	CH_2CO_2Me	CH_3	CO_2Et	47 (*E*), 11 (*Z*)	166
CH_3	CH_2CH_3	$(CH_2)_2CO_2Et$	CH_3	CO_2Et	50 (*E*), 7 (*Z*)	166
CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2Et$	CO_2Et	59 (*E*), 9 (*Z*)	166
CH_2CH_3	CH_3	CH_3	$(CH_2)_2CO_2All$	CO_2t-Bu	88	167
$(CH_2)_2STol$	CH_3	CH_3	$(CH_2)_2CO_2All$	CO_2t-Bu	77	168
CH_3	$(CH_2)_2STol$	CH_3	$(CH_2)_2CO_2All$	CO_2t-Bu	80	168
CH_3	$CH(OCH_3)CH_3$	CH_3	$(CH_2)_2CO_2All$	CO_2t-Bu	24 (*E*), 60 (*Z*)	165, 169
$(CH_2)_2Ts$	CH_3	CH_3	$(CH_2)_2CO_2Me$	CO_2t-Bu	73	61, 170
CH_3	$CH(Ts)CH_3$	CH_3	$(CH_2)_2CO_2All$	CO_2t-Bu	29 (*E*), 44 (*Z*)	165, 169
CH_2CH_3	CH_3	$(CH_2)_2Cl$	$(CH_2)_2CO_2All$	CO_2t-Bu	80	171
	CH_3	CH_3	$(CH_2)_2CO_2All$	CO_2t-Bu	87	165, 172
CH_3		CH_3	$(CH_2)_2CO_2All$	CO_2t-Bu	73	172

* All = CH_2=$CHCH_2$-; Tol = *p*-$CH_3C_6H_4$-; Ts = *p*-$CH_3C_6H_4SO_2$-.

Consistent with the suggestion by Inomata,[61,170] the (4*E*)-isomer of dipyrrinones prepared by a Wittig-type reaction is the kinetic product (80-90% stereoselectivity), and it was isolated as a stable compound when treatment with iodine was omitted.[166]

The last two entries in *Table 4* have incorporated a photoreactive diazirine group, potentially useful in investigations of the structural relationship between the chromophore (**12**) and the apoprotein in both P_r and P_{fr} forms of reconstructed phytochrome.[172] Other dipyrrinones (**78**) of *Table 4* are allyl-protected esters suitable for total synthesis of phytochromobilin.[168,170] The total synthesis of its dimethyl ester[173] was reported earlier by Gossauer, but the diester was not converted to the diacid **12**.

In a similar fashion, a Horner-Emmons variant of coupling between a 5-diethylphosphono-3-pyrrolin-2-one (**79**) and an α-formylpyrrole (**80**) has been applied to the synthsis of dipyrrinones **81** and **82** (*Scheme 17*).[174]



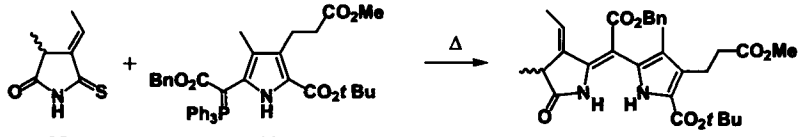
79 80 83 84

Scheme 17

The pyrrolinones of type **79** are available by bromination/hydrolysis[58] (as in *Scheme 6*) of the corresponding 2-pyrrolylphosphonates which, in turn came from phase-transfer catalyzed cyclization of nitroalkenes with diethyl isocyanomethylphosphonate[175] (in parallel to Barton-Zard's use of isocyanoacetates[59]). Both useful synthons: tosylpyrrolinones like **84** (or **53** and **55** in *Schemes 6* and *7*) and (diethylphosphono)pyrrolinones like **79** (in *Scheme 17*) can be obtained also from a common precursor – 5-acetoxy-5-*tert*-butoxycarbonyl-3-pyrrolin-2-ones (**83**)[165] which are products of lead tetraacetate oxidation of the corresponding 2-iodopyrroles. It appears that dipyrrinone syntheses using 5-tosylpyrrolinones (**84**) have superseded those with 5-phosphonopyrrolinones (**79**) probably due to the synthetic availability of their acyclic precursors: TosMIC[157,176] *vs* diethyl isocyanomethylphosphonate.[177]

Methodologically new in 1978, the thio-Wittig reaction was introduced by Gossauer in syntheses of intermediates such as 3-ethylidene-5-substituted-2,3-dihydro-(10*H*)-dipyrrin-1-one (**87**), for phycocyanobilin (**13** in *Fig. 2*) dimethyl ester,[178-180] phytochromobilin (**12**), and "iso"-phytochromobilin diacids[181] preparations.

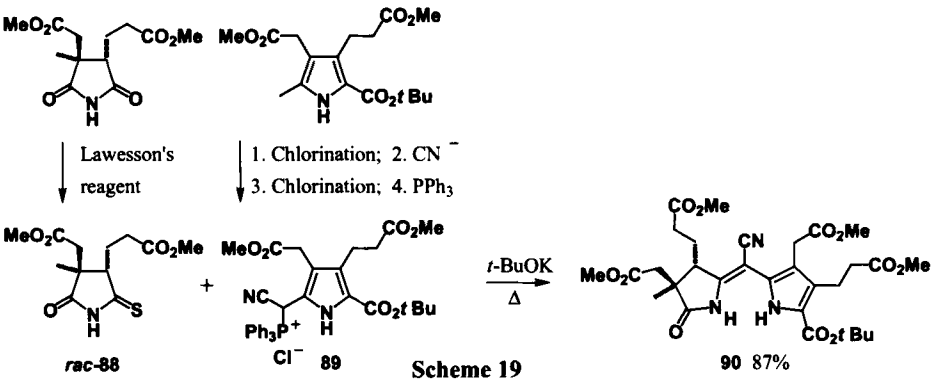
A thermal reaction of a stabilized ylide **86** with monothiosuccinimide **85** affording **87**, *Scheme 18*, was studied by Henry Rapoport[182] in great experimental and theoretical details. The



85 86 87 79%

Scheme 18

thioimides are accessible from selective thionation of succinimides or, better, from succinimidines;[178] whereas, the ylides are usually obtained from bromomethylpyrrole derivatives (some of them are very unstable), or generated *in situ* from phosphonium salts (*Scheme 19*).[183]



Scheme 19

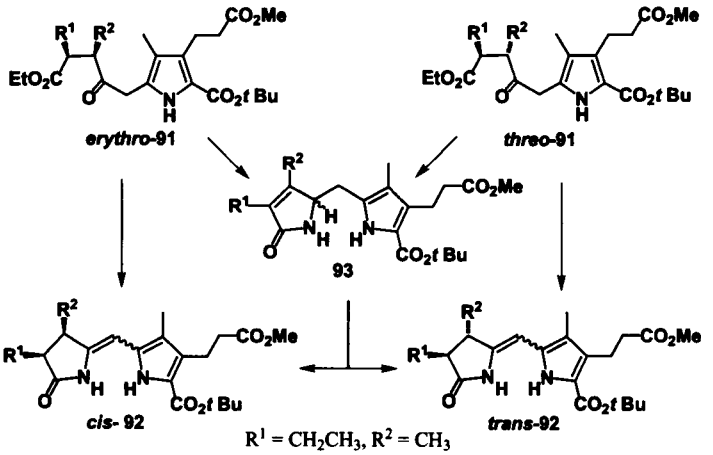
A disadvantage of the thio-Wittig reaction is the necessary presence of an ylide-stabilizing group, such as the benzyl ester in **86** or the cyano group in **89**, thus requiring additional steps for its removal. For example, formylation[111] (TFA / $CH(OC_2H_5)_3$) of **87** followed by benzyl ester hydrogenolysis furnishes 5-carboxy-9-formyl-dipyrrinone which is coupled with methyl isoneoxanthobilirubinate (*Table 3*).[114] The resulting tetrapyrrole is decarboxylated at C(5) in TFA to give racemic phycocyanobilin (**13**) dimethyl ester.[178] Since the auxiliary group at C(5) of **87** and its analogs is lost at later stages, the configuration of C(4)-C(5) exocyclic double bond is usually not determined, although in later work Battersby assigned the (*E*)-configuration (as indicated in *Scheme 19*) for the 3,3-dimethyl-2-unsubstituted analog of **87**.[184] Racemic[131] and optically active[147] phycoerythrobilin (**14**, *Figure 2*) dimethyl ester diastereomers have been obtained by total synthesis using the C(5)-carboxy analog of **87**, where both 5-carboxy and 9-*tert*-butoxycarbonyl groups are decarboxylated in the neat TFA used to achieve condensation of two different dipyrrinones to tetrapyrrole. A variety of substituents on C(2) and C(3) of the thioimide **85** and *bis*-allyl protection in **86** have been used recently in this thio-Wittig approach to synthesize phycocyanobilins for structure-function analysis.[185]

More elaborate transformation of the cyano group in **90** into methyl is necessary to achieve total synthesis of C-methylated isobacteriochlorins[184] or altogether elimination of one carbon fragment (aminomethyl *via* retro-Mannich reaction)[186] to reach Faktor I[183] and Faktor II (sirohydrochlorin) *via* a regioisomeric to **88** thioimide.[187]

4. Lactam Ring Formation

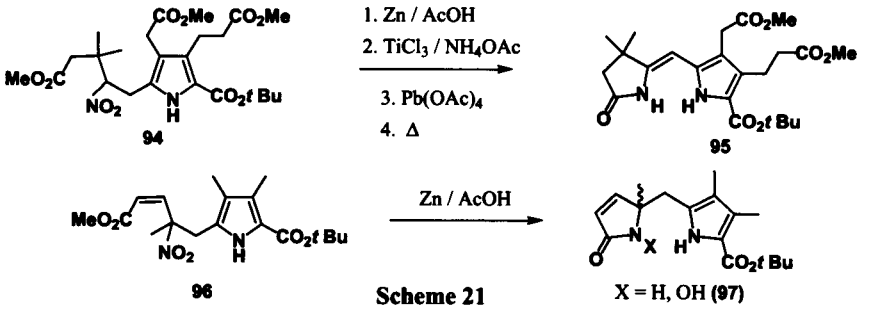
Cyclization of an open chain substituent at 2-pyrrolyl position to form a dipyrrinone lactam ring is an approach almost 30 years old, but it has only recently become a viable methodology. Earlier cyclizations of separated racemic *erythro*-**91** and *threo*-**91** in molten ammonium

acetate to give (*Z*)- and (*E*)-2,3-dihydrodipyrrinones **92** occurred with varying stereospecificity depending on the substrate structure and were accompanied by formation of 4,5-dihydro regio-isomers **93**, *Scheme 20*.[145,188]



Scheme 20

Since isomerically pure *cis*- and *trans*-**92** can be obtained in some instances more easily by catalytic hydrogenation of the dipyrrinone (see *Section IV-2*), or by the modern cyclization method (see for instance *Scheme 22*), the route of *Scheme 20* is not of synthetic significance. However, model compounds have been prepared efficiently by a reductive cyclization of γ-nitroesters (**94**, **96**) using first Zn-AcOH, then $TiCl_3$, *Scheme 21*.[189-192] Battersby in particular has made elegant use of this strategy in a number of chlorin and isobacteriochlorin syntheses, as well as in studies on vitamin B_{12} biosynthesis using intermediates such as **95**.[192-194]

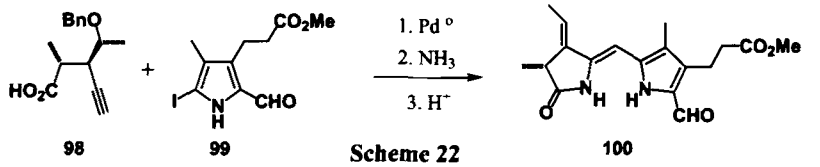


Scheme 21

Cyclization in the absence of $TiCl_3$, yields a hydroxamic acid (**97**) rather than a lactam (*Scheme 21*). Resolution of the hydroxamic acid into enantiomers and determination of the absolute configuration by X-ray analysis correlated the helicity of the corresponding urobilin chromophore with chiroptical data.[195]

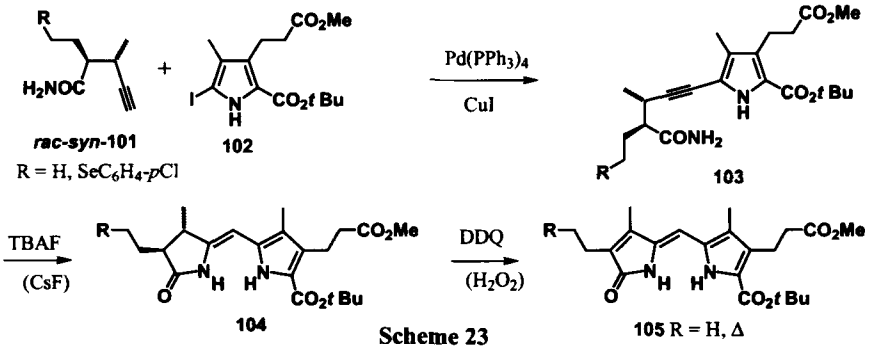
A versatile regio- and stereoselective synthesis that accomodates a wide variety of pyrrole- and meso-substituents and can be adapted to prepare homochiral 2,3-dihydrodipyrrins

and 2,3-dihydro-(10*H*)-dipyrrin-1-ones similar to **63** has been developed by Jacobi.[66,196] The key step in this synthesis (*Scheme 9*) is a cascade of the Pd°-catalyzed Sonogashira coupling between a β-acetylenic acid similar to **60** (amides are inert[197]) and an α-iodopyrrole like **61**, followed by cyclization to enelactones (**62**) that are aminolyzed and re-cyclized. The acids (**60**) of *Scheme 9* need not have terminal alkynes, and substituents ranging from H, Me, $(CH_2)_nCH_3$ n = 4,9 to Ph have been used in synthesis of lactones **62**, thereby allowing variations at the future C(5) dipyrrinone meso-position (R in **63**).[66] When the two-carbon unit connecting alkyne and acid functions incorporates stereogenic centers as in **98**, the Pd°-initiated coupling-cyclization between **98** and iodopyrrole **99** is stereospecific and is reported to lead ultimately to the homochiral, natural (2*R*)-phytochromobilin (**12**) dimethyl ester[198] *via* the dipyrrinone synthon (**100**, *Scheme 22*). ^{13}C-Labels at the meso-carbons C(5), C(10) and C(15) may also be incorporated by the same reaction sequence.



98 **99** **Scheme 22** **100**

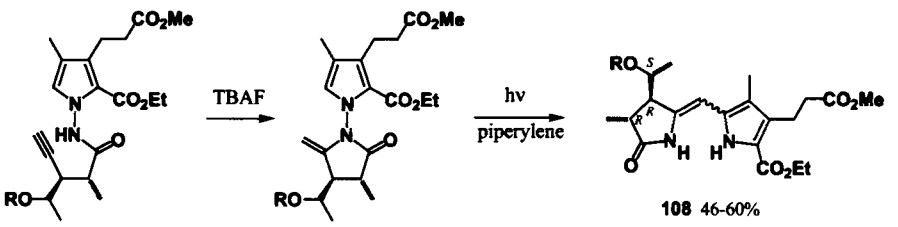
A two step process utilizing racemic or optically pure *syn*-β-alkyne carboxamides (**101**) in a Sonogashira coupling with **102** followed by fluoride ion promoted cyclization of **103** has provided suitable dipyrrinone (**104**, **105**) building blocks[76,199] (*Scheme 23*) for construction of phytochrome and phycocyanine.



***rac-syn*-101** R = H, SeC_6H_4-*p*Cl **102** **103**

104 **Scheme 23** **105** R = H, Δ

Homochiral acetylenic acids (**98**) were used in earlier work by Jacobi to acylate an N-aminopyrrole[200] and then, the resulting N-(1-pyrrolyl)-amide **106** was cyclized with fluoride ion catalysis to enamide **107**, *Scheme 24*.[201] A next (key) step involved photochemical 3,5-sigmatropic rearrangement of the enamide **107** under triplet quenching conditions to afford a 1:1 mixture of (*Z*) - (*E*) (2*R*, 3*R*, 3'*S*)-dihydrodipyrrinones **108**. The reaction sequence of *Scheme 24* is a representative example extrapolated from numerous achiral and enantiomerically pure model compounds obtained with rigorous control over both relative and absolute stereochemistry.[201]

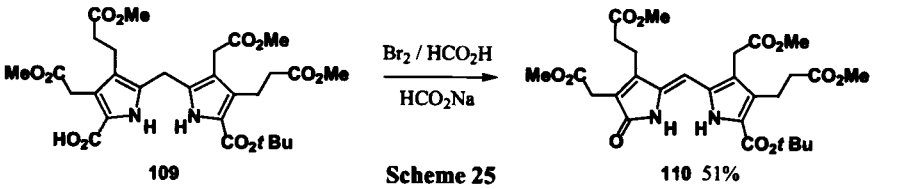


106 107 **Scheme 24**

The finding of catalytic fluoride ion activity in the cyclization (*Scheme 24*) of an unactivated alkyne (**106**) (previously only acetylenic esters had been used[202]) prompted an examination of n-$Bu_4N^+F^-$ catalyst. This performed very well on preformed 2-pyrrolylacetylenes containing terminal amides (such as **103** in *Scheme 23*), thus eliminating[199,203] the need for the photochemical rearrangement of *Scheme 24*. Prior to a CsF[204] promoted cyclization, oxidation-elimination of R = p-ClC_6H_4Se introduced a C(2)-vinyl group in **105** of *Scheme 23*.[76] Or after cyclization catalyzed by TBAF, the absolute configuration at C(3') in an analog of **108** was inverted using a thia-Mitsunobu reaction.[199] Similarly after the cyclization, C(2)–C(3) unsaturation was achieved by oxidation using DDQ.[76,205] The methodology outlined in *Scheme 23* has been applied to synthesizing a novel 1,9-diiododipyrrin that serves as the central core of linear tetrapyrroles related to phytochrome. Both outer lactam rings were built enantiospecifically by Pd°-coupling and TBAF-cyclization, a sequence that was executed either simultaneously (to give symmetric) or sequentially (to give unsymmetric) tetrapyrroles.[206]

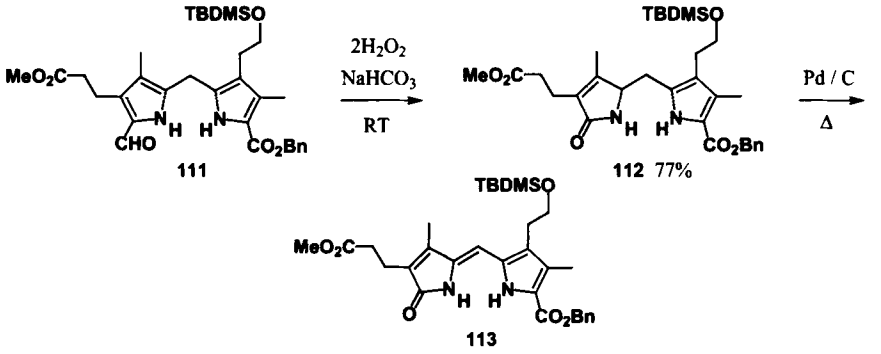
5. Miscellaneous Reactions

Oxidations of dipyrrylmethanes **4** (*Fig. 1*) directly to dipyrrinones **3** are rare; nevertheless, some examples of synthetic value are found in Battersby's extensive work. 1-Carboxydipyrrylmethane (**109**) was converted by mild oxidative bromination and hydrolysis into a dipyrrinone **110**, while retaining a *tert*-butyl ester (*Scheme 25*).[183b,193a,207] This oxidation-bromination-hydrolysis pathway resembles the very early[42,68] pyrrole synthetic chemistry, as illustrated in the conversion of **37** into **38** in *Scheme 1*, and is found more recently in bilin-1,19-dione (biliverdin, **15**) syntheses involving decarboxylative bromination-hydrolysis.[208] Oxidation of an 5-ethoxycarbonyl-5'-free dipyrrylmethane with H_2O_2 - pyridine led to 4,5-dihydrodipyrrinone; whereas, MnO_2 oxidized further to a 10*H*-dipyrrin-1-one.[79]



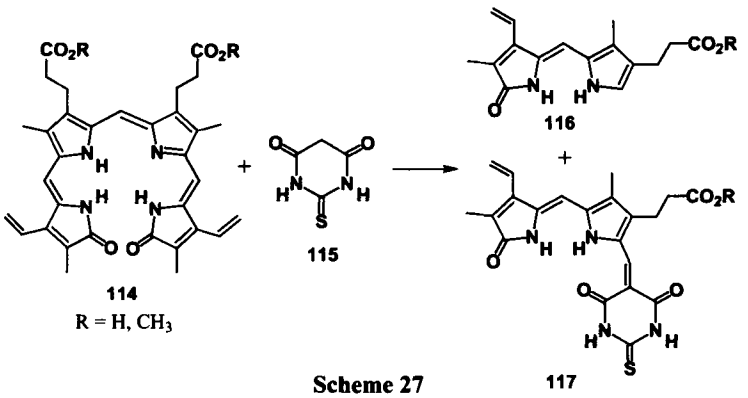
109 **Scheme 25** 110 51%

Oxidation of 1-formyl-9-alkoxycarbonyldipyrrylmethanes (**111**) with hydrogen peroxide under controlled buffered conditions (*Scheme 26*) led to good yields of 4,5-dihydrodipyrrinones (**112**),[209] which could be further thermally dehydrogenated to **113**. Also under H_2O_2 / $NaHCO_3$ oxidation conditions, α-formyl monopyrroles (**44**, R^3 = H) afforded the corresponding useful 3-pyrrolin-2-ones (**43**) by concomitant loss of the formyl group.[57,209] Unfortunately, neither the dehydrogenation procedure[210] nor follow-up references to such monopyrrole oxidations were reported subsequently.



Scheme 26

Paolo Manitto and Diego Monti found a spontaneous fragmentation of synthetic biliverdin-XIIIα (**114**) and its dimethyl ester on treatment with thiobarbituric acid (**115**).[211] Both verdins afforded 3-vinyl-neoxanthobilirubinic acid **116** or its methyl ester and a violet dipyrrinone adduct with thiobarbituric acid (**117**), *Scheme 27*. Natural biliverdin-IXα (**15** in *Fig. 2*) gave a 1:1 mixture of **116** and its exo-vinyl regioisomer.

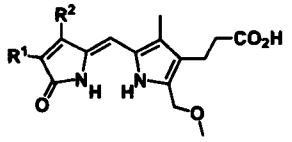


Scheme 27

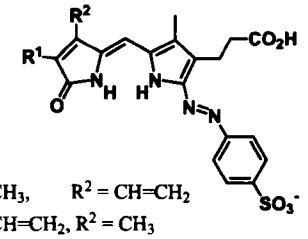
Symmetric verdins similar to **114** are often prepared synthetically by oxidative self-coupling of a methyl xanthobilirubinate (9-CH_3, as in **40**).[77,78] Since the verdin **114** gives only one equivalent of methyl neoxanthobilirubinate (9-H in **116**) or the corresponding acid, and the second equivalent is lost as a covalent adduct with thiobarbituric acid (**117**), the verdin cleavage reaction of Manitto and Monti might be viewed as an inefficient way to remove the C(9)-methyl

from xanthobilirubinates such as **40**. Yet, the reaction provided straightforward and rapid access to chromatographically separable 2-(and 3-)vinyl-neoxanthobilirubinic acids and their esters (**116**)[181,212] from a natural source – and methyl neoxanthobilirubinate[213] from mesobiliverdin-XIIIα dimethyl ester.

The classical diazo-reaction[214] of bilirubin (**16**, *Fig. 2*) also proceeds with cleavage of a tetrapyrrole at its central methylene bridge, and it affords yellow 9-methoxymethyl-dipyrrinones (**118**, **119**) and violet 9-azo derivatives (**120**, **121**).[215] The latter have practical uses in clinical chemistry for qualitative and quantitative determination of bilirubin in body fluids.[214c]

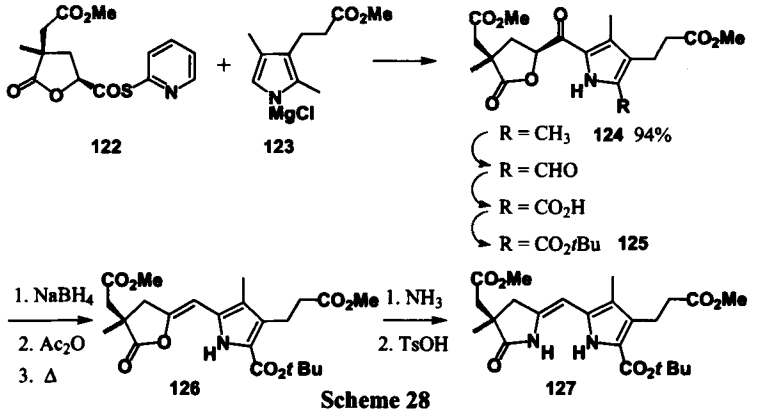


118 $R^1 = CH_3$, $R^2 = CH{=}CH_2$
119 $R^1 = CH{=}CH_2$, $R^2 = CH_3$



120 $R^1 = CH_3$, $R^2 = CH{=}CH_2$
121 $R^1 = CH{=}CH_2$, $R^2 = CH_3$

In interrelated synthetic efforts toward naturally-occurring, partially saturated porphyrins, Battersby often relied on the thio-Wittig reaction to obtain dipyrrinones such as **90** of firmly established absolute configuration at C(2) and C(3).[216] In certain cases, however, he characterized the tailoring of the initial products of type **88** as "experimentally very demanding"; therefore, a novel approach to optically active 2,3-dihydrodipyrrinones (**127**) was developed during the total synthesis of haem d_1 of 3,8-dioxoisobacteriochlorin type. The novelty lies in an one-step attachment of the lactam ring to be and its C(5) carbon to an α-free pyrrole-Grignard (**123**) by acylation using the soft S-pyridyl thioester of a γ-carboxy-γ-lactone (**122**), *Scheme 28*.[217] The resulting ketolactone **124** is further elaborated in three stages: (i)

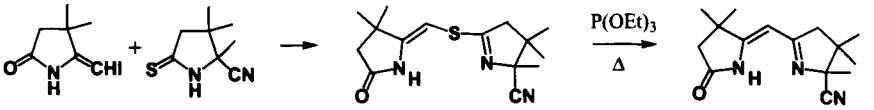


Scheme 28

conversion of 9-CH_3 in **124** to a 9-CO_2t-Bu ester intermediate (**125**); (ii) removal of the keto group to give enelactone **126**, and (iii) conversion of the lactone into a lactam ring in **127**. The same reaction sequence has been applied to regioisomeric of **122** thioester with a quaternary β-

stereogenic center, and the resulting dipyrrinone has been coupled with **127** to afford (after photochemical macrocyclization and oxidation) the natural product with correct absolute configuration.[218]

Albert Eschenmoser's famous sulfide contraction method, designed during the total synthesis of vitamin B_{12}, is undoubtedly one of the greatest achievements of synthetic organic chemistry.[219,220] It has usually been applied to more complex systems of lower oxidation state than dipyrrinones. An outline of this method as applied to model system is shown in *Scheme 29*.[221]

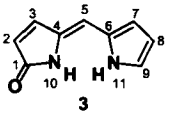


Scheme 29

IV. MODIFICATION OF SUBSTITUENTS

1. Electrophilic Reactions on Dipyrrinones

Pyrrole is classified as a π-excessive heteroaromatic compound, and this character is retained within the dipyrrinone **3** (*Fig. 1*) framework.



3

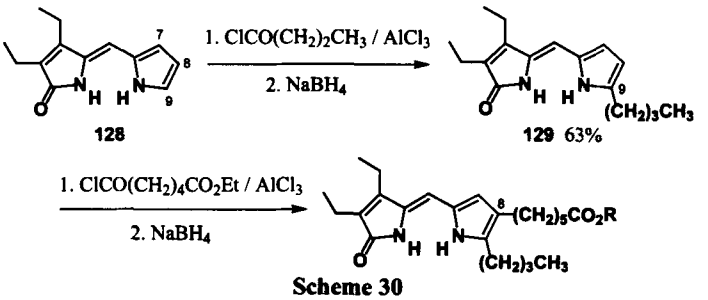
All positions of the entire π-rich dipyrrinone are susceptible to electrophilic attack but in the majority of literature examples electrophilic attack occurs at an unsubstituted pyrrole site. Electrochemical oxidation of various dipyrrinones has been studied, and, as expected, the lower oxidation potential corresponds to the higher degree of alkylation.[81,222] Oxidative dimerization of an C(9)-unsubstituted dipyrrinone, similar to **116**, has been reported to give *b-nor*-biladiene-*ac* and *b-nor*-bilatriene-*abc* framework.[223] In the absence of unsubstituted pyrrole positions, 2,3-dihydrodipyrrinones (**7** in *Fig. 1*) are more easily attacked by electrophiles (D^+, $(CH_3)_2N^+CH_2$) at the C(5)-position than is the parent dipyrrinone **3**, but nucleophiles react at C(4).[224,225]

Bromination is probably the oldest reported electrophilic reaction of dipyrrinones. Bromine is highly reactive towards both the dipyrrinone skeletal core[133] and its side chains,[226] but conditions have also been found for: (1) bromination[227] and nitration[228] at the C(5) carbon when all other carbons are substituted; or (2) selective bromination at C(9) in favor of bromination at C(7) or C(8).

Both nitrogens of dipyrrinones can be methylated[83,122,229] using dimethyl sulfate, following deprotonation, but reaction with trimethyloxonium tetrafluoroborate affords lactim ethers (1-methoxy derivatives of **1**, *Fig. 1*).[230] Electrophilic C-alkylations[231] are usually not carried out on dipyrrinones because short chain alkyls can be incorporated easily in the early stages of the pigments' classical (*Scheme 1*) or modern (*Scheme 2* and *4*) syntheses. A Mannich reaction on methyl 3-vinyl-*neo*-xanthobilirubinate (**116**) using formaldehyde and dimethylamine

has been reported.[126] In contrast, electrophilic acylation is common in dipyrrinone chemistry, usually employing Lewis acid-catalyzed Friedel-Crafts reaction of polysubstituted **3** (*Fig. 1*) derivatives with acyl chlorides.

Aliphatic acid chlorides are suitable for introduction of long C_{11} – C_{20} hydrocarbon chains by Friedel-Crafts reaction on **3** and subsequent borane reduction of the initially obtained ketone.[232-234] The *ortho*-effect from C(7) and C(9) methyl groups does not inhibit the Friedel-Crafts reaction at sterically hindered C(8) of **3** with ω-chloroacyl chlorides.[235] Aromatic acid chlorides are also reactive in Friedel-Crafts acylations of dipyrrinones.[231] Both aluminum chloride[232,236,237] and tin (IV) chloride[233] catalysts (boron trifluoride might complex strongly with both nitrogens of **3**) perform well, but in some instances $SnCl_4$ is superior.[231,234] If several substitution sites are available, for example in **128**, then the favored attack is at C(9) to give **129** as illustrated in *Scheme 30* for two regioselective acylations.[238] In the presence of TFA at reflux an intramolecular acylation at C(9) occurred in a dipyrrinone bearing methyl C(8)-butyrate.[236]

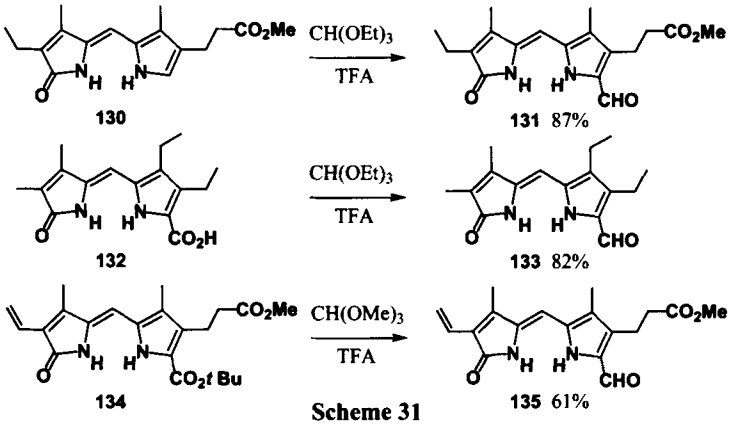


Scheme 30

Driven by the electron-rich systems, numerous condensations of C(9)-unsubstituted dipyrrinones such as **116** and **130** with mono-[239,240] or dipyrrolic [103,122,123,125,131,147,165,178,241-247] aldehydes (frequently 9-formyldipyrrinones, *e. g.* **131, 133, 135**) or solvolyzed α-acetoxymethyl pyrroles[138] have led to linear oligopyrroles. Double condensations of 2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one with 2,5-dimethoxy-2,5-dihydrofuran (a masked dialdehyde),[248] glyoxal,[136] benzene dialdehydes,[249] or 3,4-dimethyl-2,5-(1*H*)-pyrroledialdehyde[250] gave *b*-elongated verdin chromophores.

The Vilsmeier-Haack formylation procedure provides a most effective synthesis of formylpyrroles and indoles. Electrophilic reaction of the parent heterocycles with an immonium cation derived from dimethylformamide or N-methylformanilide with an acid chloride such as phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride, benzoyl chloride or bromotriphenylphosphonium bromide yields as an intermediate heteroarylimmonium salt which under suitable conditions could be isolated.[242] Alkaline hydrolysis of the immonium salt affords formyl derivatives. However in recent modern research these classical conditions have rarely been applied to dipyrrinones,[125,210] after Peter Clezy[111] showed that triethyl (or trimethyl) orthoformate in the presence of TFA is a very effective formylation agent for pyrroles. Soon

thereafter[179] this reaction was applied to dipyrrinones, usually unsubstituted at C(9), **130** in *Scheme 31*.[83,122,123,251,252]



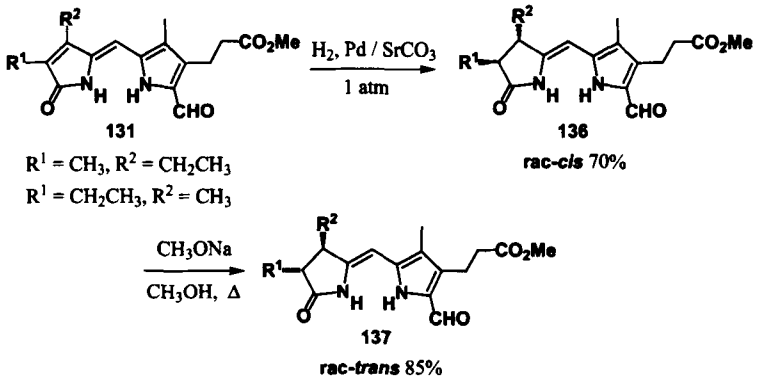
Scheme 31

The reaction is equally applicable to C(9)-acids such as **132**[236] and their *tert*-butyl esters (**134**) which deprotect and decarboxylate *in situ*,[107,140,148,173,178] *Scheme 31*. A 9-(α-methylfenchyl) ester of 4,5-dihydrodipyrrinone behaves like a *tert*-butyl ester and is transformed directly into formyl group using $CH(OCH_3)_3$ - TFA.[147] When given a choice, the $CH(OR_3)_3$ - TFA formylation method is regioselective at the α-pyrrolic carbon *vs* β-pyrrolic position.[129] A vinylogous Vilsmeier formylation[253] using 3-dimethylaminoacrolein has been applied to a C(9)-free dipyrrinone.[254]

2. Hydrogenation

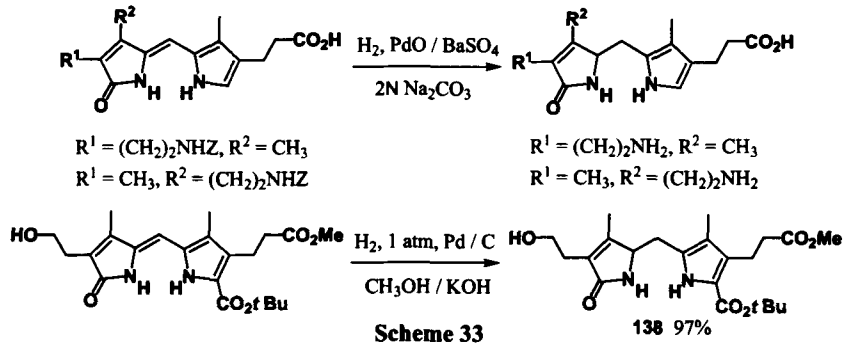
Partial selective reduction of the most unsaturated dipyrrin (**1** of *Fig. 1*) system to dihydro and tetrahydro derivatives has been used frequently as a valuable entry into urobilins, stercobilins, bilirhodins, and phycoerythrobilins (*Fig. 2*) since the more stable starting 10*H*-dipyrrin-1-ones are easier to synthesize. The mildest conditions for a catalytic hydrogenation (1 atm H_2, Pd/C, RT) usually afford a mixture of products reduced at C(2)-C(3) (**7**) and at the exocyclic C(4)-C(5) double bond (**6**) as well as tetrahydro material (**8**).[135] The initially isolated major 2,3-dihydro derivative is with 2,3-*cis* relative configuration (**136**)[255] which can be converted quantitatively and irreversibly with base into the 2,3-*trans* isomer (**137**). Similar hydrogenation (Pd/C) on the parent unsubstituted (*E*) or (*Z*)-dipyrrinones proceeded preferentially at C(2)-C(3) double bond without C(4) isomerization.[256] Much higher yields and better selectivity for *cis*-2,3-dihydro products (**136**) is observed when using $Pd/SrCO_3$,[103,257] $Pd/CaCO_3$,[148] or $PdCl_2/SrCO_3$,[108] *Scheme 32*.

By using $Pd/BaSO_4$[114,143,145] under normal conditions or, even better, in alkaline solution the catalytic hydrogenation (Pd/C,[107,129,131,135,147] $Pd/BaSO_4$[125]) of 10*H*-dipyrrin-1-ones results in strongly preferential C(4)-C(5) saturation, *Scheme 33*. The so-obtained 4,5-dihydro derivatives (analogs of **138**) isomerize in the presence of base to *trans*-2,3-dihydro-(10*H*)-dipyrrin-1-ones.[135]



Scheme 32

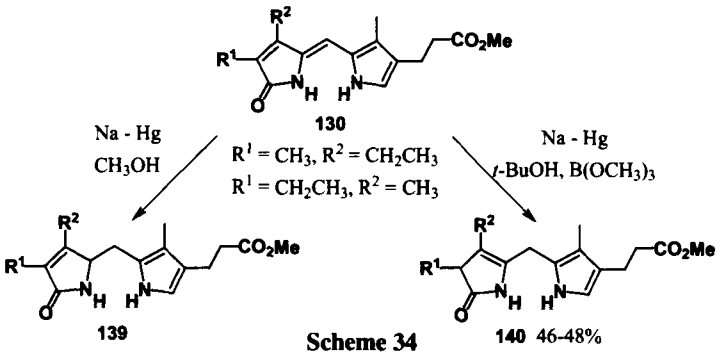
Hydrogenation using Raney-Ni under forcing conditions (130 atm H_2 and 120°C) affords 2,3,4,5-tetrahydro-(10*H*)-dipyrrin-1-ones (**8** in *Fig. 1*),[114,143] which can be isomerized from the kinetically obtained 2,3-*cis* into 2,3-*trans* diastereomers in the presence of base. Such compounds contain three contiguous stereogenic centers, posing a challenge in purifying a homogeneous diastereomer.



Scheme 33

Very mild conditions are necessary to reduce dipyrrinones (**130**) chemically with sodium amalgam and alcohol to give **139** – a historically important reducing system in bile pigment chemistry. Moderate to high yields of 2,5-dihydro derivatives (**140**) have been reported using buffered conditions, *Scheme 34*.[103,131,243,257] These compounds are stable but isomerize to 2,3-dihydrodipyrrinones in the presence of $TiCl_4$ which simultaneously can catalyze C(9) formylation with $CH(OCH_3)_3$ to give **137**,[103] or to a 4,5-dihydro isomer (**139**) in the presence of CH_3ONa.[131] In presence of base, however, the sodium amalgam - water system reduces selectively the exocyclic C(4)-C(5) double bond of 9-carboxy-xanthobilirubinic acid and its 2-ethyl regioisomer.[241]

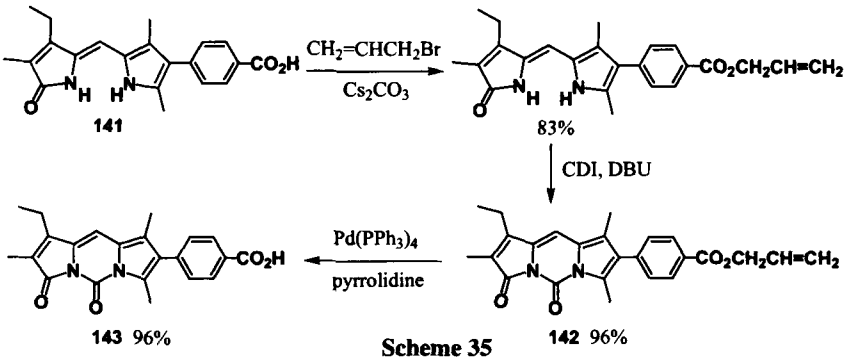
Sodium dithionite ($Na_2S_2O_4$) reduces selectively the C(4)-C(5) double bond in 10*H*-dipyrrin-1-ones with or without an C(9)-alkoxycarbonyl group.[258,259] Electrochemical reduction[260] of dipyrrinones has been reported to give C(5)-C(5') dimeric structures from an initial C(4)-C(5) saturation.[261,262]



Scheme 34

3. Side-chain Manipulations

Certain goals of research for macrocyclic tetrapyrroles and linear oligopyrroles, including dipyrrinones, frequently require side chain modifications to be made after construction of the dipyrrinone core. Battersby[183,218] and Gossauer,[173,178] in particular have applied elaborate transformations of functional groups in order to arrive at the desired substitution pattern. Some of the natural products of *Fig. 2* contain vinyl and ethylidene groups, often necessitating lengthy routes for their installation.[76,107,125,131,147,148,173,198] Standard conversions of a side chain acid group into an ester,[233,263-265] or amide,[264,266-268] saponification (deprotection) of a side chain ester,[102,107,109,147,152,178,180,233,265] reduction of a conjugated to dipyrrinone keto group[231,233-235,238,269] and many other tranformations have been carried out using the ever enriching variety of modern synthetic methods.[270] An example of specific use of allyl ester protection of a dipyrrinone is presented in *Scheme 35*. The methyl ester of **141** is readily available but it cannot be carried



Scheme 35

through the N,N'-cyclization with CDI to a highly fluorescent[271] analog of **142** because the resulting tricycle opens during saponification in aqueous base. The acid sensitive *tert*-butyl ester of **141** was prepared in an unsatisfactory yield, and deprotection of the benzyl ester corresponding to **142** by hydrogenation was not regioselective.

In contrast, a high yield S_N2 reaction between allyl bromide and the cesium carboxylate of **141** gave the allyl ester, which was cyclized and then deprotected in almost quantitative yield,

Scheme 35.[265] Intensely fluorescent acid **143** was used as a probe for exciton coupling detected by circular dichroism. Allyl ester protection at dipyrrinone stage and deprotection at highly sensitive linear tetrapyrrole stage has been also applied by Inomata and Kinoshita.[163,165,168,171] Thia-Mitsunobu inversion[199] of a hydroxy-bearing stereogenic center in an analog of **108** with thioacetic acid, and Knoevenagel condensation involving a C(8)-formyl dipyrrinone have been reported.[272] Formation of polymer bound xanthobilirubinic acid (**20**, propionate ester linkage) has been described.[89,273]

Reactions involving *tert*-butyl 9-dipyrrinonecarboxylates akin to **57**, **81**, **105** and **134** are conspicuous in the literature, typically for liberation or modification of C(9) in subsequent condensation chemistry. Most examples of *tert*-butyl esters listed in *Tables 3* and *4* were subjected to acid-catalyzed deprotection. Due to the greater susceptibility of the heterocyclic rings to C-protonation, 2- and 3-carboxypyrroles (and indoles) are more readily decarboxylated under acidic conditions, than is benzoic acid. The same explanation applies to dipyrrinone C(8)-

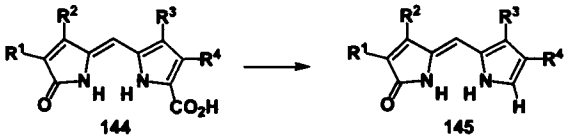


Table 5. Dipyrrinones from Decarboxylation of 9-Carboxy Derivatives

R^1	R^2	R^3	R^4	Yield (%)	Reference
CH_3	CH_3	H	CH_3		123
CH_3	CH_2CH_3	CH_3	H	53	236
CH_2CH_3	CH_2CH_3	CH_3	H	50	236
$(CH_2)_2CO_2Me$	CH_3	H	CH_3	51	130, 193b
CH_3	CH_3	CH_3	CH_3	57	133
CH_2CH_3	CH_3	CH_3	CH_3	58	133
CH_3	CH_3	$CH_2C(CH_3)_3$	CH_3	80	139
CH_3	CH_2CH_3	CH_2CH_3	CH_3	72	210
CH_3	CH_3	CH_2CH_3	CH_2CH_3	80	137, 269
CH_2CH_3	CH_3	CH_2CH_3	CH_2CH_3	85	138
$(CH_2)_2CO_2H$	CH_3	CH_2CH_3	CH_3	50	133
CH_3	CH_3	CH_3	$(CH_2)_2CO_2H$	88	141
CH_3	CH_3	CH_3	$(CH_2)_3CO_2Me$	73	236
CH_2CH_3	CH_3	CH_3	$(CH_2)_2CO_2Me$		143
CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2Me$		143
CH_3	$CH{=}CH_2$	CH_3	$(CH_2)_2CO_2H$	65	103
$CH{=}CH_2$	CH_3	CH_3	$(CH_2)_2CO_2H$	69	103
CH_3	CH_2CH_3	CH_3	$(CH_2)_2CO_2H$		146
CH_3	CH_2CH_3	CH_3	$(CH_2)_5CO_2H$		127

and C(9)-carboxylic acids (**144** in *Table 5*)which decarboxylate thermally to afford unsubstituted derivatives **145** (sometimes isolated[114,193b]) that are typically formylated *in situ* by trialkylortho-formate-TFA to give analogs of **131**, **133** and **135**.[107,140,148,163,178,185,193a] Decarboxylation of 9-carboxydipyrrinones (**144**) occurs in neat TFA at or slightly above (<60°C) ambient temperature, in CH_3OH-10% H_2SO_4 at reflux,[236] and (as is often used) in molten sodium acetate trihydrate - potassium acetate at 130-160°C for a short time.[38] These methods provided C(9)-unsubstituted dipyrrinones (**145**), a selection of which is shown in *Table 5*.

On several occasions, a chiral auxiliary has been attached to a dihydrodipyrrinone, thereby allowing for resolution of enantiomers[129,147,195] that are used subsequently in syntheses of naturally occurring tetrapyrroles. Classical resolutions of carboxylic acid-containing dipyrrinones derived from **93** by fractional crystallization of diastereomeric salts have been described.[107,143,241]

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