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# UNUSUAL OXIDATION IN THE COURSE OF SYNTHESIS OF *N*-CONFUSED NICKEL TETRAHYDROBILINS

**Jan-Erik Damke,[a] Torben König,[a] Gerold Haake,[a] Lechosław Latos-Grażyński,[b] and Franz-Peter Montforts[a],***

[a] Institute of Organic Chemistry, FB2, University of Bremen, Leobener St. NW2C, D-28359 Bremen, Germany
(phone: +49-421-21863110; e-mail: mont@uni-bremen.de)
[b] Department of Chemistry, University of Wrocław, F. Joliot-Curie St. 14, PL-50383 Wrocław, Poland

**Abstract** – *N*-confused Tetrahydrobilins *rac*-**16** and *rac*-**17** were prepared to investigate their cyclization directed to the formation of *N*-confused chlorins. For achieving the desired cyclization the 5´-position of *rac*-**16** respectively *rac*-**17** was activated by an electron withdrawing cyano function and their 2´-positions were blocked by a methyl group. In addition, the insertion of Ni(II) was accomplished for exercising a template effect during the cyclization process, but the formed nickel complexes *rac*-**18** and *rac*-**19** underwent oxidation to yield oxo-tetrahydrobilins *rac*-**20** and *rac*-**21**.

## INTRODUCTION

Since the pioneering work of *A.W. Johnson*[1] and *A. Eschenmoser*[2] the cyclization of bilin type tetra(hydro)pyrroles became an important synthetic concept for the construction of macrocyclic porphyrinoid and corrinoid structures.

In our laboratory cyclization of tetrahydrobilins *rac*-**2** were investigated with regard to the construction of hexahydrocorrins *rac*-**1**[3] or dihydroporphyrins (chlorins) **3**.[4] Depending on functional groups or/and substituents at the cyclization positions the tetrahydrobilins *rac*-**2** show different modes of reaction.

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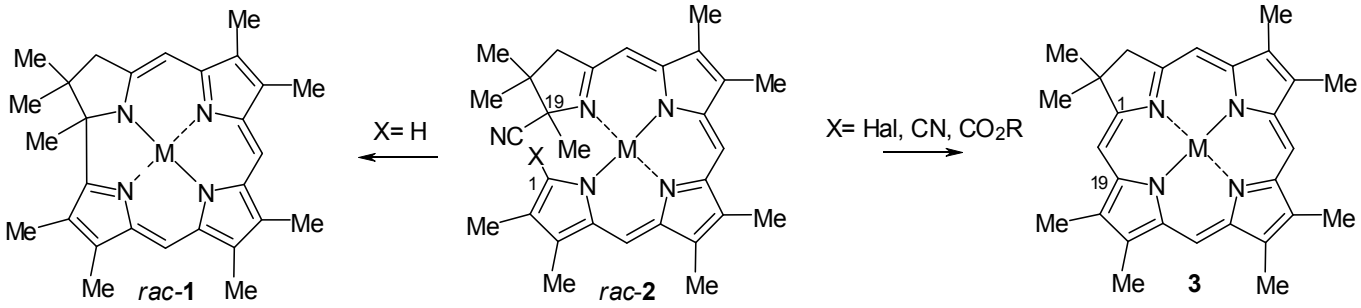
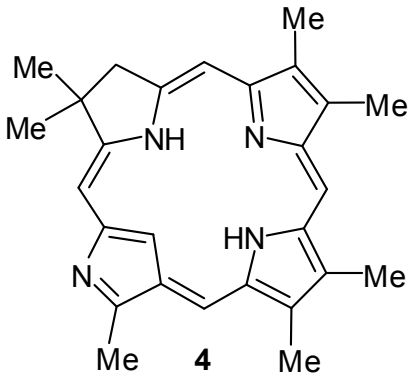
Dedicated to Professor Dr. Albert Eschenmoser, ETH Zürich, on occasion of his 85th birthday

Electron withdrawing groups (X = Hal, CN, $CO_2R$) favour the formation of chlorins **3** whereas the 1-unsubstituted bilin (X = H) *rac*-**2** forms the corrin structure *rac*-**1** (*Scheme 1*).[1]

In the course of investigations directed to synthesis of chlorins like **4** with nitrogen turned to the periphery of the chromophore (*N*-confused chlorins) we aimed on the preparation of the tetrahydrobilins *rac*-**16** and *rac*-**17** with cyano groups at the 5′-positions and methyl groups at the 2′-positions.




**Scheme 1.** Cyclization of tetrahydrobilins *rac*-**2** to hexadehydrocorrinates *rac*-**1** or dihydroporphyrinates (chlorins) **3**




## RESULTS AND DISCUSSION

Synthesis of tetrahydrobilins *rac*-**16** and *rac*-**17** should be achieved starting from the known nickel complex *rac*-**15**[4] to which pyrrol building blocks **8** and **14** should be attached to form the tetrapyrrolic systems. Pyrrole carbaldehyde **8** could be obtained along two different routes (*Scheme 2*) adopting literature procedures.[5a,b] Methylpyrrole carbonitrile **7** could be obtained[5b] directly by reaction of acetamido cyanoacetate **5** and 1,4-dichlorobutyne **6** forming the pyrrole cycle. Alternatively the aldehyde function of known pyrrole **9**[5a] was transformed into the cyano group of **7**. Expected regioselective formylation yielded pyrrole building block **8**.

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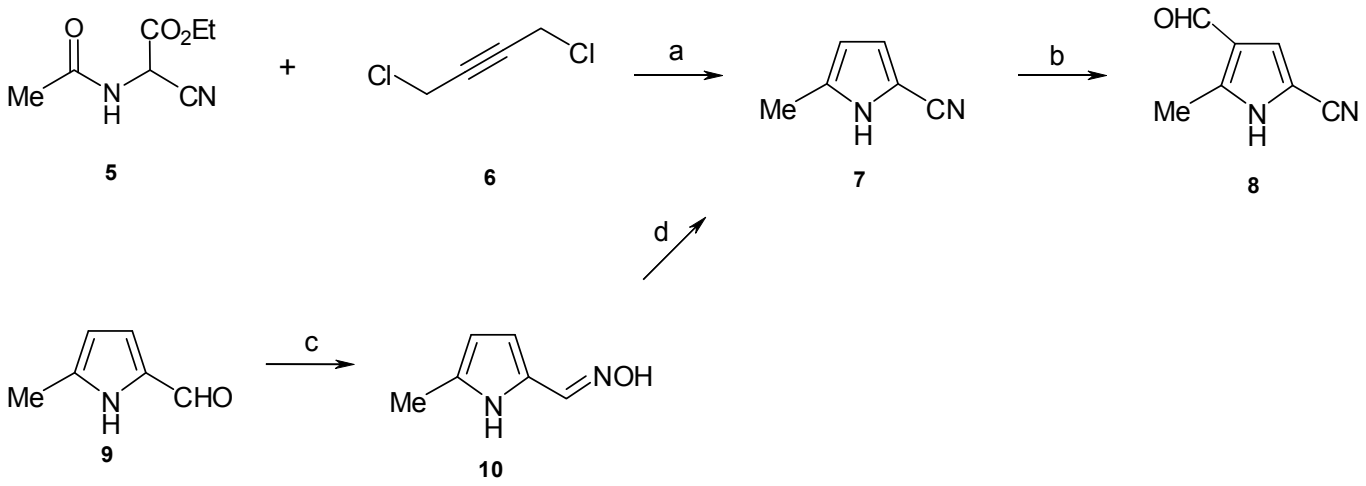
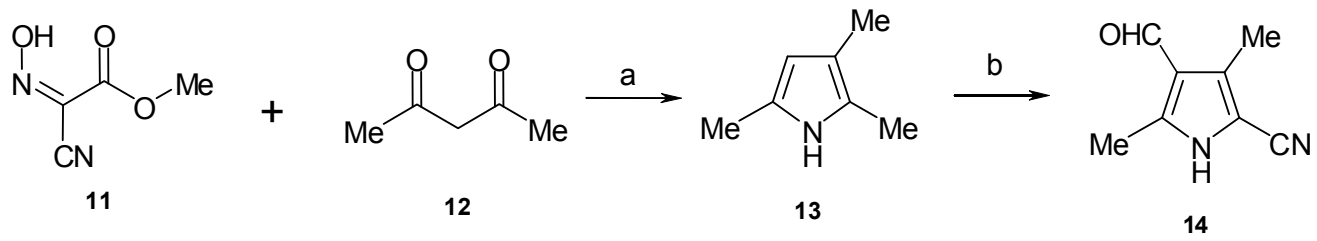
[1]) As a consequence of IUPAC nomenclature the numbering of the carbon framework of tetrahydrobilins is different from that of their cyclization products.




**Scheme 2.** *a)* NaOEt/EtOH, reflux, 2 h (43 %). *b)* 1) $AlCl_3$, $CH_2Cl_2$, $MeNO_2$; 2) $Cl_2CHOMe$, 0 °C, 5 min, rt, 15 min; 3) $H_2O$, rt, 15 min, chromatogr, cryst. (74 %). *c)* $H_2NOH{\cdot}HCl$, NaOAc, MeOH, RT, 30 min. *d) N,N*-carbonyldiimidazole, $CHCl_3$, rt, 16 h, chromatogr. (98 % relative to **9**)

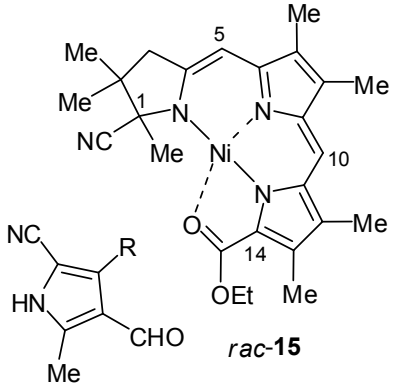
Pyrrole carbaldehyde **14** was prepared by *Knorr's* pyrrole synthesis[6] and subsequent *Vilsmeier* formylation (*Scheme 3*).




**Scheme 3.** *a)* 1) MeCOOH dil., 80 °C, Zn; 2) 80 °C, 30 min (63%). *b)* DMF*, $POCl_3$ (3eq.), 80 °C, 30 min (73%)

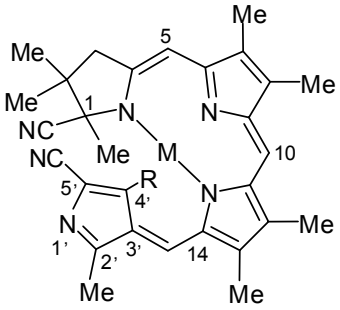
Tetrahydrobilins *rac*-**16** and *rac*-**17** were obtained from nickel complex *rac*-**15**[4] and pyrroles **8** and **14** (*Scheme 4*). Alkaline hydrolysis of the ester function of the nickel complex *rac*-**15**, followed by acid-induced condensation with decarboxylation and decomplexation with the pyrrole carbaldehydes **8** and **14** furnished the tetracyclic bilins *rac*-**16** and *rac*-**17** respectively.

Both tetrahydrobilins *rac*-**16** and *rac*-**17** should be recomplexed with nickel acetate to give the nickel tetrahydrobilins *rac*-**18** and *rac*-**19**.

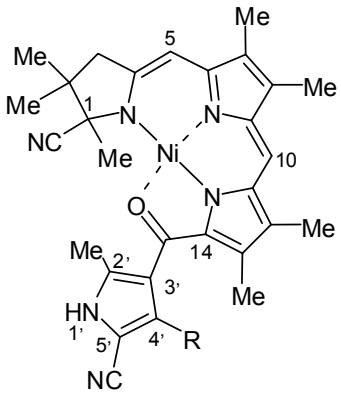


*rac*-**15**

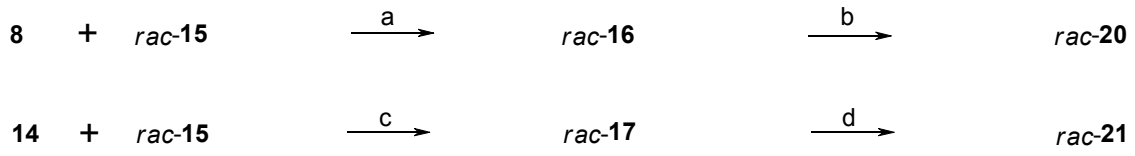
**8** R = H,
**14** R = Me



*rac*-**16** R = H, M = 2H
*rac*-**17** R = Me , M = 2H
rac-**18** R = H, M = Ni
rac-**19** R = Me , M = Ni



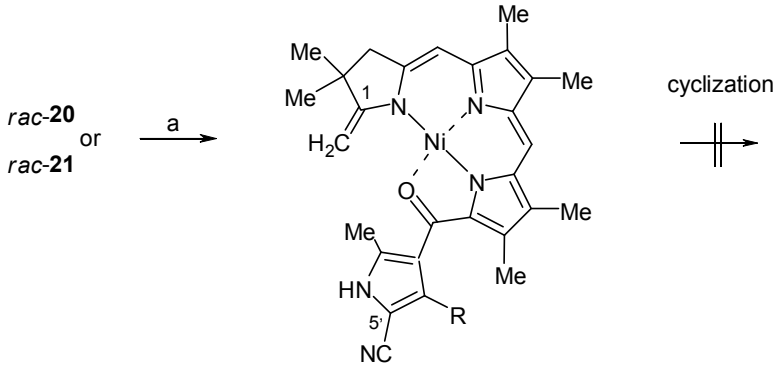
*rac*-**20** R = H
*rac*-**21** R = Me




**Scheme 4.** *a)* 1) 5*N* KOH, MeOH/$H_2O$ 9+1, THF, reflux, 45 min; 2) 1.8 eq. **8**, *p*-TsOH, $CHCl_3$, reflux, 30 min. *b)* $Ni(OAc)_2$, NaOAc, rt, Ar, 20 min, 35% (relative to *rac*-**15**). *c)* 1) 5*N* KOH, MeOH/$H_2O$ 9+1, THF, reflux, 45 min; 2) 1.8 eq. **14**, *p*-TsOH, $CHCl_3$, reflux, 30 min. *d)* $Ni(OAc)_2$, NaOAc, rt, Ar, 20 min, chromatogr., 39% (relative to *rac*-**15**)

Interestingly however, apart of complexation of the macrocycles the methine bridges underwent oxidation to ketofunctions to form the very stable compounds *rac*-**20** and *rac*-**21**.

To achieve the required cyclization for chlorin formation the Ni tetrahydrobilins *rac*-**20** and *rac*-**21** were simply heated in trichlorobenzene. It could be seen that the primary required eliminations of HCN from C-1[1] gave tetrahydrobilins *rac*-**22** and *rac*-**23** respectively. But the formed exocyclic enamine double bonds (*Scheme 5*) did not undergo the desired cyclization reactions.

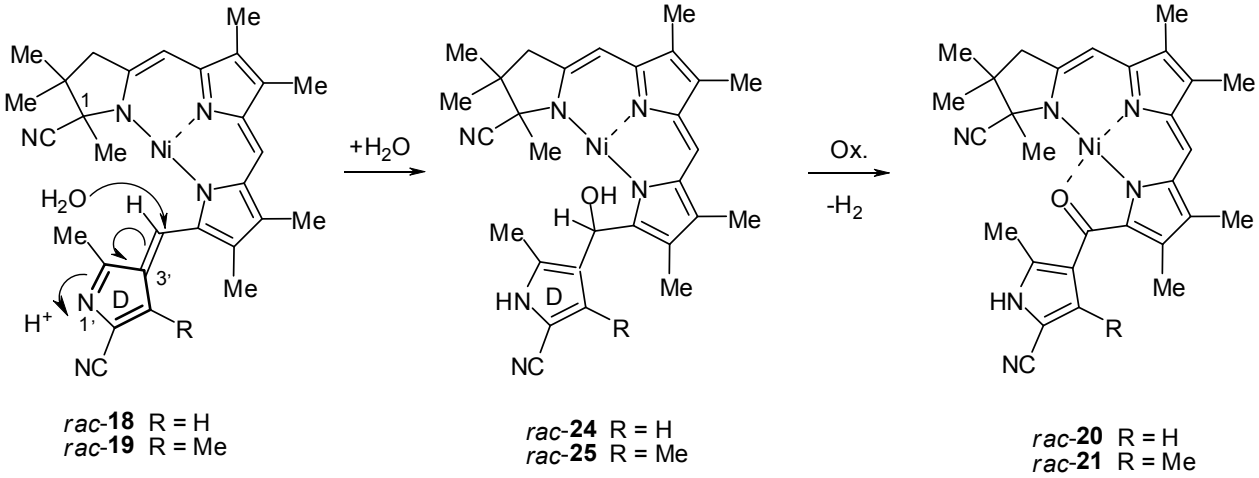



*rac*-**22** R = H,
*rac*-**23** R = Me

**Scheme 5.** 1,2,4-Trichlorobenzene, 220 °C, Ar, 30 min

A possible interpretation of the observed oxidation during complexation of tetrahydrobilins *rac*-**16** and *rac*-**17** with nickel acetate is summarized in *scheme 6*. It can be assumed that the primary formed products *rac*-**18** and *rac*-**19** undergo nucleophilic addition of water at the electrophilic C(3´´)-methylidene positions. The C(3´´)-methylidene positions of *rac*-**18** or *rac*-**19** are activated as parts of azafulvene structures and the additional electron-withdrawing cyano functions.

Aerial oxidation of the allylic alcohol functions of intermediates *rac*-**24** and *rac*-**25** yields the nickel ketobilins *rac*-**20** and *rac*-**21**. The keto functions are ideal ligands for coordinating the central nickel ion.




**Scheme 6.** Possible mechanistic courses of oxidation of tetrahydrobilins *rac*-**18** and *rac*-**19**

Semiempirical PM3-calculations and NOESY experiments indicate the planarity of the metallo complex core of *rac*-**20** and *rac*-**21**. The central nickel ion is in planar square coordination by the three nitrogen atoms of the ABC part and by the carbonyl function of the 3´´-bridge of the extra pyrrole ring D (*Figure 1*).

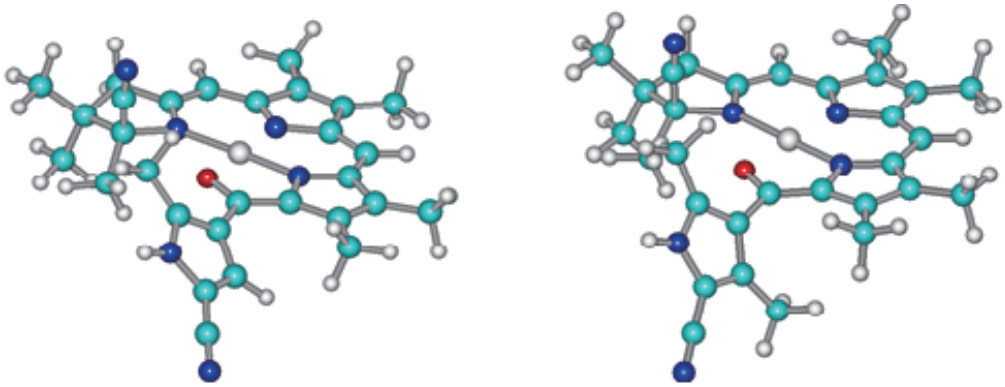


**Figure 1.** Semiempirical PM3-calculations of [1-Cyano-14-(5´-cyano-2´-methyl-1´*H*-pyrrole-3´-carbonyl)-1,2,3,17-tetrahydro-1,2,2,7,8,12,13-heptamethyl-15*H*-tripyrrinato] nickel(II) *rac*-**20** and [1-Cyano-14-(5´-cyano-2´,4´-dimethyl-1´*H*-pyrrol-3´-carbonyl)-1,2,3,17-tetrahydro-1,2,2,7,8,12,13-heptamethyl-15*H*-tripyrrinato] nickel(II) *rac*-**21** (ball and stick representation)

The rigidity of the structure was confirmed experimentally by two-dimensional NOESY experiments which showed distances of ca. 3.6 Å between the C(1) methyl groups of rings A and C(2′) methyl substitutents of rings D (*Figure 2*). The whole Ring D moieties are tilted against the coordination plane.

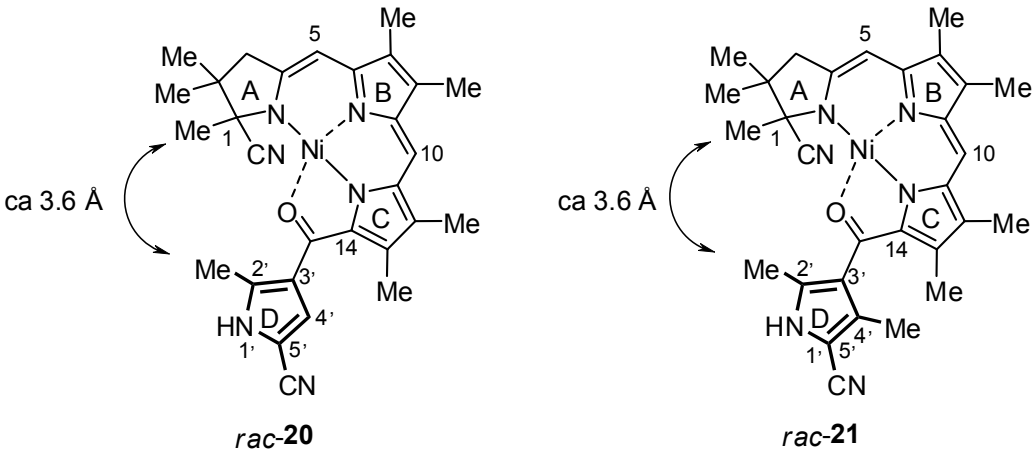



**Figure 2.** Results of two dimensional NOESY experiments

Also the comparison of the UV/Vis-spectra (*Figure 3*) of the tricyclic nickel complex *rac*-**15** and of the tetracyclic nickel complex *rac*-**20** containing the extra pyrrole ring shows striking similarities of the spectra thus confirming NMR experiments and calculations. The extra pyrrole ring of *rac*-**20** causes only a moderate bathochromic shift on the tricyclic metallo complex part of *rac*-**20** thus indicating twisting of the D ring against the chromophoric system.

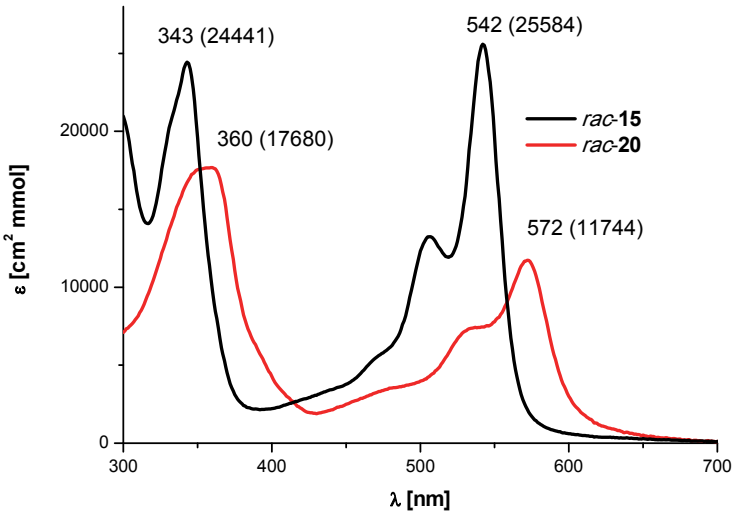



**Figure 3.** UV/Vis-spectra in $CH_2Cl_2$ of tricyclic nickel complex *rac*-**15** and of tetracyclic nickel complex *rac*-**20**

## EXPERIMENTAL

*General.* Starting materials were either prepared according to literature procedures or were purchased from *Fluka*, *Merck*, or *Aldrich* and used without further purification. All solvents were purified and dried by standard methods. All reactions were carried out under argon. Column chromatography (CC): silica gel *60 Å, 32-63μm (ICN Biomedicals).* Thin layer chromatography (TLC): precoated silica gel *Kieselgel 60 $F_{254}$ (Riedel de Haen)* plates.

$^1$H-NMR Spectra: *Bruker DPX-200 Avance* spectrometer; δ in ppm rel. to $SiMe_4$ as internal standard, *J* in Hz; δ(H) from spectra in $CDCl_3$ at 23 °C, if not otherwise noted. MS and HR-MS: *Finnigan MAT 8200*, *Finnigan MAT 95* or *Esquire*- spectrometer [EI (70 eV, direct inlet) and ESI]; in *m/z* (rel. %). IR Spectra (KBr, $cm^{-1}$): *Perkin-Elmer Paragon 500 FT-IR* spectrometer. UV/Vis Spectra: *Varian Cary 50* spectrophotometer, $\lambda_{max}$ (relative intensity) in nm. Melting points are uncorrected and were determined on a *Reichert Thermovar* hot-stage apparatus or on *Gallenkamp* apparatus.

### 5-Methyl-1*H*-pyrrole-2-carbonitrile (7)

(Method A) 1.24 g (11.4 mmol) of 5-methyl-1*H*-pyrrole-2-carbaldehyde[5a] (**9**) were dissolved in 30 mL of MeOH and then sodium acetate (5.4 g) followed by hydroxylamine hydrochloride (3.8 g, 55 mmol) were added at room temperature. The immediately formed colorless suspension was stirred for 30 min at room temperature. The mixture was transferred with 150 mL of $CH_2Cl_2$ into a separatory funnel containing 100 mL of brine.

The product was exhaustively extracted with $CH_2Cl_2$ and the combined organic extracts were filtered through oven dried cotton wool to remove water. The solvent was evaporated. The crude oximino pyrrole was dissolved under an Ar atmosphere in 40 mL of dry $CHCl_3$ and then *N*,*N*-carbonyldiimidazole (3.4 g, 21.0 mmol) was added in small portions. For completion of the reaction the mixture was stirred at room temperature for 16 h. The solvent was evaporated and the residue was purified by flash chromatography (Matrex silicagel, $CH_2Cl_2$/EtOAc, 9+1). After removal of the solvent 1.18 g (11.1 mmol, 98%) of a colorless oil of **7** was obtained. For analytical characterization the sample was crystallized from $CHCl_3$/*n*-pentane.

(Method B[5b]) 8.5 g (50 mmol) of ethyl 2-acetamido-2-cyanacetate (**5**) were added to a stirred solution of 250 mL 1*M* NaOEt/EtOH. The reaction mixture was refluxed and 1,4-dichloro-2-butyne (**6**) ( 4.9 mL, 50 mmol) was added at once. The solution was stirred for 1 h before adding another 4.9 mL (50 mmol) of 1,4-dichloro-2-butyne. Stirring was continued for another hour. After cooling to room temperature the solvent was evaporated and the precipitate was dissolved in 175 mL of EtOAc. Water (175 mL) was added

to the redish mixture, the organic phase was separated, and the water phase was exhaustively extracted with EtOAc. The combined organic extracts were washed with sat. aq. $NaHCO_3$, 1*N* HCl and sat. aq. NaCl-solutions and dried by filtration through oven dried cotton wool. The solvent was evaporated and the crude product was purified by column chromatography (silicagel, $CH_2Cl_2$/EtOAc, 9+1). After removal of the solvent 2.31 g (21.7 mmol, 43.5%) of solid **7** was obtained, which was recrystallized from $CHCl_3$/*n*-pentane.

**5-Methyl-1*H*-pyrrole-2-carbonitrile (7)**

Colorless crystals, mp 54 °C, (lit.,[5c] mp 54-56 °C). TLC ($SiO_2$, $CH_2Cl_2$/AcOEt 9+1): $R_f$ = 0.62. IR (KBr): $\tilde{\nu}$ = 3300 (NH), 3150, 2985 (CH), 2925 (CH) 2820 (w), 2210 (s, ν CN), 1575 (m), 1480 (s), 1395 (m), 1290 (m), 1270 (m), 1190 (s), 1050 (s), 995 (w), 785 (s) $cm^{-1}$. MS (EI) *m/z* (%): 107 ($M^+$, $^{13}C$, 4), 106 ($M^+$, 53), 105 (100), 78 (19), 64 (5). $^1$H-NMR (360 MHz, $CDCl_3$): 2.27 (3H, s, 5C-$CH_3$), 5.95 (1H, ddq, $^3J$ = 3.6, $^4J$ = 2.71, $^4J$ = 0,87, H-C(4)), 6.49 (1H, dd, $^3J$ = 3.62, $^4J$ = 2.65, H-C(3)), 8.23 (1H, s, br, NH). HRMS *m/z*: $C_6H_6N_2^+$ calcd. 106.05310, found 106.05329.

**4-Formyl-5-methyl-1*H*-pyrrole-2-carbonitrile (8)**

To a suspension of $AlCl_3$ (1.20 g, 8.99 mmol) in 6 mL of dry $CH_2Cl_2$ were added under an Ar atmosphere at room temperature nitromethane (640 µL) and then 316 mg (2.99 mmol) of pyrrolecarbonitrile **7**. The solution was cooled to 0 °C and dichloromethyl methyl ether (666 µL, 7.47 mmol) was added by a syringe. The mixture was stirred for 5 min at 0 °C and 15 min at room temperature. 20 mL of water was cautiously added and the mixture was stirred for additional 15 min at room temperature. The mixture was exhaustively extracted with EtOAc (total ca. 50 mL), the combined organic extracts were dried by filtration through oven dried cotton wool and the solvent was evaporated. The crude product was purified by flash chromatography (Matrex silicagel, $CH_2Cl_2$/MeOH, 9+1) and crystallization from EtOAc. Yield 296 mg (2.21 mmol, 74%) **8** as colorless crystals.

**4-Formyl-5-methyl-1*H*-pyrrole-2-carbonitrile (8)**

74% yield, colorless crystals, mp 179 °C. TLC ($SiO_2$, $CH_2Cl_2$/MeOH 9+1): $R_f$ = 0.32. IR (KBr): $\tilde{\nu}$ = 3100 (NH), 3050 (s), 2975 (m), 2925 (m), 2820 (m), 2210 (s, (CN)), 1650 (s, (C=O)-formyl), 1575 (m), 1495 (s), 1450 (m), 1405 (m), 1395 (m), 1370 (s), 1340 (m), 1155 (m), 1130 (s), 1045 (w), 1005 (w), 980 (w), 860 (m), 840 (m). 810 (w). MS (EI) *m/z* (%): 135 ($M^+$, $^{13}C$, 6), 134 ($M^+$, 84), 133 (100), 108 ($M^+$-CN, 6), 105 ($M^+$-CHO, 22), 78 (13), 53 (14). $^1$H-NMR (200 MHz, $CDCl_3$): 2.81 (3H, s, $CH_3$-C(2)), 6.98 (1H, d, $^4J$ = 2.0, H-C(4)), 9.64 (1H, s, CHO-C(5)), 11.08 (1H, s, br, NH). HRMS *m/z*: $C_7H_6N_2O^+$ calcd. 134.04801, found

134.04796.

**3,5-Dimethyl-1*H*-pyrrole-2-carbonitrile (13)**[6]

4 g (40 mmol, 4.1 mL) of acetylacetone **12** and 5.12 g (40 mmol) of 2-cyano-2-oximino acetic acid methyl ester **11** were dissolved in 80 mL of 50% aq. acetic acid and the mixture was heated to 80 °C. During 45 min 10 g (154 mmol) of zinc dust were added in portions so that the temperature could be kept between 75 to 85 °C. Subsequently the mixture was heated for 30 min to 80 °C. The mixture was poured on 400 mL of ice water. The pyrrole carbonitrile **13** precipitated on standing overnight and it was filtered off. The residue was dissolved in $CH_2Cl_2$ and zinc residues were filtered off. After evaporation of the solvent the residue was purified by column chromatography ($SiO_2$, $CH_2Cl_2$/EtOAc, 9+1) to afford after crystallization from dichloromethane/*n*-pentane 3.03 g (25.2 mmol, 63%) of pyrrolecarbonitrile **13** as colorless crystals.

**3,5-Dimethyl-1*H*-pyrrole-2-carbonitrile (13)**

63% yield, colorless crystals, mp 76 °C. TLC ($SiO_2$, $CH_2Cl_2$/AcOEt 9+1): $R_f$ = 0.61. IR (KBr): $\tilde{\nu}$ = 3270 (NH), 3160, 3070 (m, C=CH), 2915 (m, CH), 2845 (m), 2760 (m), 2525 (m), 2210 (s, (CN)), 1585 (m, (C=C)), 1500 (m), 1440 (m), 1380 (m), 1300 (m), 1265 (m), 1165 (w), 1145 (w), 1040 (w), 985 (m), 980 (w), 800 (s), 725 (w), 645 (w), 610 (m), 545 (w), 495 (w). $^1$H-NMR (200 MHz, $CDCl_3$): 2.20 (3H, s, $CH_3$-C(5)), 2.26 (3H, s, $CH_3$-C(3)) 5.81 (1H, s, H-C(4)), 8.06 (1H, s, br, NH). MS (EI) *m/z* (%): 120 ($M^+$, 58), 119 (100), 105 (14), 92 (5), 65 (7), 39 (7). HRMS *m/z*: $C_7H_8N_2^+$ calcd.120.06875, found 120.06854.

**3,5-Dimethy-4-formyl-1*H*-pyrrole-2-carbonitrile (14)**

364 µL (3.98 mmol) $POCl_3$ was added to 636 µL of dry DMF at 0 °C under an argon atmosphere and the mixture was stirred for 15 min. To a solution of 159.8 mg (1.33 mmol, 3 eq.) of 3,5-dimethyl-1*H*-pyrrole-2-carbonitrile **13** in 10 mL of dry DMF cooled to 10 °C the previously prepared *Vilsmeier reagent* was added dropwise under an argon atmosphere and the solution was then heated for 2.5 h at 60 °C. The reaction was quenched by addition of 20 mL of saturated sodium-acetate solution and stirred for further 20 min at 60 °C. The reaction mixture was diluted with 20 mL of water, extracted four times with $CH_2Cl_2$ and dried by filtration through oven dried cotton wool. After removal of $CH_2Cl_2$ in a rotary evaporator, DMF was evaporated by a Kugelrohr distillation apparatus under a reduced pressure. The residue was purified by column chromatography ($SiO_2$, $CH_2Cl_2$/EtOAc, 15+1) to afford 143.9 mg (0.971 mmol, 73.0%) of pyrrolecarbonitrile **14** as a colourless solid.

**3,5-Dimethy-4-formyl-1*H*-pyrrole-2-carbonitrile (14)**

73% yield, colourless solid, mp 154 °C. TLC ($SiO_2$, $CH_2Cl_2$/AcOEt 15+1): $R_f$ = 0.38. $\tilde{\nu}$ = 3230 (s, NH), 2965, 2940 (m, CH), 2690 (w), 2480 (w), 2210 (s, (CN)), 1670 (s, (C=O)), 1460 (m), 1430 (w), 1375 (m), 1320 (m), 1240 (s), 1200 (m), 1185 (m), 1120 (s), 1070 (w), 1020 (w), 960 (w), 910 (w), 850 (m), 730 (m), 720 (w). $^1$H-NMR (200 MHz, $CDCl_3$): 2.93 (3H, s, $CH_3$-C(2)), 3.01 (3H, s, $CH_3$-C(2)), 8,08 (1H, s, CHO-C(4)), 8.91 (1H, s, br, NH). MS (EI) *m/z* (%):149 ($M^+$, $^{13}$C, 5), 148 ($M^+$, 60), 147 (100), 119 ($M^+$-CHO, 6), 105 (1), 92 (3), 65 (5). HRMS *m/z*: $C_8H_8N_2O^+$ calcd. 148.06366, found 148.06330.

**General procedure for preparation of tetrahydrobilins *rac*-20 and *rac*-21**

A 5*N* solution of potassium hydroxide in MeOH/$H_2O$ 9:1 (4 mL) was added to a solution of 13.0 mg (27.2 μmol) 1-Cyano-14-ethoxycarbonyl-1,2,3,17-tetrahydro-1,2,2,7,8,12,13-heptamethyl-15*H*-tripyrrin-nickel (II) (*rac*-**15**) in dry THF (5 mL). The mixture was heated at 80 °C for 45 min under an argon atmosphere. After cooling, the reaction mixture was diluted with $CH_2Cl_2$ (20 mL) and washed with a aq. $NaHCO_3$ solution (20 mL). The aqueous layer was vigorously extracted with $CH_2Cl_2$ (4 x 30 mL), the combined organic layers were dried by filtration through oven dried cotton wool and concentrated *in vacuo* to afford the free carboxylic acid of *rac*-**15**. Degassed solutions of pyrroles 6.9 mg **8** or 7.7 mg **14** (51.7 μmol) in dry $CHCl_3$ (6 mL) and 0.4*N* *p*-toluenesulfonic acid in $CHCl_3$ (0.68 mL, 272 μmol, 10 eq.) were successively added by a syringe through a septum to the degassed solution of carboxylic acid under an argon atmosphere. The mixture was refluxed with stirring for 20 min. The green reaction mixture was diluted with $CH_2Cl_2$ (20 mL), poured into a separatory funnel containing water (30 mL) and it was vigorously extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried by filtration through oven dried cotton wool and concentrated *in vacuo*. The metal free bilins *rac*-**16** or *rac*-**17** were used without further purification for the next reaction step. Therefore, a solution of 24.1 mg of dry $Ni(OAc)_2$ (136 μmol) and NaOAc (11.2 mg) in dry MeOH (3 mL) was added to solutions of *rac*-**16** or *rac*-**17** in dry $CH_2Cl_2$ (6 mL). The mixture was reacted at room temperature for 30 min under an argon atmosphere. The reaction mixture was transferred into a separatory funnel containing water (20 mL) and it was vigorously extracted with $CH_2Cl_2$ (3 x 20 mL). The organic layers were dried by filtration through oven dried cotton wool and concentrated under a reduced pressure. The residue was purified by column chromatography ($SiO_2$, $CH_2Cl_2$/EtOAc, 15:1) to yield *rac*-**20** or *rac*-**21** as dark red-purple solids.

**[1-Cyano-14-(5′cyano-2′-methyl-1′*H*-pyrrole-3′-carbonyl)-1,2,3,17-tetrahydro-1,2,2,7,8,12,13-heptamethyl-15*H*-tripyrrinato] nickel(II)** (*rac*-**20**). 35% yield (5.1 mg, 9.5 μmol), dark red-purple solid. TLC ($SiO_2$, $CH_2Cl_2$/MeOH AcOEt 99+1): $R_f$ = 0.70. UV-VIS ($CH_2Cl_2$): $\lambda_{max}$ (c = $1.25 \cdot 10^{-5}$ M) = 572 (11744), 360 (17680 $cm^2 \cdot mmol^{-1}$). $^1$H-NMR (200 MHz, $CDCl_3$): 1.21 (3H, s, $CH_3$-C(2) *trans* rel.

NC-C(1)), 1.29 (3H, s, $CH_3$-C(2) *cis* rel. NC-C(1)), 2.13 (3H, s, $CH_3$-C(7)), 2.17 (3H, s, $CH_3$-C(13)), 2.24 (3H, s, $CH_3$-C(12)), 2.27 (3H, s, $CH_3$-C(8)), 2.52 (3H, s, $CH_3$-C(2′)), 2.82, 2.93 (2H, *AB*, *J* = 16,6 Hz, 2H-C(3)), 5.78, (1H, s, H-C(5)), 6.70, (1H, s, H-C(10)), 7.16, (1H, s, H-C(4′)), 8.74, (1H, s, H-N(1′)). MS (EI) *m/z* (%): 536 ($M^+$, $^{58}Ni$, 36), 509 (M-$HCN^+$, $^{58}Ni$, 12). HRMS *m/z*: $C_{29}H_{30}N_6O^{58}Ni^+$ calcd. 536.18346, found 536.18268.

**[1-Cyano-14-(5′-cyano-2′,4′-dimethyl-1′*H*-pyrrol-3′-carbonyl)-1,2,3,17-tetrahydro-1,2,2,7,8,12,13-heptamethyl-15*H*-tripyrrinato] nickel(II)** (*rac*-**21**). 39% yield (5.8 mg, 10.6 μmol), dark red-purple solid. TLC ($SiO_2$, $CH_2Cl_2$/MeOH 99+1): $R_f$ = 0.74. UV-VIS ($CH_2Cl_2$): $\lambda_{max}$ (relative intensity) = 572 (0.68), 538 (0.40, sh), 360 (1). $^1$H-NMR (200 MHz, $CDCl_3$): 1.20 (3H, s, $CH_3$-C(2) *trans* rel. NC-C(1)), 1.30 (3H, s, $CH_3$-C(2) *cis* rel. NC-C(1)), 2.14 (3H, s, $CH_3$-C(7)), 2.19 (3H, s, $CH_3$-C(13)), 2.25 (3H, s, $CH_3$-C(12)), 2.27 (3H, s, $CH_3$-C(8)), 2.40, (3H, s, $CH_3$-C(4′)), 2.53 (3H, s, $CH_3$-C(2′)), 2.82, 2.93 (2H, AB, J = 16,6 Hz, 2H-C(3)), 5.78, (1H, s, H-C(5)), 6.71, (1H, s, H-C(10)), 8.74, (1H, s, H-N(1′)). MS (EI) m/z (%): 550 ($M^+$, $^{58}Ni$, 100), 535 (M-$CH_3^+$, $^{58}Ni$, 11) 523 (M-$HCN^+$, $^{58}Ni$, 60). HRMS m/z: $C_{30}H_{32}N_6O^{58}Ni^+$ calcd. 550.19911, found: 550.19921.

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