Synthesis of a chlorin with an annelated lactam ring as subunit for artificial photosynthetic reaction centres

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Dedicated to Prof. Gordon Gribble

Received 12-31-2017  Accepted 02-12-2018  Published on line 03-04-2018

Abstract

A chlorin with an annelated cyclic ketone moiety was synthesized from a tricyclic nickel complex and appropriate pyrrole building blocks. Ketone functionality of the target chlorin allows Beckmann rearrangement to yield chlorin lactams. Lactam moieties on the chlorin represent masked amino acid structures which should allow formation of peptide-like backbones, along which chlorin pigments are arranged. Due to the “natural” chlorin chromophores and the peptide backbone the devices should represent artificial mimetics of natural photosynthesis systems.

![Image of chlorin structure]

**Keywords:** Chlorin, pyrrole, Beckmann rearrangement, lactam, artificial photosynthesis
Introduction

The elementary step of photosynthesis in bacteria, algae and plants consists of a light-induced electron transfer from so-called special pair chlorophylls along a chain of further chlorophyll pigments to quinone acceptors. The so-formed hydroquinone structure provisionally stores two electrons for subsequent biochemical transformations.\textsuperscript{1-3} The process of light induced-electron transfer is accompanied by formation of proton gradients which are used for ATP production. Knowledge of the structure of photosynthetic reaction centres of bacteria and plants originates from crystal structure investigations.\textsuperscript{4-7} Crystal structure investigations revealed not only the spacial orientation but also that of the membrane protein environment in which the chlorophyll pigments are embedded by lipophilic interactions. For studying the complex photophysical/photochemical process of light-induced electron transfer in natural photosynthesis on a level of lower complexity, numerous artificial photosynthesis model systems were designed and synthesized.\textsuperscript{8-11} The majority of those model systems made use of porphyrin pigments; chlorin based systems are less widespread.\textsuperscript{12-16} Chlorin 2 the dihydroporphyrin chromophore of chlorophyll a 1 has different photophysical properties compared to the completely unsaturated porphyrins (Figure 1). The ubiquitous green colour of chlorophylls and the red of porphyrinoid blood pigment heme make this difference palpable.\textsuperscript{17-21}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chlorophyll_chlorin.png}
\caption{Chlorophyll a 1 and parent framework of chlorin 2.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{artificial_peptide.png}
\caption{Schematic representation of chlorin subunits arranged along an artificial peptide backbone.}
\end{figure}
To obtain more biomimetic photosynthesis models we aimed at the synthesis of chlorin type pigments with amino acid functionality. The chlorin subunits could then be covalently linked to peptide-like oligomers using established coupling methods from peptide chemistry (Figure 2).

Chlorin pigments arranged along the artificial peptide backbone could mimic the natural design in which chlorophylls are held together by lipophilic interactions with the protein environment.

**Results and Discussion**

The tricyclic nickel complex 9 (Scheme 2) which was used for several syntheses of chlorins in our laboratory is also an ideal intermediate for preparation of chlorins with the desired amino acid functionality.22-28 The task therefore was to connect 9 with pyrrole ring D building blocks which contain annulated cycloketone moieties as masked amino acid functions.

![Chemical structures](image)

**Scheme 1.** Preparation of ring D building blocks for chlorin synthesis. Reaction conditions. (a) POCl₃, DMF, 40 °C, 45 min (86%). (b) POCl₃, DMF, 40 °C, 16 h (61%). (c)(i) H₂ (1 atm), Pd/C, THF, NEt₃, rt, 30 min (100%); (ii) NBS, DMF, 50 °C, 1 h (44%). (d)(i) H₂ (1 atm), Pd/C, THF, NEt₃, rt, 30 min (100%); (ii) NaHCO₃, H₂O, I₂, KI, MeOH, 70 °C, ca. 40 min (47%).

Pyrroles 3 and 6 were chosen as starting materials for ring D building blocks (Scheme 1). Preparation of 3 and 6 was achieved from cyclohept-4-ene-1-one and isocyanides according a general protocol for pyrrole synthesis developed in our laboratory.29,30 Condensation of ring D building pyrroles with nickel tricycle 9 requires aldehyde functions. Therefore pyrrole benzyl ester 3 was subjected to Vilsmeier reaction conditions to yield 4. Debenzylation by catalytic hydrogenolysis and subsequent decarboxylative halogenations gave potential ring D building blocks 5 and 8. Bromide and iodide should function as leaving groups for the final cyclization step forming the chlorin. An alternative route started from cyano pyrrole 6 which yielded ring D building block directly by Vilsmeier formylation. The cyano group acts as leaving group for the final cyclization reaction.

With ring D building blocks in hand, synthesis of chlorin 12 could be achieved (Scheme 2). The sequence started with hydrolysis of the ester group of nickel complex 9 and condensation with ring D pyrrole aldehyde 7. Hydrolysis is facilitated by nickel complexation of the ethyl carboxylate group. Acid induced condensation proceeded with decarboxylation and decomplexation of nickel. The acidic reaction conditions also led to partial hydrolysis of the ketal function.
Scheme 2. Synthesis of chlorin 12. Reaction conditions. (a)(i) 5N KOH, MeOH/H₂O (9:1), THF, 70 °C, 45 min; (ii) + 7, CHCl₃, pTsOH, 70 °C, 10 min (72% mixture of 10a, 10b). (b) Zn(OAc)₂, DBU, sulfolane, 145 °C, 14 h (mixture of 11a,11b, 49% related to 9). (c) HClO₄, MeCN, H₂O, rt, 15 min (97%).

Thus tetracyclic bilin was formed in good yield as mixture of ketone 10a and ketal 10b derivatives. Because keto chlorin 12 was envisaged as the final target, we did not make any attempts to separate ketone and ketal derivatives on a preparative scale. To perform cyclization of bilin 10a,b to chlorins 11a,b the bilin was recomplexed with zinc(II) diacetate. The zinc stabilizes the quite sensitive bilin and, what is more important, it exercises an essential template effect for the cyclization process. Cyclization was initiated by base-induced elimination of HCN from the reduced pyrrole ring with formation of an enamine structure. The enamine attacks as a nucleophile at the cyano-substituted position of pyrrole ring D. Thus a methine bridge between rings A and B is formed with loss of a second HCN fragment. The obtained zinc chlorin 11a,b existed again as mixture of ketone 11a and ketal 11b derivatives.

Treatment of the mixture of chlorin derivatives 11a,b with perchloric acid removes the central zinc(II) and hydrolysed the ketal function to yield single keto chlorin 12 in good overall yield.

With iodo pyrrole aldehyde 8 as ring D building block only negligibly lower overall yields for the entire reaction sequence were achieved, but here reproducibility suffered due to the sensitivity of the bilin intermediates. With bromo pyrrole aldehyde 5, synthesis of bilins/chlorins failed completely.
Using keto chlorin 12 a Beckmann rearrangement for formation of lactam targets was performed (Scheme 3).

Scheme 3. Formation of chlorin lactams. Reaction conditions. (a)(i) O-mesityl sulfonyl hydroxylamine, \( \text{CH}_2\text{Cl}_2 \), 0 °C to rt; (ii) \( \text{Al}_2\text{O}_3 \) basic, activity I, in MeOH, benzene, rt, 3 h (77% mixture of 13a, 13b).

Figure 3. HPLC of reaction mixture from the Beckmann rearrangement indicating the ratio of formed lactams 13b (\( t_R^2 = 16 \) min) and 13a (\( t_R^1 = 17.5 \) min). Separation conditions: Nucleosil Chiral 2, \( n \)-heptane/dioxane 7:3, 1 mL/min, UV detection at 405 nm.
O-Mesityl sulfonyl hydroxylamine (Tamura reagent) was reported as a reagent that allows very gentle reaction conditions (temperatures around 0 °C) for Beckmann rearrangements. Another advantage of this hydroxylamine derivative could be its sterical strain with possible preferred formation of one constitutional lactam isomer. Indeed, the rearrangement reaction of keto chlorin 12 could be achieved with good yields under very gentle reaction conditions.

Analytical HPLC and 1H NMR spectroscopy revealed that a mixture of constitutionally isomeric lactams 13a and 13b was formed. Though constitutional isomer 13a was slightly preferred (13a:13b = 1.5:1), the observed selectivity cannot be attributed to sterical strain of the Tamura reagent. Possible less favorable orientation of the mesityl residue in the oxime intermediate towards ring A with bulky geminal dimethyl substitution should favor constitutional isomer 13b and not the observed isomer 13a. The constitutions of 13a and 13b were tentatively assigned by 2D-NOESY- and 2D-NOESY-HH-COSY experiments. Assignment was facilitated by the fact that the isomers have different proportions in the mixture.

Conclusions

Condensation of tricyclic nickel complex 9 and cyanopyrrole aldehyde 7 provided a facile synthetic access to ketochlorin 12. Subsequent cyclization of bilin intermediates 10 formed the macrocyclic chlorin in a 48% yield. The desired lactams were obtained by Beckmann rearrangement, also in good yields. Lactams 13a,b as protected amino acid like subunits should open an access to artificial photosynthesis models with a peptide/polyamide backbone.

Experimental Section

General. Starting materials were prepared either according to literature procedures or were purchased from Fluka, Merck, Acros Organics or Sigma Aldrich and used without further purification. All solvents were purified and dried by standard methods. All reactions were carried out under argon. Melting points are not corrected. TLC: Silica gel plates (Riedel de Haën, silica gel 60 F 254; Macherey-Nagel, Polygram SIL G/UV 254) and aluminium oxide plates (Macherey & Nagel, Polygram Alox N/UV 254). Column chromatographic separations were performed on silica gel (ICN Biomedicals, 32-63 μm, 60 Å). HPLC: Knauer HPLC instrument with pump 64, two-channel potentiometer BBC Metrawatt Servogor 120 recorder and Knauer UV spectrometer. UV/Vis: Kontron UVikon 810 spectrophotometer and Perkin Elmer UV/Vis spectrophotometer Lambda 2. IR: Perkin-Elmer Paragon 500 FT-IR-spectrometer. NMR spectra: Bruker DPX-200 AVANCE, Bruker AM 360 spectrometer and Bruker AMX spectrometer. All chemical shifts were referenced to TMS lock signal. Exact assignment of proton signals in 1H NMR spectra was achieved by two dimensional H,H-COSY and NOESY experiments. MS: Finnigan MAT 8200 and CH7A MAT spectrometer [E (70 eV) and DCI (NH3, 8 mA/s)]. HRMS: Finnigan MAT 8200 spectrometer according peak matching method. Elemental Analysis: Microanalytical Laboratories Beller, Göttingen, Germany and Pascher, Remagen, Germany.

Benzyl 3-formyl-4,5,7,8-tetrahydrospiro-[cyclohepta[c]pyrrole-6(2H),2’-[1,3]dioxolane]-1-carboxylate (4).
To a solution of benzyl 4,5,7,8-tetrahydrospiro-[cyclohepta[c]pyrrole-6(2H),2’-[1,3]dioxolane]-1-carboxylate (3) (394 mg, 1.2 mmol) in DMF (8 mL) was added with stirring under an argon atmosphere a solution of Vilsmeier reagent (440 µL) at 0 °C. The Vilsmeier reagent was separately prepared from POCl3 (330 µL, 554 mg,
3.6 mmol) and DMF (560 µL) under an argon atmosphere. After being stirred for 45 min at 40 °C, aqueous saturated NaOAc (20 mL) was added and stirring was continued for 15 min. After being cooled to rt, the reaction mixture was poured into a separating funnel which contained ice water (30 mL) and it was extracted five times with CH₂Cl₂ (20 mL each portion). The combined organic layers were dried by filtration through cotton wool and evaporated. The colorless solid was purified through flash chromatography [silica gel (40 g), CH₂Cl₂/EtOAc 9:1]. After removal of the eluent and crystallization from CHCl₃/n-pentane 4 was obtained as colorless crystals (366 mg, 86%). mp 101 °C. TLC (silica gel, CH₂Cl₂/EtOAc 9:1): Rf 0.54. IR (solid, KBr, vmax, cm⁻¹): 3298s (N-H), 2949m (CH, aliph), 1705s (C=O), 1660s (C=O), 1560, 1464, 1253, 1192, 1109, 1282, 1032, 983, 947. ¹H NMR (360 MHz, CDCl₃): δH 2.84 [4H, m, H₂C(5), H₂C(7)], 2.91 [2H, m, H₂C(4)], 3.07 [2H, m, H₂C(8)], 4.02 [4H, m, H₂C(4”), H₂C(5”)], 5.32 (2H, m, CH₂Ph), 7.40 (5H, m, C₆H₅), 9.37 (1H, broad s, NH), 9.77 (1H, s, CHO). El-MS (70 eV, 200 °C): m/z (%) 355 (66, M⁺), 264 (100, [M-C₆H₅]⁺), 246 (22), 174 (12), 91 (96, [C₃H₇]⁺). Anal. calcd for C₂₀H₂₁NO₅ (355.39): C, 67.59; H, 5.97; N, 3.94. Found: C, 67.69; H, 6.04; N, 3.87.

3-Bromo-4,5,7,8-tetrahydrospiro[cyclohepta[c]pyrrole-6(2H),2’-[1,3]dioxolane]-1-carbaldehyde (5). To a solution of formyl benzyl ester 2 (80 mg, 225 µmol) in THF (15 mL) were added few drops of NE₃ and a small amount of Pd/C catalyst under an argon atmosphere. After replacement of argon by hydrogen the mixture was hydrogenated under stirring for ca. 30 min. The catalyst was removed by filtration through Celite 521, washed with THF and, the solvent evaporated. After removal of NE₃ in vacuo of an oil pump, 3-formyl-4,5,7,8-tetrahydrospiro[cyclohepta[c]pyrrole-6(2H),2’-[1,3]dioxolane]-1-carboxylic acid (4a) was obtained as a colorless solid (60 mg, 100%). TLC (silica gel, CH₂Cl₂/EtOAc 9:1): Rf 0.1. El-MS (70 eV, 200 °C): m/z (%) 265 (69, M⁺), 221 (8, [M-C₆H₄O]⁺), 86 (100), 44 (10, C₆H₄O⁻).

The carboxylic acid was used for the next reaction step without complete characterization. To a solution of pyrrole carboxylic acid 4a (60 mg, 225 µmol) in DMF (2 mL) was added slowly N-bromo succinimide (80 mg, 450 µmol) dissolved in DMF (2 mL) and the mixture was stirred for 1 h at 50 °C. After being cooled to rt, the reaction mixture was poured into a separating funnel which contained water (10 mL) and extracted three times with CH₂Cl₂ (10 mL each portion). The combined organic extracts were dried by filtration through cotton wool and evaporated. The residue was purified by flash chromatography [silica gel (20 g), CH₂Cl₂/EtOAc 9:1]. After removal of the eluent a light-yellow oil was obtained which was crystallized from CHCl₃/n-pentane to yield light pink crystals of 5 (30.4 mg, 45%). mp 172 - 173 °C. TLC (silica gel, CH₂Cl₂/EtOAc 9:1): Rf 0.21. IR (solid, KBr, vmax, cm⁻¹): 3222s (N-H), 3015, 2937, 2880, 1639s (C=O), 1428, 1377, 1339, 1278, 1200, 1110, 1068, 1034, 948, 948, 877, 816, 743. ¹H NMR (360 MHz, CDCl₃): δH 1.80 [2H, m, H₂C(5)], 1.87 [2H, m, H₂C(7)], 2.57 [2H, m, H₂C(4)], 2.9 [2H, m, H₂C(8)], 4.01 [4H, s, H₂C(4’), H₂C(5’)], 9.12 (1H, broad s, NH), 9.49 (1H, s, CHO). Exact attribution of proton signals was determined by 1D-HH-SEL-NOESY and 1D-HH-SEL-COSY experiments. El-MS (70 eV, 200 °C): m/z (%) 301 (100, [M, ⁸¹Br⁺]). 299 (97, [M, ⁷⁹Br⁺]), 258 (12, [M, ⁸¹Br⁺-C₆H₅O]), 256 (31, [M, ⁷⁹Br⁺-C₆H₅O]), 220 (36, [M-Br⁺]), 213 (19), 186 (6), 148 (7), 118 (5), 105 (10), 87 (13), 65 (11), 43 (17). HRMS: Calcd for (C₁₂H₁₄NO₃⁷⁹Br⁻) 299.01572. Found: 299.015.

3-Iodo-4,5,7,8-tetrahydrospiro[cyclohepta[c]pyrrole-6(2H),2’-[1,3]dioxolane]-1-carbaldehyde (8). Pyrrole carboxylic acid (4a) (143 mg, 0.54 mmol) was prepared by hydrogenolysis as described above and mixed together with NaHCO₃ (181 mg, 2.16 mmol) in water (20 mL). The mixture was heated under an argon atmosphere to 70 °C until the solution became homogenous. At the same time KI (266 mg, 1.6 mmol) and I₂ (150 mg, 670 µmol) were dissolved in MeOH (6 mL) by treatment in an ultrasonic bath. The iodine solution was then added during 30 min at 70 °C to the solution of carboxylic acid. After stirring for additional 10 min at 70 °C, Na₂O₃ was added and the reaction mixture was cooled to rt. The aqueous layer was extracted four times with CH₂Cl₂ (10 mL each portion). The combined organic extracts were dried by filtration through cotton
wool, the solvent evaporated and the residue dried in vacuo of an oil pump. The residue was purified by flash chromatography [silica gel (30 g), CH₂Cl₂/EtOAc 9:1]. After removal of the eluent the obtained solid was crystallized from CHCl₃/n-pentane to yield brownish crystals (90 mg, 47%). mp 189 - 190 °C. TLC (silica gel, CH₂Cl₂/EtOAc 9:1): Rf 0.3. IR (solid, KBr, vmax, cm⁻¹): 3217, 2948, 2877, 1644s (C=O), 1438, 1422, 1375, 1195, 1111, 1068, 1032, 745. ¹H NMR (360 MHz, CDC₁₃): δH 1.79 [2H, m, H₂C(5)], 1.87 [2H, m, H₂C(7)], 2.54 [2H, m, H₂C(4)], 2.91 [2H, m, H₂C(8)], 4.02 [4H, m, H₂C(4''), H₂C(5'')], 8.93 (1H, broad s, N-H), 9.40 (1H, s, CHO). El-MS (70 eV, 200 °C): m/z (%) 347 (91, M⁺), 304 (20, [M-C₂H₅O⁺]), 285 (19), 274 (20, [M-C₂H₆O⁺ CHO⁺]), 261 (30), 260 (23), 233 (11), 220 (46, [M-I⁻]), 176 (22, [M-C₂H₅O⁻ I⁺]), 148 (21), 147 (21), 134 (17), 130 (13), 120 (15, [M-C₆H₁₂O₂⁺]), 119 (12), 118 (22), 106 (35), 105 (45), 104 (24), 103 (11), 93 (10), 91 (14), 87 (100), 79 (23), 77 (23), 45 (10), 43 (11). HRMS: Calcd for (C₁₀H₁₀N₂O⁺) 347.00183. Found 347.00173.

3-Formyl-4,5,7,8-tetrahydrospiro[cyclohepta[c]pyrrole-6(2H),2'-[1,3]dioxolene]-1-carbonitrile (7). To a solution of 4,5,7,8-tetrahydrospiro[cyclohepta[c]pyrrol-6(2H),2'-[1,3]dioxolane]-1-carbonitrile (6) (94 mg, 431 µmol) in DMF (10 mL) was added with stirring under an argon atmosphere a solution of Vilsmeier reagent (163 µmol) at 5 °C. The Vilsmeier reagent was separately prepared from POCl₃ (120 µL, 202 mg, 1.31 mmol) and DMF (210 µL, 2.62 mmol) with stirring for 15 min at 15 °C under an argon atmosphere. After being stirred for 16 h at 40 °C, aqueous saturated NaOAc (25 mL) was added and stirring was continued for 15 min. After being cooled to rt the reaction mixture was poured into a separating funnel which contained ice water (40 mL) and extracted three times with CH₂Cl₂ (15 mL each portion). The combined organic layers were dried by filtration through cotton wool and evaporated. DMF residues were removed in vacuo of an oil pump and the obtained solid was purified by flash chromatography [silica gel (20 g), CH₂Cl₂/EtOAc 9:1]. After removal of eluent the residue was crystallized from CHCl₃/n-pentane to yield colorless crystals (65 mg, 61%). mp 180 °C. TIC (silica gel, CH₂Cl₂/EtOAc 9:1): Rf 0.31. IR (solid, KBr, vmax, cm⁻¹): 3259, 3026, 2928, 2887, 2855, 2728, 2222s (CN), 1653s (CHO), 1464, 1386, 1203, 1115, 1085, 1029, 949, 876, 825. ¹H NMR (360 MHz, CDC₁₃): δH 1.89 [2H, m, H₂C(5)], 1.95 [2H, m, H₂C(7)], 2.81 [2H, m, H₂C(8)], 2.98 [2H, m, H₂C(4)], 4.09 [4H, m, H₂C(4''), 2 H₂C(5'')], 9.34 (1H, broad s, N-H), 9.81 (1H, s, CHO). Exact attribution of proton signals was determined by 1D- and 2D-NMR-experiments. EI-MS (70 eV, 200 °C): m/z (%) 247 (14, [M, 13C]⁺), 246 (100, M⁺), 216 (6), 203 (11, [M+1-C₂H₄O⁺]⁺), 202 (6, [M-C₂H₅O⁺]), 201 (11), 184 (8), 175 (5), 174 (19), 173 (34), 172 (14), 171 (5), 160 (21), 159 (31), 157 (8), 155 (5), 147 (7), 146 (15), 145 (16), 143 (10), 142 (6), 133 (8), 132 (24), 131 (48), 130 (6), 129 (9), 119 (5), 118 (10), 117 (7), 116 (8), 105 (17), 104 (23), 103 (8), 102 (7), 99 (5), 97 (7), 91 (12), 90 (6), 89 (6), 88 (5), 87 (61), 86 (7), 86 (14), 84 (20), 83 (6), 78 (8), 77 (21), 76 (6), 73 (11), 71 (10), 69 (10), 67 (6), 65 (12), 64 (7), 63 (6), 57 (18), 56 (6), 55 (19), 53 (9), 52 (7), 51 (9), 51 (11), 49 (33), 47 (5), 46 (15), 44 (18), 44 (20), 43 (20), 42 (18), 40 (15), 29 (8), 27 (9), 27 (12), 17 (17). HRMS: Calcd for (C₁₃H₁₄N₂O⁺) 246.10045. Found 246.10070. Anal. calcd for C₁₃H₁₄N₂O (248,66): C, 63.40; H, 5.73; N, 11.38. Found C, 64.23; H 6.20; N 10.66.

20,21,22,23-Tetrahydro-10,11,15,16,21,22,23-heptamethyl-3-oxo-24H-cyclohepta[b]bilin-6,22-dicarbonitrile (10a) and its [1,3]-dioxolane derivative (10b). To [Ethyl-(14RS)-(14-cyano-12,13,14,17-tetrahydro-2,3,8,13,13,14-heptamethyl-15H-tripyrrol-1-carboxylato)nickel(II)] (9) (5 mg, 10.5 µmol) in THF (2 mL) was added under stirring a 5 N solution of KOH in MeOH/H₂O (9:1) (0.9 mL, 2.8 mmol) and the mixture was heated at 70 °C under an argon atmosphere for 45 min. After being cooled to rt, the mixture was poured with CH₂Cl₂ (10 mL) into a separating funnel which contained a saturated aqueous NaHCO₃ solution (50 mL). The aqueous layer was subsequently extracted with CH₂Cl₂, the combined organic extracts were dried by filtration through cotton wool and evaporated in vacuo. To the obtained crude carboxylic acid of 9 was added under an argon atmosphere a solution of cyanopyrrole carbaldehyde 7 (3.9 mg, 16 µmol) in CHCl₃ (2 mL). To this solution was added via a syringe a 0.4 N degassed solution of dry p-TsOH in CHCl₃ (0.21 mL, 84 µmol). After being refluxed...
for 10 min and cooled to rt, the reaction mixture was poured with CH₂Cl₂ (10 mL) into a separating funnel which contained a saturated aqueous NaHCO₃ solution (50 mL). The aqueous layer was extracted five times with CH₂Cl₂ (10 mL each portion) and the combined organic extracts were dried by filtration through cotton wool and evaporated in vacuo. The residue was purified by chromatography [Alox N (30 g), activity II-III, CH₂Cl₂/MeOH 97:3] to yield a mixture of deep blue bilins 10a,b (4.4 mg 72%, yield is calculated for ketal 10b which predominates in the mixture). Due to instability of bilins the crude mixture was used for the next synthesis step without an extensive characterization. TLC (silica gel, CH₂Cl₂/EtOAc 9:1): Rᵢ¹ 0.72 10b; Rᵢ² 0.62 10a. UV/Vis [CHCl₃, λ, nm, (relative intensities)]: 370 (100), 570 (45), 608 (46). DCI-MS (negative, NH₃/NH₄⁺, mA/sec): m/z (%) 576 (12, [C₃₄H₄₆N₆O]), 533 (15, [C₃₂¹³CH₃₆N₆O⁺]), 532 (100, [C₃₃H₃₇N₅O⁺]), 507 (12, [C₃₂H₃₂N₂O⁺]).

[9,10-Dihydro-9,9,14,15,19,20-hexamethyl-3-oxo-24H,26H-cyclohepta[b]porphinato}zinc(II) (11a) and its [1,3]-dioxolane derivative (11b). Bilin mixture 11a,b (4.4 mg, 7.6 µmol) was transferred with CH₂Cl₂ (ca. 2 mL) into a glass ampule. After CH₂Cl₂ was removed in a stream of argon, Zn(OAc)₂ (12 mg, 52.5 µmol, 7 equiv.), sulfolane (1 mL) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (452 µL, 3.02 mmol) were added. The mixture was carefully degassed in vacuo of an oil pump and the ampule sealed by melting off. The reaction mixture was heated at 145 °C for 14 h. After being cooled to rt, the ampule was cautiously opened and, the mixture was poured with CH₂Cl₂ (10 mL) into a separating funnel. The organic layer was washed three times with brine (15 mL each portion). The combined brine layers were re-extracted with CH₂Cl₂ (10 mL). The combined organic extracts were dried by bulb to bulb distillation in vacuo of an oil pump at 120 °C. The dark-green residue was purified by flash chromatography (silica gel (30 g), CH₂Cl₂/MeOH 97:3, 0.5% NEt₃) to yield a dark-blue-solid (2.3 mg, 49% related to 9). For analytical purposes solids from different batches were combined and crystallized from CHCl₃/n-pentane.

Analytical data of 11b: mp > 350 °C (decomposition). TLC (silica gel, CH₂Cl₂/EtOAc 9:1): Rᵢ¹ = 0.73. UV/Vis [CHCl₃/petroleum ether, λ, nm, (ε, Lmol⁻¹·cm⁻¹)]: 398 (100309), 502 (4687), 536 (3750), 573 (4687), 617 (30000). IR (solid, NaCl, vmax, cm⁻¹): 3422, 3017, 2958, 2926, 2855, 1725, 1620, 1461, 1379, 1263, 1216, 1075, 948, 759, 668. 1H NMR (360 MHz, CDC₁₃ + trace of D₅ pyridine): δH 1.84 [6H, s, 2 H₂C-C(9)], 2.35 [4H, m, H₂C(2)], 2.12 [6H, d, H₂C(19)], 2.37 [4H, m, H₂C(20)], 3.65 [6H, d, H₂C(14)], 3.92 [2H, m, H-C(5)], 3.99 [2H, m, H₂C(1)], 4.12 [4H, m, OCH₂CH₂O], 4.36 [2H, s, H₂C(10)], 8.38 [1H, s, HC(22)], 8.44 [1H, s, HC(12)], 9.37 [1H, s, HC(17)]. Exact attribution of protons at C(22), C(17), C(12), 36 (7) and at C(1) und C(5) was determined by a 2D-NOESY experiment. El-MS (70 eV, 200 °C): m/z (%) 590 (7, [M,¹³C₂,⁶²Zn⁺]), 589 (19, [M,¹³C,⁶⁸Zn⁺]), 588 (34, [M,⁶⁸Zn⁺]), 587 (18, [M,¹³C,⁶²Zn⁺]) 586 (46, [M,⁶²Zn⁺]), 585 (22, [M,¹³C,⁶⁴Zn⁺]), 584 (73, [M,⁶⁴Zn⁺]), 556 (5, [M-C₂H₄⁺]), 543 (5), 529 (7), 528 (8, [M-C₂O₂⁺]), 527 (8), 526 (7), 525 (6), 472 (6), 471 (5), 470 (11), 468 (5), 457 (6), 455 (7). Isotope distribution of M⁺-Peaks (%): Calcd 590 (4.3), 589 (15.9), 588 (45.6), 587 (31.3), 586 (64.5), 585 (38.5), 584 (100). Found 590 (10), 589 (25.6), 588 (47.1), 587 (25.2), 586 (62.6), 585 (30.6), 584 (100). HRMS: Calcd for (C₃₃H₃₆N₄O₂⁶²Zn⁺) 584.21295. Found 584.21206.

Analytical of of 11a were not determined because 11a was only present as a minor component and due to the fact that in the next synthesis step a single product 12 is formed from 11a,b.

9,10-Dihydro-9,9,14,15,19,20-hexamethyl-24H,26H-cyclohepta[b]porphinato}zinc(II) (11a) and its [1,3]-dioxolane derivative (11b). To chlorin ketal 11b together with 11a (2 mg, 3.4 µmol) in CH₃CN was added perchloric acid (0.22 µL, 70%) and water (10 µL). The mixture was treated for 15 min at rt under an argon atmosphere in an ultrasonic bath. The reaction mixture was poured with CH₂Cl₂ into a separating funnel which contained aqueous, saturated NaHCO₃ (10 mL). After being exhaustively extracted with CH₂Cl₂, combined organic layers were dried by filtration through cotton wool and evaporated. The green solid was purified by flash chromatography (silica gel (10 g), CH₂Cl₂/EtOAc,
1% NEt₃). Crystallization from CHCl₃/n-pentane gave 12 as dark green microcrystals (1.6 mg, 97%). For analytical purposes crystals from different batches were combined. mp > 350 °C (decomposition). TLC (silica gel, CH₂Cl₂/MeOH 9:1): Rf = 0.66. UV/Vis [CHCl₃/petroleum ether λ, nm (ε, Lmol⁻¹cm⁻¹)]: 390 (190945), 495 (11811), 593 (3937), 646 (61024). IR (solid, KBr, vmax, cm⁻¹): 3340 (NH), 3020, 2918, 2850, 1702 (C=O), 1615, 1559, 1522, 1457, 1163, 1047, 906. 1H NMR (360 MHz, CDCl₃): δH -2.51 (2H, broad s, 2 NH), 2.06 [6H, s, 2 MeC(9)], 3.37 [2H, m, H₂C(2)], 3.42 [2H, m, H₂C(4)], 3.39, 3.49 (12H, 2 s, Me-C(14), Me-C(15), Me-C(19), Me-C(20)], 4.35 [2H, m, H₂C(5)], 4.45 [2H, m, H₂C(1)], 4.63 [2H, m, H₂C(10)], 8.75 [1H, s, HC(7)], 8.91 [1H, s, HC(12)], 9.64 [1H, s, HC(17)], 9.69 [1H, s, HC(22)]. Exact attribution of protons was determined by 2D-NOESY experiments. El-MS (70 eV, 200 °C): m/z (%) 480 (10, [M, ¹³C₂⁺]), 479 (39, [M, ¹³C⁺]), 478 (100, M⁺). HRMS: Calcd for (C₁₃H₁₃N₃O) 478.27325. Found 478.27265. Anal. calcd for (C₁₃H₁₃N₃O) 0.24 CHCl₃ 507,33: C, 73.39; H, 6.76, N, 11.04. Found C, 73.25; H, 6.55; N, 12,30.

### 10,11-Dihydro-10,10,15,16,20,21-hexamethyl-25H,27H-3-azacycloocta[b]porphin-4-on (13a) and 10,11-dihydro-10,10,15,16,20,21-25H,27H-4-azacycloocta[b]porphin-3-on (13b).

To a solution of chlorin ketone (12) (1 mg, 2.1 µmol) in CH₂Cl₂ (1mL) was added a solution of O-mesityl sulfonyl hydroxylamine (0.8 mg, 3.7 µmol) in CH₂Cl₂ (1mL) at 0 °C under an argon atmosphere. After being treated in an ultrasonic bath for 30 min at rt, the solvent was completely evaporated. The residue was re-dissolved in benzene (1 mL) under treatment in an ultrasonic bath and a suspension of Alox Super I basic in MeOH (0.1 mL) was added. After being stirred for 3 h at rt, the suspension was filtered through a glass frit and the solvent evaporated. The residue was purified by flash chromatography [silica gel (ca. 5 g), CH₂Cl₂/MeOH 9:1, 1% NEt₃]. After evaporation of eluent, the mixture of constitutionally isomeric lactams 13a,b was obtained as a dark green solid (0.8 mg, 77%). For analytical purposes samples from different batches were combined and crystallized from CHCl₃/n-pentane to give microcrystals of 13a,b. mp > 350 °C.

TLC (silica gel, CH₂Cl₂/MeOH 9:1): Rt = 0.81. HPLC (Nucleosil Chiral 2, n-heptane/dioxane 70:30, 1 mL/min): tr₁ = 16 min (peak integral 1); 13b ; tr₂ = 17.5 min (peak integral 1.5): 13a.

UV/Vis [CHCl₃, λ, nm (ε, Lmol⁻¹cm⁻¹)]: 391 (126903), 495 (15663), 590 (2708, 616 (2655), 647(45133). IR (solid, KBr, vmax, cm⁻¹): 3436, 3020, 2924, 2853, 1732, 1694, 1653, 1615, 1520, 1455, 1367, 1262, 1192, 1038, 817, 725, 663. I'N NMR (360 MHz, CDCl₃) for 13a: δH 2.1 [6H, s, 2 MeC(10)], 3.44, 3.54 [12H, m, MeC(15), MeC(16), MeC(20), MeC(21)], 3.5 [2H, m, H₂C(5)], 3.53 [2H, m, H₂C(2)], 4.45 [2H, m, H₂C(6)], 4.57 [2H, m, H₂C(1)], 4.68 [2H, m, H₂C(11)], 5.89 [1H, m, HN(3)], 8.75 [1H, s, HC(8)], 8.91 [1H, s, HC(13)], 9.67 [1H, s, HC(18)], 9.74 [1H, s, HC(23)]. For 13b: δH [6H, s, 2 MeC(10)], 3.44, 3.54 [12H, m, MeC(15), MeC(16), MeC(20), MeC(21)], 3.45 [2H, m, H₂C(5)], 3.46 [2H, m, H₂C(2)], 4.49 [2H, m, H₂C(6)], 4.55 [2H, m, H₂C(1)], 4.68 [2H, m, H₂C(11)], 5.37 [1H, broad s, HN(4)], 8.83 [1H, s, HC(8)], 8.93 [1H, s, HC(13)], 9.67 [2H, s, HC(18), HC(23)]. Tentative attribution of protons of constitutional isomers 13a and 13b was achieved by 2D-NOESY and 2D-NOESY-HH-COSY experiments. Attribution and designation of constitutions was facilitated by the fact that the constitutional isomers 13a and 13b were formed and are present in the NMR sample in a 1.5:1 ratio. DCI-MS (negative, NH₃/NH₄⁺, mA/sec): m/z (%) 480 (6), 547 (8), 494 (15 [M,¹³C⁺]), 493 (60, M⁻), 492 (10 [M-H⁻]), 491 (10), 477 (14), 476 (15), 475 (40), 474 (5), 473 (17), 460 (14), 391 (5), 390 (14), 199 (21), 198 (11), 168 (5), 166 (11), 152 (6), 151 (18), 150 (25), 148 (13), 147 (23), 136 (5), 125 (11), 121 (10), 119 (25), 83 (15).

HRMS: Calcd for (C₃₃H₳₃N₃O) 493.28415. Found 493.28470.
Acknowledgements

We thank Dr. P. Schulze, Mrs. I. Erxleben, Dipl.-Ing. J. Stelten (Institute of Organic and Analytical Chemistry, Laboratory Prof. Dr. D. Leibfritz, University of Bremen) for mass spectrometry and NMR spectroscopy measurements. In particular we are indebted Mrs. A. Lincke for performing HPLC separations. This work was supported by Deutsche Forschungsgemeinschaft.

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