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Synthesis of a Peptide-Linked Chlorin Dyad as a Model Compound for the Photosynthetic Reaction Centre

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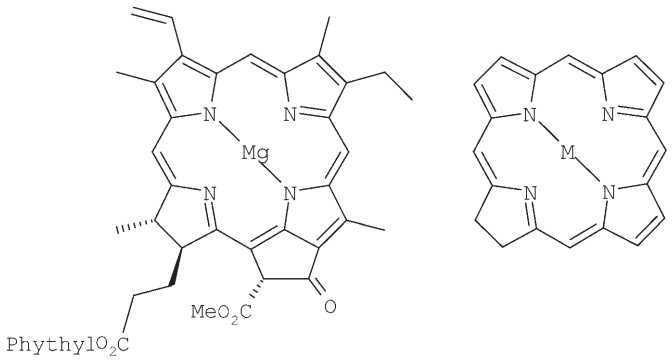
Dedicated to Professor Gerhard Quinkert on the occasion of his 80th birthday

Abstract: The enantiomerically pure chlorins **19** and **21** were synthesised from tripyrrolic nickel complex *rac*-**17** and pyrrole building blocks **12** and **16**. The pyrroles are annelated with norbornane moieties which contain the chiral information as well as two different functionalities. The functional groups, namely a carboxylic acid ester and a carbonitrile group, of chlorin **21** finally allowed the formation of an amino acid functionality at the periphery of the macrotetracycle. By using principles of peptide chemistry, the two chlorin subunits were joined to form the peptide-linked chlorin–chlorin dyad **24**, which mimics the molecular parts of the natural photosynthetic reaction centre.

Keywords: chlorin · dyes/pigments · peptide linkages · photosynthesis · porphyrinoids

Introduction

The elementary step of photosynthesis in bacteria and plants is the light-induced electron transfer from the special pair of (bacterio)chlorophylls *a* (**1**) and *b* along a chain of further (bacterio)chlorophyll pigments to quinone acceptors, in which the electrons are first stored in a hydroquinone structure.[1] Knowledge of the structures of naturally occurring photosynthetic reaction centres originates from crystal-structure investigations.[2] The first investigations into the bacterial photosynthetic reaction centres not only elucidated the spacial arrangement of pigments (Figure 1) but also that of the membrane proteins to which the bacteriochlorophylls are anchored by lipophilic interactions.[3]



Numerous artificial-photosynthesis model systems were designed to study the factors influencing the light-induced electron-transfer reaction that is the key photosynthesis step.[4] The majority of model systems so far consist of porphyrin subunits,[4,5] which have different photophysical properties to the "natural" chlorin chromophore **2**. There are, however, a few exceptions which make use of pigments derived from naturally occurring chlorophyll *a* (**1**).[6].

To obtain photosynthesis models based on chlorin pigments which mimic the spacial arrangement of naturally occurring systems, we aimed to synthesise the enantiomerically pure chlorin **7** (Scheme 1). The carboxylic acid group and

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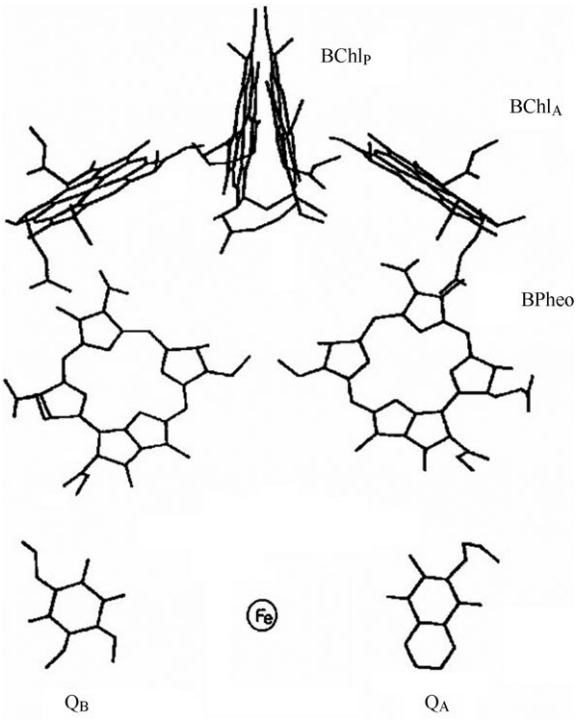


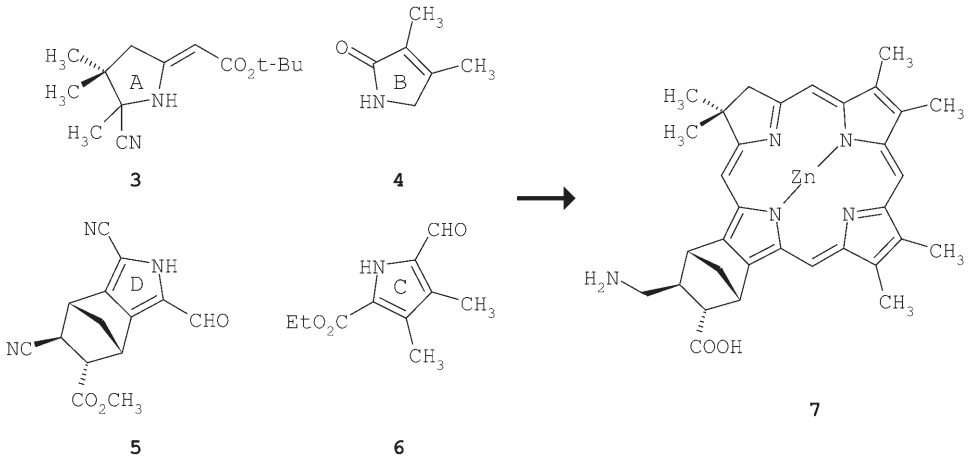
Figure 1. Schematic representation of the spacial arrangement of the pigments in the bacterial photosynthetic reaction centre of *Rhodopseudomonas viridis*.[2] BChl: bacteriochlorophyll; BPheo: bacteriopheophytin.

flexibility and selectivity due to the application of four distinct building blocks, **3**–**6**, which can be structurally modified with respect to the envisaged substitution pattern of the target chlorin.

Results and Discussion

An intermediate in previous syntheses of chlorins and corrins, the tricyclic nickel complex *rac*-**17** (see Scheme 4), is also useful for the synthesis of the desired chlorin intermediates **19** and **21**. The nickel complex *rac*-**17** was synthesised previously from the pyrrolic building blocks **3**, **4** and **6**.[7a,b]

To achieve a chlorin structure such as **7**, a new enantiomeric D-ring building block was required for the synthetic route. Pyrroles attached to chiral norbornane moieties with carboxylic acid functions were prepared in our laboratory from α,β-unsaturated sulfone derivatives[9] according to Schöllkopf's isocyanide method[10] for the construction of heterocyclic ring systems. The α,β-unsaturated sulfone starting compound for the pyrrole synthesis was obtained from the sulfone lactone carboxamide **8**.[9a] Carboxamide **8** was prepared from norbornene dicarboxylic acid[11] in 100% enantiopurity, which is preserved during the whole synthetic sequence. During the course of the present synthetic studies, we found that the enantiomerically pure tricyclic lactone carboxamide **8** could be treated directly with isocyanides to yield the pyrrole intermediate **9** (Scheme 2).



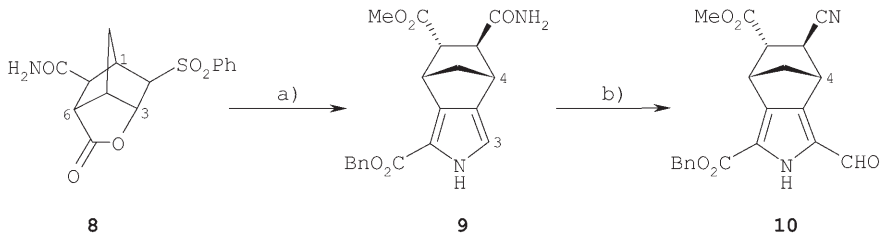
Scheme 1. Synthetic concept for the construction of chlorin subunit **7** from monocyclic building blocks **3**–**7**.

The reaction of **8** with benzyl isocyanoacetate under basic reaction conditions first yields the α,β-unsaturated sulfone function desired for pyrrole-ring formation with the isocyanide. The pyrrole **9** was further functionalised by Vilsmeier formylation at the free α-position to form pyrrole **10**. Under the reaction conditions of the formylation process, the carboxamide group at the norbornane periphery was also transformed into a cyano function, which is thus ready for the reduction reaction planned for the very end of the whole synthetic sequence.

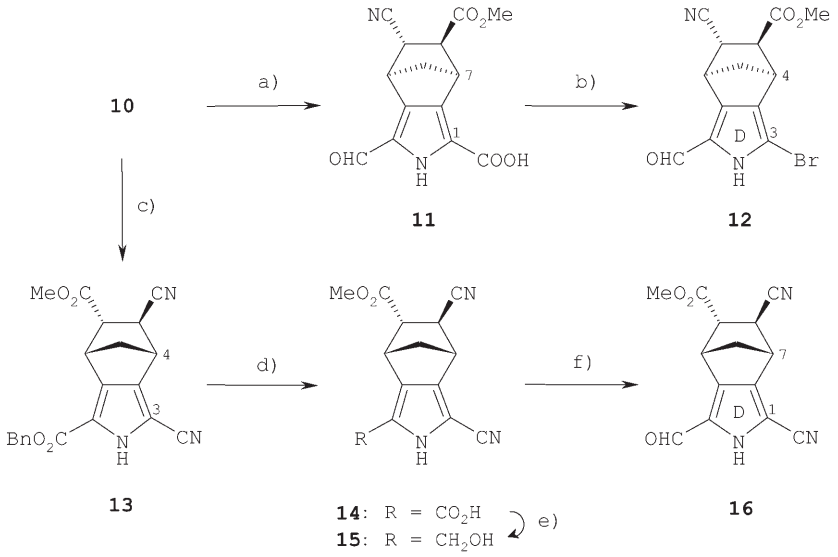
From the pyrrole aldehyde **10**, two routes were followed to produce the slightly different D-ring building blocks **12** and **16** (Scheme 3). On the more direct path, the α-benzyl ester function of **10** was cleaved by hydrogenation and this was followed by decarboxylative bromination to yield the bromopyrrole aldehyde **12**. With the aldehyde function and the bromo substituent, building block **12** is ready to be introduced into the synthetic scheme that leads to chlorin **19**.[7c] At first glance, this reaction sequence looks very at-

the amino function of **7** should allow covalent linkages, similar to those in peptides, between the chlorin subunits, thereby forming oligomers or chlorin acceptor systems. The conformation of the peptide-like backbone could lead to similar orientations of the pigments to those found in the protein–pigment interactions of the natural systems.

Enantiomerically pure subunits are required to obtain stereochemically homogenous oligomeric systems. It should be possible to construct the target chlorin subunit **7** according to the concept we developed for the total synthesis of chlorins[7] and corrins.[8] The merits of this concept are the high



Scheme 2. a) 1) $CNCH_2CO_2Bn$, THF, *t*BuOK, RT, 1 h; 2) THF, CH_2N_2/diethyl ether, 73%; b) DMF, $POCl_3$, 80°C, 2 h, 60%.



Scheme 3. a) Pd/C, H_2, THF/NEt_3, RT, 30 min, 100%; b) pyridinium perbromide, pyridine, CH_2Cl_2, room temperature, 18 h, 45%; c) 1) NaOAc, $HONH_2$·HCl, MeOH, RT, 30 min; 2) carbonyl diimidazole, $CHCl_3$, RT, 16 h, 84%; d) THF, HOAc, Pd/C, H_2, RT, 2 h, 100%; e) 1) THF, $SOCl_2$, 50°C, 2 h; 2. THF, Li 9-BBNH, −80°C, 30 min, 60%; f) THF, H_2O, HOAc, CAN, room temperature, 2 h, 77%. CAN: ceric ammonium nitrate; Li 9-BBNH: lithium 9-borobicyclo[3.3.1]nonane hydride.

tractive, but the yield of 45% after the bromination step is rather low and unfortunately not very reproducible.

Therefore, we envisaged an alternative route that leads to the D-ring building block **16** in a similar yield but with high reproducibility. The formyl function was transformed through oxime formation into an α-cyano group and this was followed by debenzylation to yield the carboxylic acid derivative **14**. As expected, a direct decarboxylative Vilsmeier formylation of **14** failed, due to deactivation of the pyrrole ring by the electron-withdrawing cyano substituent.

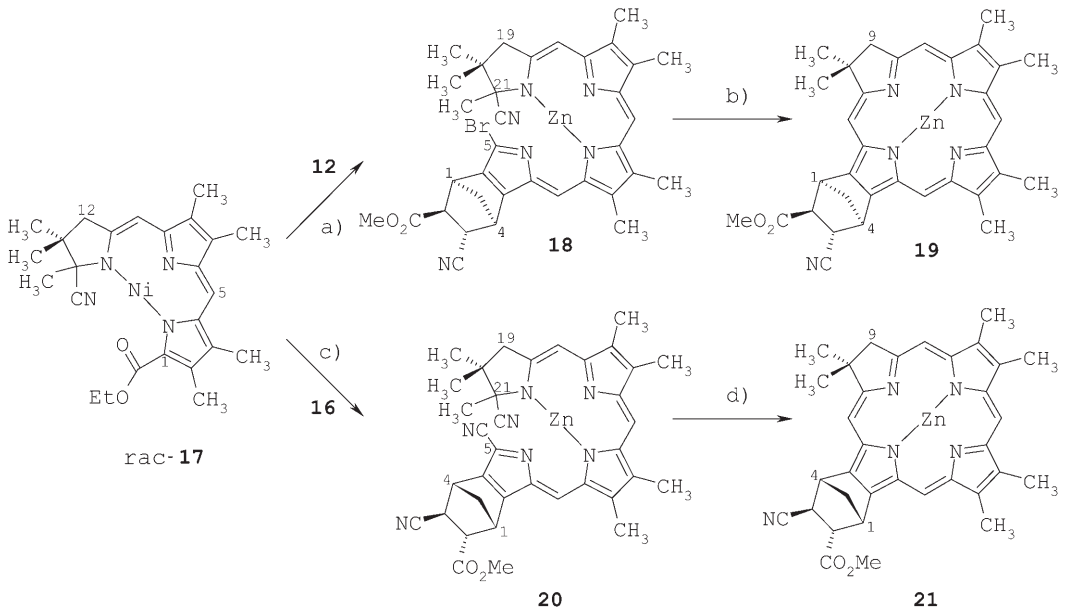
To achieve the goal, the carboxylic acid chloride was prepared and reduced with lithium 9-BBN hydride at low temperature to produce alcohol **15**. CAN oxidation of the alcohol function yielded the D-ring building block **16** with the formyl and cyano functionalities necessary for completion of the synthesis of chlorin macrotetracycle **20**. This protocol for the transformation of a pyrrolic α-carboxylic acid group into an α-hydroxymethyl or α-formyl function could be of general interest for pyrrole and tetrapyrrole chemistry because these functions are generally used for linking pyrrole units together.

Synthesis of chlorin subunits: With the D-ring building blocks **12** and **16** at hand, the target chlorins **19** and **21** could be synthesised. After hydrolysis of the ester group in *rac*-**17**, the pyrrole aldehydes **12** or **16** were linked in the presence of acid to the tricycle by decarboxylation and decomplexation (Scheme 4). Recomplexation of the resulting linear tetrapyrrolic macrocycles with zinc(II) acetate gave the metal complexes **18** and **20**. The zinc stabilises the quite sensitive macrocycles and exercises a template effect in the final cyclisation process.

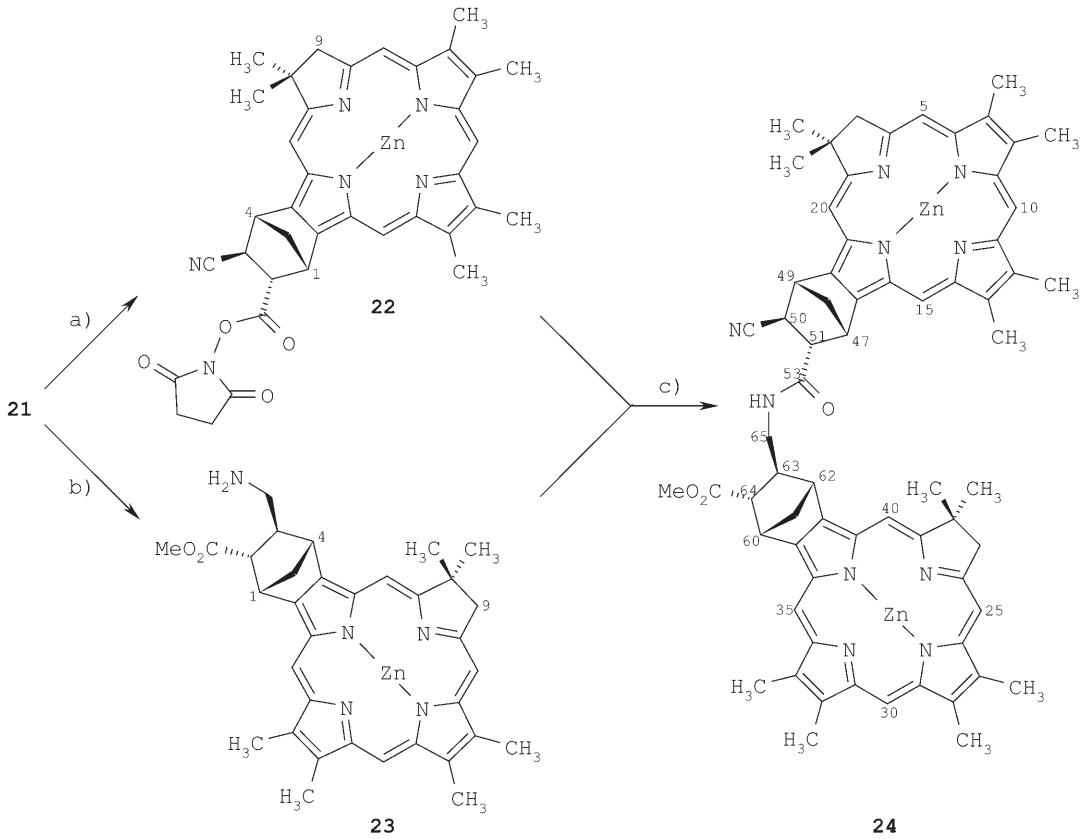
Both metal complexes **18** and **20** were obtained as a ternary mixture of enantiomerically pure diastereomers on account of the chiral centres at the C21 atoms and because of the helicity of the tetrapyrrolic chromophore. Due to these stereochemical features, we did not carry out full characterisations of the linear tetrapyrroles **18** and **20**. In the case of the zinc complex **18**, cyclisation was initiated by base-induced elimination of HCN from C21 and this was followed by attack of the resulting enamine structure on C5. The formation of the target chlorin **19** was completed by HBr elimination. The zinc complex **20** cyclised on heating in trichlorobenzene to yield the desired chlorin **21**. Here, enamine formation is also initiated by HCN elimination from C21 and the cyclisation process is completed by loss of HCN from C5. The two chlorins differ from each other constitutionally in the positions of the cyano and methoxycarbonyl groups and stereochemically by the configuration of the bridge-head atoms of the norbornane moieties. The stereochemical difference is reflected in opposite Cotton effects in the CD spectra of **19** and **21**. As chlorin **21** could be synthesised with higher reliability, it was chosen for continuation of the synthetic pathway.

Synthesis of a chlorin dyad: Chlorins **21** and **19** represent masked amino acid units, which could be transformed into amino acids by ester hydrolysis and by reduction of the cyano functions into aminomethyl groups.

The ester function of **21** was hydrolysed with potassium hydroxide under the usual reaction conditions (Scheme 5). The activation of the carboxylic acid group was best ach-



Scheme 4. a) 1. KOH, MeOH/H_2O 9:1, THF, reflux, 45 min; 2) **12**, $CHCl_3$, *p*TsOH, reflux, 20 min; 3) CH_2Cl_2, $Zn(OAc)_2$/NaOAc, MeOH, RT, 20 min, 52%; b) DBU, $Zn(OAc)_2$, sulfolane, 60°C, 2 h, 40%; c) 1) KOH, MeOH/H_2O 9:1, THF, 70°C, 30 min; 2) **16**, $CHCl_3$, *p*TsOH, reflux, 30 min; 3) CH_2Cl_2, $Zn(OAc)_2$/NaOAc, MeOH, RT, 40 min, 59%; d) 1,2,4-trichlorobenzene, 210°C, 40 min, 42%. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; *p*TsOH: *para*-toluenesulfonic acid.



Scheme 5. a) 1) **21**, KOH, MeOH/H_2O 9:1, THF, 60°C, 40 min; 2) DCC, NHS, CH_2Cl_2, RT, 90 min, 63%; b) 1) **21**, $CoCl_2 \cdot 6H_2O$/$NaBH_4$, THF/H_2O, 0°C, 20 min, then RT, 2 h; 2) NH_3, 15 min, 60–80%; c) **22**+**23**, DMAP, THF, RT, 3 h, 76%. DCC: *N*,*N*′-dicyclohexylcarbodiimide; DMAP: 4-dimethylaminopyridine; NHS: *N*-hydroxysuccinimide.

ieved by the N-hydroxy succinimide derivative **22**. Other activation reagents, such as *iso*-butyl chloroformate, did not work because the nucleophilic amino component reacted at the carbonyl function of the activation group and not at the activated but sterically hindered carboxyl group itself. The undesired reaction was established to have occurred by isolation of the corresponding carbamate derivative of amino component **23**.

The cyano group of chlorin **21** represents an ideal case of a protected amino function. Selective reduction of the cyano group with sodium borohydride/cobalt chloride transformed chlorin **21** into its amino derivative **23**,[12] which was thus ready for peptide coupling with the activated ester **22**. The actual reduction agent is a suspended heterogenous cobalt hydrido compound which is formed in situ from sodium borohydride and the cobalt salt.

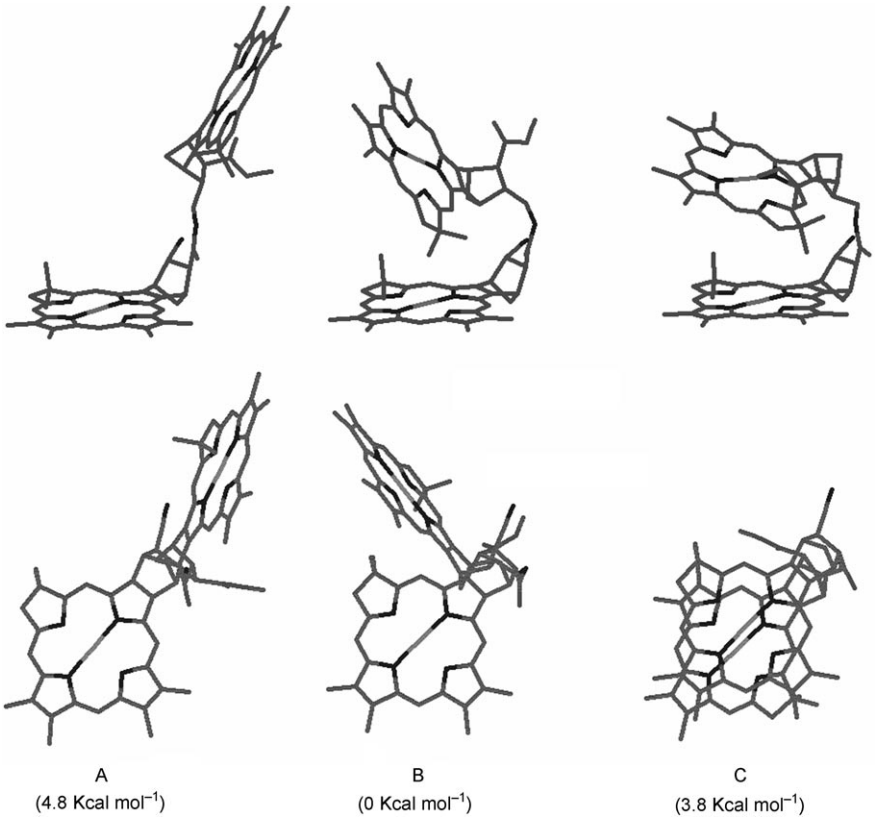


Figure 2. Two different views of stick drawings for each of the PM3-calculated preferred conformations A–C of dyad **24**. (Hydrogen atoms are omitted for clarity.)

Conformation of dyad 24: The structure of chlorin–chlorin dyad **24** was confirmed by its spectroscopic properties. ESI mass spectrometry (positive and negative) showed a molecular mass of 1186 and, with high-resolution conditions, a molecular formula of $C_{67}H_{66}N_{10}O_3Zn_2$. ^{1}H NMR and ^{13}C NMR spectra each consisted of two sets of ^{1}H and ^{13}C spectroscopic signals, respectively, which represented the two subunits. The ^{1}H and ^{13}C signals of the CO−NH−CH_2 part occurred at $\delta = 6.69$ (NH) and 2.93/3.29 ppm (CH_2) for the protons and at $\delta = 170.0$ (CO) and 45.3 ppm (CH_2) for the ^{13}C atoms.

The molar extinction coefficients of the UV/visible spectra of **24** showed double intensities (**24**: λ_{max} (ε) = 618 (87900), 395 nm (218000 mol^{-1} dm^3 cm^{-1})) compared to the monomers (for example, **19**: λ_{max} (ε) = 620 (33600), 396 nm (84900 mol^{-1} dm^3 cm^{-1})). The unchanged positions of the absorption bands of dyad **24** compared with those of the monomeric structure **21** also indicate that the two chlorin subunits do not interact electronically. The CD spectrum of dyad **24** is more complicated than those of the monomeric chlorins **19** and **21**.

The energetically preferred perpendicular conformation B of the chlorin subunits of dyad **24** follows from semi-empirical PM3 calculations (Figure 2). From a cofacial arrangement, as found in the special pair of the bacterial photosynthetic reaction centre (Figure 1), a semiempirical PM3 calculation gave three energetically favoured conformations.

Conformation B is lowest in energy and shows a perpendicular arrangement of the two chlorin subunits, which therefore should not show orbital interactions. This is indicated by the UV/visible spectrum as well as by NOE measurements on **24** and is confirmed by the PM3 calculation.

Interestingly, a similar arrangement of two chlorin subunits was found by PM3 modelling of covalently unlinked chlorins. It can be supposed that this particular arrangement originates in Coulomb interactions between the macrocycles.

Conformation C, the next highest in energy, shows a cofacial arrangement of the chlorin subunits and is structurally similar to the arrangement of the special-pair chlorins of the bacterial photosynthetic reaction centre. In contrast to the natural special pair (Figure 1) with an average distance of 3.4 Å between the two subunits, the artificial pair exhibits a distance of 7.5 Å between the centres of the monomers.

Conformation A is the highest in energy and the two chlorin subunits have again a perpendicular orientation; however, in contrast to conformation B, which has a roof-like shape, one side of the roof here is turned outside around one edge. It is most likely that additional energetically favoured conformations exist, but it is impossible to

calculate the whole conformational space of the molecule due to the extended size of dyad **24**.

Conclusion

The conformational arrangement B found for the peptide-linked chlorin–chlorin dyad mimics, more or less, the accessory bacteriochlorophyll–bacteriopheophytin part of the bacterial photosynthetic reaction centre (Figure 1). However, similar spacial arrangements can also be found in photosynthetic systems I and II of plants. With the concept described here, a module system is available which could be applied for mimicking more complicated parts of the naturally occurring photosynthetic systems.

Experimental Section

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. ^{1}H NMR spectra were measured with Bruker DPX-200 Avance or Avance NB-360 MHz spectrometers; all chemical shifts were referenced to the tetramethylsilane lock signal. MS and HRMS were performed on a Finnigan MAT 8200 spectrometer (EI (70 eV), DCI (NH_3, 8 mA s^{-1}) and ESI (solvent)) while ESI-HRMS was performed with an APEX Qe9.4T instrument (9.4 T superconducting magnet) with an Apollo II electrospray ioniser. IR spectra were measured with a Perkin–Elmer Paragon 500 FTIR spectrometer. UV/visible analysis was carried out on a Varian Cary 50 spectrophotometer. Column chromatographic separations were performed on silica gel (32–63 μm, 60 Å, ICN). Melting points are uncorrected and were determined on a Reichert Thermovar hot-stage apparatus or on a Gallenkamp apparatus. Optical rotations were measured with a Perkin–Elmer 243 polarimeter with a water-jacket cell length of 1 dm and the concentration, c, is given in g 100 mL^{-1}. CD spectra were recorded on a JASCO J-600 spectropolarimeter with a water-jacket cell length of 1 dm. Elemental analyses were performed by Mikroanalytisches Laboratorium Beller, Göttingen (Germany).

1-Benzyl-6-methyl-[(4*R*,5*S*,6*S*,7*S*)-5-carbamoyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-isoindole-1,6-dicarboxylate] (9): Benzyl isocyanide (266 mg, 1.5 mmol, 2.5 equiv) was dissolved in dry THF (1 mL) and then a solution of potassium *tert*-butylalcoholate (170 mg, 1.5 mmol, 2.5 equiv) in dry THF (5 mL) was added quickly under an argon atmosphere and the mixture was vigorously stirred at room temperature. After 5 min, a solution of (−)-(1*R*,2*R*,3*R*,6*S*,7*S*,9*R*)-5-oxo-2-*exo*-(phenylsulfonyl)-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-*exo*-carboxamide (**8**,[9a] 195 mg, 0.6 mmol) in dry THF (15–20 mL) was added to the colourless suspension. After 1 h of stirring at room temperature, the reaction mixture was quenched by addition of brine and stirred for a further 20 min. The organic layer was separated and washed with sodium bicarbonate solution. The combined aqueous layers were acidified to pH 2 with a 2 N solution of HCl and were extracted four times with ethyl acetate. The organic layers were dried by filtration over cotton wool and concentrated in vacuo. The colourless residue was dissolved in dry THF and treated with diazomethane until no more N_2 evolved. Thereafter, the solvent was removed in vacuo and the yellow crude product was chromatographed on silica gel with elution with CH_2Cl_2/MeOH 9:1. After removal of the eluent in vacuo, **9** was obtained as a yellow oil. For analytical purposes, the product was crystallised from $CHCl_3$/*n*-hexane. Yield: 160 mg (0.434 mmol, 73 %); R_f = 0.38 (silica gel, CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20} = -85.8$ (c = 3.74 in CH_2Cl_2); m.p. 180 °C (racemic); ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 1.72 (d, ^2J = 8.64 Hz, 1H; 8-CH$_2$), 2.08 (d, ^2J = 8.64 Hz, 1H; 8-CH$_2$), 2.50 (m, 1H; 5-CH), 3.25 (s, 3H; OCH_3), 3.32 (m, 1H; 7-CH), 3.53 (t, ^3J = 4.32 Hz, 1H; 6-CH), 3.74 (m, ^3J = 4.03 Hz, 1H; 4-CH), 5.23 (AB, ^2J = 12.67 Hz, 2H; CO_2CH_2Ph), 6.66 (d, ^3J = 2.88 Hz, 1H; 3-CH), 6.95 (br s, 2H; NH), 7.34 (m, 1H; H$_p$), 7.41 (m, 2H; H$_o$), 7.48 (m, 2H; H$_m$), 7.57 (br s, 1H; NH), 11.11 ppm (br s, 1H; 2-NH); IR (KBr): $\tilde{\nu}$ = 3410 (NH), 3380 (NH), 1730 (C=O), 1700 (C=O), 1675 cm^{-1} (C=O); MS (EI, 70 eV, T = 168 °C): m/z (%): 368 (21) [M^+], 337 (3) [$M^+ - OCH_3$], 277 (1) [$M^+ - CH_2Ph$], 239 (48), 148 (19), 130 (100); elemental analysis: calcd (%) for $C_{20}H_{20}N_2O_5$: C 65.21, H 5.47, N 7.60; found: C 65.35, H 5.60, N 5.72.

1-Benzyl-6-methyl-[(4*R*,5*S*,6*S*,7*S*)-5-cyano-3-formyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-isoindole-1,6-dicarboxylate] (10): For preparation of the Vilsmeier reagent, $POCl_3$ (372 μL, 4.07 mmol, 10 equiv) was added to dry DMF (1.2 mL) at 0 °C under an argon atmosphere and the mixture was stirred for 15 min. The Vilsmeier reagent was added to a solution of **9** (150 mg, 0.407 mmol) in dry DMF (4 mL) cooled to 5 °C and the solution was then heated for 2 h at 80 °C. The reaction was quenched by addition of saturated sodium acetate solution (5 mL) and stirred for a further 20 min at 80 °C. Thereafter, the reaction mixture was diluted with water (10 mL), extracted four times with CH_2Cl_2 and dried by filtration over cotton wool. After removal of CH_2Cl_2, the DMF was evaporated by Kugelröhr distillation under reduced pressure. The brown residue was chromatographed on silica gel (20 g) with CH_2Cl_2/EtOAc 15:1 as the eluent to give **10** as a colourless solid. For analytical purposes, the product was crystallised from $CHCl_3$/*n*-hexane. Yield: 92.4 mg (0.24 mmol, 60 %); R_f = 0.23 (silica gel, CH_2Cl_2/EtOAc 15:1), 0.76 (silica gel, CH_2Cl_2/MeOH 10:1); m.p. 225–227 °C; $[\alpha]_D^{20} = -49.0$ (c = 0.78 in CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.25 (2 dd, ^2J = 9.8, $^3J = {}^4J$ = 1.5 Hz, 1H; 8-CH$_2$), 2.36 (d, ^2J = 9.8 Hz, 1H; 8-CH$_2$), 3.03 (dd, ^3J = 4.4, ^4J = 1.5 Hz, 1H; CHCN), 3.39 (s, 3H; OCH_3), 3.57 (dd ("t"), ^3J = 4.4 Hz, 1H; 6-CH), 4.01 (s, 1H; 4-CH), 4.09 (d, ^3J = 3.9 Hz, 1H; 7-CH), 5.33 (s, 2H; CO_2CH_2Ph), 7.43 (m, 5H; Ph), 9.54 (br s, 1H; NH), 9.69 ppm (s, 1H; CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.83 (5-C), 44.34 (7-C), 44.72 (4-C), 52.22 (6-C), 52.73 (8-C), 52.85 (OCH_3), 67.55 (CH_2Ph), 120.78 (1-C), 121.53 (CN), 125.94 (3-C), 128.89, 129.14, 129.29 (2′-C, 3′-C, 4′-C), 135.47, 135.61 (1′-C, 7a-C), 139.62 (3a-C), 160.14 (CO_2Bn), 171.35 (CO_2CH_3), 179.29 ppm (CHO); IR (KBr): $\tilde{\nu}$ = 3290 (NH), 2237 (CN), 1726 (C=O), 1668 cm^{-1} (C=O); MS (EI, 70 eV, T = 188 °C): m/z (%): 379 (5), 378 (14) [M^+], 347 (2) [$M^+ - OCH_3$], 319 (1) [$M^+ - CO_2CH_3$], 287 (2) [$M^+ - CH_2Ph$], 267 (34) [$M^+ - C_5H_5NO_2$], 239 (5) [$M^+ - OCH_3 - OCH_2Ph$], 92 (9), 91 (100) [CH_2Ph^+]; HRMS (EI): calcd for $C_{21}H_{18}N_2O_5$: 378.12157 [M^+]; found: 378.12152.

(4*R*,5*S*,6*S*,7*S*)-5-Cyano-3-formyl-6-(methoxycarbonyl)-4,5,6,7-tetrahydro-4,7-methano-2*H*-isoindole-1-carboxylic acid (11): NEt_3 (4 drops) was added to a solution of **10** (348 mg, 0.92 mmol) in dry THF (3 mL). The mixture was degassed three times under reduced pressure and placed under an argon atmosphere. After addition of some milligrams of palladium catalyst (10 % palladium on activated charcoal), the system was evacuated three times and placed under hydrogen from a balloon fitted to the reaction flask. The reaction mixture was stirred at room temperature until complete conversion of the starting material, as monitored by TLC. The catalyst was removed by filtration over Celite 521 and the filtrate was concentrated in vacuo to afford **11** as colourless oil. Yield: 265 mg (0.92 mmol, 99 %); R_f = 0.20 (silica gel, CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20} = -18.8$ (c = 1.63 in MeOAc); ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.10 (AB, ^2J = 9.60, ^4J = 2.06 Hz, 2H; 8-CH$_2$), 2.74 (dd, ^3J = 4.80, ^4J = 2.06 Hz; 5-CH), 3.46 (s, 3H; OCH_3), 3.69 (dd ("t"), ^3J = 4.46 Hz, 1H; 6-CH), 3.89 (d, ^3J = 4.11 Hz, 1H; 4-CH), 3.93 (s, 1H; 7-CH), 9.67 (s, 1H; 3-CHO), 12.20 (br s, H; 2-NH), 13.02 ppm (br s, 1H; 1-CO_2H); IR (KBr): $\tilde{\nu}$ = 3280 (NH, OH), 2240 (CN), 1730 (C=O), 1660 cm^{-1} (C=O); MS (EI, 70 eV, T = 188 °C): m/z (%): 288 (10) [M^+], 257 (3) [$M^+ - OCH_3$], 229 (3) [$M^+ - CO_2CH_3$], 211 (3), 177 (100) [$M^+ - C_5H_5NO_2$], 159 (25), 149 (18), 131 (30); HRMS (EI): calcd for $C_{14}H_{12}N_2O_5$: 288.07462 [M^+]; found: 288.07333; elemental analysis (*rac*-**11**): calcd (%) for $C_{14}H_{12}N_2O_5$: C 58.33, H 4.20, N 9.72; found: C 58.50, H 4.70, N 8.96.

5-Methyl-[(4*S*,5*S*,6*S*,7*R*)-3-bromo-6-cyano-1-formyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-isoindole-5-carboxylate] (12): A solution of **11** (33.1 mg, 115 μmol) in dry CH_2Cl_2 (5 mL) was added to a solution of pyridinium perbromide (61 mg, 172.4 μmol, 1.5 equiv) in dry CH_2Cl_2 (5 mL) and dry pyridine (46 μL, 575 μmol, 5 equiv). The mixture was stirred overnight at

room temperature. The reaction mixture was then washed with a 1 N solution of HCl. The organic phases were washed with a saturated solution of sodium bicarbonate, dried by filtration over cotton wool and concentrated in vacuo. The brown residue was chromatographed on silica gel with CH_2Cl_2/MeOH 9:1 as the eluent to afford **12** as a brownish solid. The product was crystallised from CH_2Cl_2/*n*-hexane for analytical characterisation. Yield: 16.7 mg (51.6 μmol, 45%); R_f=0.60 (silica gel, CH_2Cl_2/MeOH 9:1); m.p. 120°C; $[\alpha]_D^{20}=-4.9$ (c=0.58 in CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.23 (dq, ^2J=10.08, ^4J=1.77 Hz, 1H; 8-CH_2), 2.32 (dm, ^2J=10.08 Hz, 1H; 8-CH_2), 3.03 (dd, ^3J=4.25, ^4J=1.77 Hz, 1H; 6-CH), 3.51 (t, ^3J=4.25 Hz, 1H; 5-CH), 3.69 (s, 3H; OCH_3), 3.78 (dm, ^3J=4.25 Hz, 1H; 7-CH), 3.99 (m, 1H; 4-CH), 9.15 (brs, 1H; NH), 9.42 ppm (s, 1H; 1-CHO); IR (KBr): $\tilde{\nu}$=3330 (NH), 2235 (CN), 1715 (C=O), 1655 cm^{-1} (C=O); MS (EI, 70 eV, T=140°C): m/z (%): 324 (42) [M^+(^{81}Br)], 322 (41) [M^+(^{79}Br)], 291 (6) [M^+-OCH_3], 263 (7) [$M^+-CO_2CH_3$], 243 (5) [M^+−Br], 213 (100) [M^+(^{81}Br)−$C_5H_5NO_2$], 211 (94) [M^+(^{79}Br)−$C_5H_5NO_2$],182 (15), 155 (8), 132 (28), 104 (27); HRMS (EI): calcd for $C_{13}H_{11}BrN_2O_3$: 321.99530 [M^+]; found: 321.99520.

1-Benzyl-6-methyl-[(4*R*,5*S*,6*S*,7*S*)-3,5-dicyano-6-(4,5,6,7-tetrahydro-4,7-methano-2*H*-isoindole-1,6-dicarboxylate] (13): Sodium acetate (300 mg, 3.648 mmol, 6 equiv) and hydroxylamine hydrochloride (212 mg, 3.04 mmol, 5 equiv) were added to a suspension of **10** (230 mg, 0.608 mmol) in methanol (10 mL). The mixture was stirred for 30 min at room temperature. Thereafter, a saturated solution of NaCl (10 mL) was added and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed twice with water, filtered over dry cotton wool and concentrated in vacuo to afford the oxime of **10** as a colourless solid with a yield of 229 mg (0.58 mmol, 96%). The oxime was dissolved in dry CH_2Cl_2 and cooled to 2°C under an argon atmosphere. After addition of 1,1′-carbonyldiimidazole (152 mg, 0.936 mmol, 2 equiv), the reaction mixture was stirred for 16 h at room temperature. The solvent was removed in vacuo and the yellowish residue was chromatographed on silica gel (30 g) with CH_2Cl_2/EtOAc 15:1 as the eluent to afford **13** as a colourless solid. The product was recrystallised from $CHCl_3$/*n*-hexane for analytical purposes. Yield: 153.3 mg (40.8 mmol, 87%); R_f=0.37 (silica gel, CH_2Cl_2/EtOAc 15:1); m.p. 251–253°C; $[\alpha]_D^{20}=-53.4$ (c=0.32 in CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.22 (dd, ^2J=9.9, ^3J=^4J=1.6 Hz, 1H; 8-CH_2), 2.34 (d, ^2J=9.9 Hz, 1H; 8-CH_2), 3.10 (dd, ^3J=4.3, ^4J=1.6 Hz, 1H; 5-CH), 3.45 (s, 3H; OCH_3), 3.58 (dd ("t"), ^3J=4.3 Hz, 1H; 6-CH), 3.90 (s, 1H; 4-CH), 4.06 (d, ^3J=4.0 Hz, 1H; 7-CH), 5.33 (s, 2H; CH_2Ph), 7.45 (m, 5H; Ph), 9.54 ppm (brs, 1H; NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=33.61 (5-C), 44.87 (7-CH, 4-CH), 52.13 (6-C), 52.79 (8-C), 53.24 (OCH_3), 67.67 (CH_2Ph), 97.66 (3-C), 112.50 (3-CN), 119.69 (1-C), 121.25 (5-CN), 128.78, 129.20, 129.24 (2′-C, 3′-C, 4′-C), 134.42 (7a-C), 135.44 (1′-C), 140.04 (3a-C), 159.66 (CO_2Bn), 172.11 ppm (CO_2CH_3); IR (KBr): $\tilde{\nu}$=3272 (NH), 2228 (CN), 1718 cm^{-1} (C=O); MS (EI, 70 eV, T=189°C): m/z (%): 376 (4), 375 (17) [M^+], 344 (3) [M^+-OCH_3], 265 (5), 264 (24) [$M^+-C_5H_5NO_2$], 246 (3), 202 (8), 107 (6), 92 (8), 91 (100) [CH_2Ph^+]; HRMS (EI): calcd for $C_{21}H_{17}N_3O_4$: 375.12191 [M^+]; found: 375.12137.

(4*R*,5*S*,6*S*,7*S*)-3,5-dicyano-6-(methoxycarbonyl)-4,5,6,7-tetrahydro-4,7-methano-2*H*-isoindole-1-carboxylic acid (14): Some drops of acetic acid were added to a solution of **13** (137 mg, 0.365 mmol) in dry THF (6 mL). The mixture was degassed three times under reduced pressure and placed under an argon atmosphere. After addition of some milligrams of palladium catalyst (10% palladium on activated charcoal), the system was evacuated three times and placed under hydrogen from a balloon fitted to the reaction flask. The reaction mixture was stirred at room temperature until complete conversion of the starting material, as monitored by TLC. The catalyst was removed by filtration over Celite 521 and the filtrate was concentrated in vacuo to afford **14** as a colourless solid. For analytical purposes **14** was crystallised from THF/*n*-hexane. Yield: 104 mg (36.4 mmol, 98%); R_f=0.1 (silica gel, CH_2Cl_2/EtOAc 15:1); m.p. 230–232°C; $[\alpha]_D^{20}=-14.7$ (c=0.156 in CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$+10% DMSO): δ=2.12 (dd, ^2J=9.9, ^3J=^4J=1.3 Hz, 1H; 8-CH_2), 2.22 (d, ^2J=9.9 Hz, 1H; 8-CH_2), 2.88 (dd, ^3J=4.3, ^4J=1.3 Hz, 1H; 5-CH), 3.46 (dd ("t"), ^3J=4.3 Hz, 1H; 6-CH), 3.53 (s, 3H; OCH_3), 3.77 (s, 1H; 4-CH), 4.02 (d, ^3J=3.8 Hz, 1H; 7-CH), 11.46 ppm (brs, 1H; CO_2H); ^{13}C NMR (50 MHz, $CDCl_3$+10% DMSO): δ=33.59 (5-C), 44.52, 44.84 (7-CH, 4-CH), 52.31, 52.76 (8-C, 6-C, OCH_3), 96.44 (3-C), 113.33 (3a-C), 121.31 (3-CN), 121.53 (5-CN), 134.23 (7a-C), 139.67 (1-C), 161.62 (CO_2H), 171.22 ppm (CO_2CH_3); IR (KBr): $\tilde{\nu}$=3467 (OH), 3292 (NH), 2224 (CN), 1716 cm^{-1} (C=O); MS (EI, 70 eV, T=250°C): m/z (%): 286 (3), 285 (15) [M^+], 254 (5) [M^+-OCH_3], 227 (2), 226 (4) [$M^+-CO_2CH_3$], 225 (2) [$M^+-CO_2CH_3-$H], 208 (4), 207 (3), 181 (4) [$M^+-CO_2CH_3-CO_2H$], 180 (4) [$M^+-CO_2CH_3-CO_2H-$H], 175 (11), 174 (100) [$M^+-C_5H_5NO_2$], 157 (6), 156 (53), 155 (5), 130 (9), 129 (11) [$M^+-C_5H_5NO_2-CO_2H$], 112 (18) [$C_5H_5NO_2^+$+H], 102 (5), 101 (4), 80 (6) [$C_5H_3NO_2^+-OCH_3$]; HRMS (EI): calcd for $C_{14}H_{11}N_3O_4$: 285.07496 [M^+]; found: 285.07468.

5-Methyl-[(4*S*,5*S*,6*S*,7*R*)-1,6-dicyano-3-(hydroxymethyl)-4,5,6,7-tetrahydro-4,7-methano-2*H*-isoindole-5-carboxylate] (15): $SOCl_2$ (0.47 mL, 6.46 mmol, 20 equiv) was injected with a syringe through a septum into a solution of **14** (92.3 mg, 0.323 mmol) in dry THF (5 mL) under an argon atmosphere. The reaction mixture was heated at 50°C for 2 h. Thereafter, the solvent and $SOCl_2$ were removed in vacuo with an oil pump. The acid chloride intermediate was dissolved in dry THF (10 mL) and cooled to −80°C under an argon atmosphere. Afterwards, a 1 M solution of lithium-9-borabicyclo[3.3.1]nonane hydride in THF (0.65 mL, 0.646 mmol, 2 equiv) was injected dropwise with a syringe through a septum. The reaction mixture was warmed to room temperature within 30 min and stirred for a further 15 min. The reaction was quenched by addition of NaCl solution (15 mL) and transferred into a separating funnel after being stirred for 15 min. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried by filtration over cotton wool and concentrated in vacuo. The crude product was purified by two-fold column chromatography on silica gel (with CH_2Cl_2/EtOAc 15:1 followed by CH_2Cl_2/MeOH 20:1 as the eluents) and then crystallised from $CHCl_3$/*n*-hexane to give **15** as colourless crystals. Yield: 53 mg (19.6 mmol, 60%); R_f=0.24 (silica gel, CH_2Cl_2/MeOH 20:1); ^{1}H NMR (200 MHz, $CDCl_3$+10% DMSO): δ=2.01 (dd, ^2J=10.1, ^3J=^4J=1.7 Hz, 1H; 8-CH_2), 2.13 (d, ^2J=10.1 Hz, 1H; 8-CH_2), 2.76 (dd, ^3J=3.9, ^4J=2.0 Hz, 1H; 6-CH), 3.37 (dd ("t"), ^3J=3.9 Hz, 1H; 5-CH), 3.52 (s, 3H; OCH_3), 3.69 (s, 2H; 4-CH, 7-CH), 4.34 (d, 2H; 3-CH_2), 10.67 ppm (brs, 1H; OH); ^{13}C NMR (50 MHz, $CDCl_3$+10% DMSO): δ=34.28 (6-C), 42.46 (7-CH), 44.82 (4-C), 51.71 (8-C), 53.00, 53.12 (5-C, OCH_3), 56.55 (3-CH_2), 91.96 (3-C), 114.46 (3a-C), 121.71 (6-CCN), 126.92 (1-C*C*N), 130.76 (1-C), 139.74 (7a-C), 171.68 ppm (CO_2CH_3); IR (KBr): $\tilde{\nu}$=3360 (NH, OH), 2219 (CN), 1724 cm^{-1} (C=O); MS (EI, 70 eV, T=176°C): m/z (%): 272 (6), 271 (43) [M^+], 254 (3) [M^+-OH], 253 (3), 240 (9) [M^+-OCH_3] + [M^+-CH_2OH], 222 (5) [$M^+-OCH_3-CH_2OH$], 213 (4), 212 (3) [$M^+-CO_2CH_3$], 211 (3) [$M^+-CO_2CH_3-$H], 194 (10) [$M^+-CO_2CH_3-OH-$H], 167 (4), 160 (100) [$M^+-C_5H_5NO_2$], 159 (14), 143 (21), 142 (60) [$M^+-C_5H_5NO_2-OH$], 131 (7), 130 (46) [$M^+-C_5H_5NO_2-CH_2OH$], 129 (13), 116 (4), 115 (6), 114 (4), 112 (2) [$C_5H_5NO_2^+$+H], 90 (7), 83 (8), 80 (5) [$C_5H_5NO_2^+-OCH_3$]; HRMS (EI): calcd for $C_{14}H_{13}N_3O_3$ 271.09569 [M^+]; found: 271.09639.

5-Methyl-[(4*R*,5*S*,6*S*,7*S*)-1,6-dicyano-3-formyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-isoindole-5-carboxylate] (16): Cerium ammonium nitrate (318 mg, 0.580 mmol, 5 equiv) was added to a stirred solution of **15** (31.5 mg, 0.116 mmol) in THF (1 mL), H_2O (1 mL) and acetic acid (1.2 mL) at room temperature. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated NaCl solution (5 mL). The aqueous layer was extracted three times with CH_2Cl_2, the combined organic extracts were dried by filtration over cotton wool and the solvent was removed under reduced pressure. Crystallisation from $CHCl_3$/*n*-hexane afforded **16** as colourless crystals. Yield: 24 mg (0.08 mmol, 77%); R_f=0.64 (silica gel, CH_2Cl_2/MeOH (20:1)); m.p. 205–207°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.30 (dd, ^2J=10.1, ^3J=^4J=1.7 Hz, 1H; 8-CH_2), 2.43 (d, ^2J=10.1 Hz, 1H; 8-CH_2), 3.10 (dd, ^3J=3.9, ^4J=2.0 Hz, 1H; 6-CH), 3.66 (dd ("t"), ^3J=3.9 Hz, 1H; 5-CH), 3.71 (s, 3H; OCH_3), 3.96 (s, 1H; 7-CH), 4.14 (d, ^3J=3.9 Hz, 1H; 4-CH), 9.55 (s, 1H; CHO), 9.94 ppm (brs, 1H; NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=33.77 (6-C), 43.41 (4-C), 44.46 (7-C), 52.34 (8-C), 52.50 (5-CH_3), 53.63 (OCH_3), 99.84 (1-C), 112.20 (1-CN), 120.95 (6-CN), 127.67 (3-C), 138.36 (3a-C), 140.37 (7a-C), 171.47 (CO_2CH_3), 178.61 ppm (CHO); IR (KBr): $\tilde{\nu}$=3325 (NH), 2231 (CN), 1714 (C=O), 1681 cm^{-1} (C=O); UV/Vis (MeOH): λ_{max} (ε)=220 (10909), 284 nm (13841 mol^{-1} dm^3 cm^{-1}); CD

(MeOH, $c = 4.7 \times 10^{-5}$ mol L^{-1}): λ_{max} ($[\Theta]_m$) = 222 (10481), 265 nm (−10832 deg cm^2 dmol^{-1}); MS (EI, 70 eV, T = 150 °C): m/z (%): 270 (3), 269 (18) [M^+], 238 (5) [$M^+ - OCH_3$], 210 (5) [$M^+ - CO_2CH_3$], 209 (4) [$M^+ - CO_2CH_3 - H$], 181 (3) [$M^+ - CO_2CH_3 - CHO$], 180 (2) [$M^+ - CO_2CH_3 - CHO - H$], 159 (11), 158 (100) [$M^+ - C_5H_5NO_2$], 130 (26), 129 (11) [$M^+ - C_5H_5NO_2 - CHO$], 112 (5) [$C_5H_5NO_2^+ + H$], 103 (4), 102 (5), 80 (4) [$C_5H_5NO_2^+ - OCH_3$]; HRMS (EI): calcd for $C_{14}H_{11}N_3O_3$: 269.08004 [M^+]; found: 269.08063; elemental analysis: calcd (%) for $C_{14}H_{11}N_3O_3 + CHCl_3$ (0.06 equiv): C 61.09, H 4.03, N 15.2; found: C 60.96, H 3.88, N 15.18 (the content of solvent in the crystalline sample was confirmed by ^{1}H NMR spectroscopy).

Preparation of chlorin subunit 19:

[Methyl-(1*S*,2*S*,3*S*,4*R*,21*RS*)-5-bromo-3,21-dicyano-1,2,34,19,20,21,25-octahydro-9,10,14,15,20,20,21-heptamethyl-1,4-methano-23*H*-benzo[*b*]bilin-2-carboxylato]zinc(II) (18): A 5 N solution of potassium hydroxide in MeOH/H_2O (9:1, 4 mL) was added to a solution of [ethyl-(14*RS*)-(14-cyano-12,13,14,17-tetrahydro-2,3,7,8,13,13,14-heptamethyl-15*H*-tripyrrin-1-carboxylato)]nickel(II) (*rac*-**17**; 31.2 mg, 65.44 μmol) in dry THF (6 mL). The mixture was heated at 70 °C for 45 min under an argon atmosphere. After being cooled, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with $NaHCO_3$ solution (20 mL). The aqueous layer was vigorously extracted with CH_2Cl_2 and the combined organic layers were dried by filtration over cotton wool and concentrated in vacuo to afford the free carboxylic acid derivative of *rac*-**17**. Degassed solutions of **12** (31.7 mg, 98.17 μmol, 1.5 equiv) in dry $CHCl_3$ (4 mL) and 0.4 N *para*-toluenesulfonic acid in $CHCl_3$ (1.64 mL, 654.4 μmol, 10 equiv) were successively added with a syringe through a septum to the degassed carboxylic acid under an argon atmosphere. The mixture was stirred under reflux for 20 min. The blue-green reaction mixture was diluted with CH_2Cl_2, poured into a separating funnel containing a $NaHCO_3$ solution (20 mL) and vigorously extracted with CH_2Cl_2. The combined organic layers were dried by filtration over cotton wool and concentrated in vacuo. The metal-free bilin system of **18** was used for complexation without further purification. A solution of dry zinc(II) acetate (60.0 mg, 327 μmol, 5 equiv) and sodium acetate (27 mg, 327 μmol, 5 equiv) in dry methanol (3 mL) was added to a solution of metal-free bilin **18** in dry CH_2Cl_2 (6 mL). The mixture was allowed to react at room temperature for 20 min under an argon atmosphere. The reaction mixture was transferred into a separating funnel containing a solution of $NaHCO_3$ (10 mL) and vigorously extracted with CH_2Cl_2. The organic layers were dried by filtration through cotton wool and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2/EtOAc/NEt_3 9:1:0.05 as the eluent to yield **18** as a green solid consisting of a mixture of diastereomers. Yield: 24.4 mg (0.034 mmol, 52 %); R_f = 0.71 and 0.67 (silica gel, CH_2Cl_2/EtOAc 9:1); UV/Vis ($CHCl_3$): λ_{max} (ε) = 733 (0.73), 671 (0.47), 504 (0.27), 383 (1), 328 (0.5), 282 nm (0.83 mol^{-1} dm^3 cm^{-1}); MS (DCI negative): m/z (%): 714 (13) [M^-], 687 (8) [$M^- - HCN$]. Compound **18** was used for the next synthetic step without further characterisation because of its instability.

[Methyl-{(1*S*,2*S*,3*S*,4*R*)-3-cyano-1,2,3,4,8,9-hexahydro-8,8,13,13,14,18,19-hexamethyl-1,4-methano-23*H*,25*H*-benzo[*b*]porphin-2-carboxylato}]zinc(II) (19): A degassed solution of **18** (24.4 mg, 34.03 μmol), DBU (1.02 mL, 6.806 mmol, 200 equiv) and some milligrams of $Zn(AcO)_2$ in dry sulfolane (3 mL) was heated at 60 °C for 2 h under an argon atmosphere. After being cooled to room temperature, the reaction mixture was diluted with benzene (20 mL), transferred into a separating funnel and washed three times with a saturated NaCl solution (15 mL). The combined aqueous layers were re-extracted with benzene (5 mL). The organic extracts were dried by filtration over cotton wool and evaporated in vacuo. The residual sulfolane was removed by Kugelröhr distillation at 80 °C in vacuo with an oil pump. The dark-green residue was purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/NEt_3 9:1:0.05 as the eluent to yield **19** as a turquoise-blue solid. For analytical characterisation, the product was crystallised from $CHCl_3$/*n*-hexane: Yield = 8.3 mg (13 μmol, 40 %); R_f = 0.69 (silica gel, CH_2Cl_2/EtOAc 9:1); ^{1}H NMR (200 MHz, $CDCl_3$ + 20 μL [D_5]pyridine): δ = 1.75 (s, 3H; 8-CH_3), 1.95 (s, 3H; 8-CH_3), 2.85 (s, 1H; 27-CH_2), 2.92 (m, 1H; 27-CH_2), 3.08 (s, 3H; OCH_3), 3.25 (s, 4H; 13-CH_3, 3-CH), 3.323, 3.327 (2 s, 6H; 18-CH_3, 14-CH_3), 3.37 (s, 3H; 19-CH_3), 3.98 (dd ("t"), ^3J = 2 × 3.9 Hz, 1H; 2-CH), 4.41 (AB, ^2J = 16.37 Hz, 2H; 9-CH_2), 4.99 (2 s, 2H; 1-CH, 4-CH), 8.30 (s, 1H; 6-CH), 8.53 (s, 1H; 11-CH), 9.43 (s, 1H; 16-CH), 9.50 ppm (s, 1H; 21-CH); UV/Vis ($CHCl_3$): λ_{max} (ε) = 620 (33622), 573 (4234), 496 (4008), 396 nm (84925 mol^{-1} m^3 cm^{-1}); CD ($CHCl_3$, $c = 1.2 \times 10^{-5}$ mol L^{-1}): λ_{max} ($[\Theta]_m$) = 618 (5019), 607 (−6751), 578 (16882), 553 (−5525), 541 (22558), 525 (−4968), 507 (−6581), 487 (−11917), 463 (−8013), 434 (−2089), 397 nm (20639 deg cm^2 dmol^{-1}); MS (EI, 70 eV, T = 344 °C): m/z (%): 607 (23) [M^+], 496 (47) [$M^+ - C_5H_5NO_2$] (retro-Diels–Alder reaction), 466 (17), 451 (8); HRMS (EI): calcd for $C_{34}H_{33}N_5O_2Zn$: 607.19257 [M^+]; found: 607.19320.

Preparation of chlorin subunit 21:

[Methyl-(1*S*,2*S*,3*S*,4*R*,21*RS*)-3,5,21-tricyano-1,2,3,4,19,20,21,25-octahydro-9,10,14,15,20,20,21-heptamethyl-1,4-methano-23*H*-benzo[*b*]bilin-2-carboxylato]zinc(II) (20): A 5 N solution of potassium hydroxide in MeOH/H_2O (9:1, 1.9 mL) was added to a solution of *rac*-**17** (11.7 mg, 24.5 μmol) in dry THF (2.5 mL). The mixture was heated at 70 °C for 30 min under an argon atmosphere. After cooling, the reaction mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$ solution (15 mL). The aqueous layer was vigorously extracted with CH_2Cl_2 and the combined organic layers were dried by filtration over cotton wool and evaporated in vacuo to afford the free carboxylic acid derivative of **17**. Degassed solutions of **16** (12.2 mg, 45.3 μmol) in dry $CHCl_3$ (2 mL) and 0.4 N *para*-toluenesulfonic acid in $CHCl_3$ (0.55 mL, 220 μmol, 9 equiv) were successively added with a syringe through a septum to the degassed carboxylic acid under an argon atmosphere. The mixture was stirred under reflux for 30 min. The blue-green reaction mixture was diluted with CH_2Cl_2, transferred into a separating funnel containing $NaHCO_3$ solution (15 mL) and vigorously extracted by CH_2Cl_2. The combined organic layers were dried by filtration through cotton wool, evaporated in vacuo and purified by column chromatography on silica gel with CH_2Cl_2/EtOAc 15:1 as the eluent. The eluted blue fraction was dried in vacuo with an oil pump to give the metal-free bilin **20** (8.9 mg, 61 %), which was complexed without further purification and characterisation. A solution of dry zinc(II) acetate (19.0 mg, 103.4 μmol, 6.8 equiv) and sodium acetate (8.5 mg, 103.4 μmol, 6.8 equiv) in dry methanol (1.5 mL) was added to the solution of the metal-free bilin **20** in dry CH_2Cl_2. The mixture was allowed to react at room temperature for 40 min under an argon atmosphere. The green-coloured reaction mixture was transferred into a separating funnel containing a solution of $NaHCO_3$ (15 mL) and was vigorously extracted with CH_2Cl_2. The organic layers were dried by filtration through cotton wool and the solvent was removed in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2/EtOAc 15:1 as the eluent and crystallised from $CHCl_3$/*n*-hexane to give **20** as a green solid: Yield = 6.2 mg (9.3 μmol, 61 %); R_f = 0.80 (silica gel, CH_2Cl_2/EtOAc 15:1); MS (ESI, MeOH, positive): 661 [M^+], 684 [M+Na^+]; MS (ESI, MeOH, negative): 660 [$M - H^+$], 696 [M+Cl^-]. Compound **20** was used for the next reaction step without further characterisation because of its instability.

{Methyl-[(1*S*,2*S*,3*S*,4*R*)-3-cyano-1,2,3,4,8,9-hexahydro-8,8,13,14,18,19-hexamethyl-1,4-methano-23*H*,25*H*-benzo[*b*]porphin-2-carboxylato]}zinc(II) (21): A carefully degassed solution of **20** (8.1 mg, 12.2 μmol) in dry 1,2,4-trichlorobenzene (4 mL) was heated at 210 °C for 40 min. After the reaction mixture had cooled to room temperature, the solvent was removed by Kugelröhr distillation at 60 °C in vacuo. The green residue was chromatographed on silica gel with CH_2Cl_2/MeOH 99:1 as the eluent and crystallised from $CHCl_3$/*n*-hexane to give **21** as green crystals. Yield: 3.12 mg (5.12 μmol, 42 %); R_f = 0.66 (silica gel, CH_2Cl_2/MeOH 99:1), 0.90 (silica gel, CH_2Cl_2/EtOAc 9:1); m.p. > 250 °C (decomp); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.02, 2.09 (2 s, 6H; 2 × 8-CH_3), 2.90 (2 × dd, ^2J = 9.2, ^3J = 2 × 1.4 Hz, 1H; 27-CH_2), 2.98 (2 × ddd, ^2J = 9.4, $^{3,4}J$ = 3 × 1.7 Hz, 1H; 27-CH_2), 3.16 (dd, ^3J = 4.2, ^4J = 1.8 Hz, 1H; 3-CH), 3.18 (s, 3H; 19-CH_3), 3.20 (s, 3H; 13-CH_3), 3.31 (2 s, 6H; 14-CH_3, 18-CH_3), 3.32 (s, 3H; OCH_3), 4.00 (dd ("t"), ^3J = 2 × 4.1 Hz, 1H; 2-CH), 4.54 (br s, 2H; 9-CH_2), 4.94 (br s, 1H; 4-CH), 5.11 (d, ^3J = 4.2 Hz, 1H; 1-CH), 8.53 (s, 1H; 6-CH), 8.60 (s, 1H; 11-CH), 9.35 (s, 1H; 16-CH), 9.39 ppm (s, 1H; 21-CH); IR (KBr): $\tilde{\nu}$ = 2229 (CN), 1741 cm^{-1} (C=O); UV/Vis ($CHCl_3$): λ_{max} (ε) = 620 (25757), 580 (5185), 500 (5347), 400 (78461), 300 (19984), 280 nm (18735 mol^{-1} dm^3 cm^{-1}); CD ($CHCl_3$, $c = 1.05 \times 10^{-5}$ mol L^{-1}): λ_{max}

($[\Theta]_m$) = 620 (18514), 596 (8933), 570 (−9119), 397 nm (−68405 deg cm^2 dmol^{-1}); MS (EI, 70 eV, T = 344 °C): m/z (%): 607 (65) [M^+], 496 (100) [$M^+ - C_5H_5NO_2$] (retro-Diels–Alder reaction), 466 (24) [$M^+ - C_5H_5NO_2 - CHO - H$], 451 (12), 248 (12), 91 (14), 49 (25); MS (DCI, negative, NH_3, 8 mA s^{-1}): m/z (%): 708 (15), 607 (50) [M^+], 468 (9), 398 (4), 307 (23), 293 (42), 141 (41), 111 (100) [$C_5H_5NO_2^+$]; HRMS (EI): calcd for $C_{34}H_{33}N_5O_2Zn$: 607.19103 [M^+]; found: 607.19257.

Preparation of dyad 24:

[(2′,5′-Dioxopyrrolidin-1′-yl)(1*S*,2*S*,3*S*,4*R*)-3-cyano-1,2,3,4,8,9-hexahydro-8,8,13,14,18,19-hexamethyl-1,4-methano-23*H*,25*H*-benzo[*b*]porphin-2-carboxylato]zinc(II) (22): A 5 N solution of potassium hydroxide in methanol/water (9:1, 0.5 mL) was added to a solution of **21** (2.6 mg, 4.3 μmol) in THF (1 mL). The reaction mixture was heated at 60 °C for 40 min under an argon atmosphere. After being cooled to room temperature, the mixture was diluted with CH_2Cl_2 and washed with sodium chloride solution. The combined organic extracts were dried by filtration over cotton wool. Evaporation of the solvent and drying in vacuo afforded the crude free carboxylic acid derivative of **21** in an almost quantitative yield. For the activation reaction, the carboxylic acid was dissolved in dry CH_2Cl_2 (1 mL), then DCC (17.6 mg, 85.2 μmol, 20 equiv) and NHS (9.8 mg, 85.2 μmol, 20 equiv) were added. The mixture was stirred for 90 min at room temperature under an argon atmosphere. After evaporation of the solvent, the residue was purified by column chromatography on silica gel with CH_2Cl_2/EtOAc 15:1 as the eluent and crystallised from $CHCl_3$/*n*-hexane to yield **22** as blue-green crystals. Yield: 1.86 mg (2.7 μmol, 63 %); R_f = 0.64 (silica gel, CH_2Cl_2/EtOAc 9:1); m.p. > 200 °C (decomp); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.03, 2.07 (2 s, 6 H; 2 × 8-CH_3), 2.47 (br s, 4 H; 3′-CH_2, 4′-CH_2), 3.00 (m, 2 H; 27-CH_2), 3.20 (m, 1 H; 3-CH), 3.22 (s, 3 H; 19-CH_3), 3.33, 3.34 (2 s, 6 H; 14-CH_3, 18-CH_3), 3.42 (s, 3 H; 13-CH_3), 4.32 (dd, ^3J = 4.1 Hz, 1 H; 2-CH), 4.54 (br s, 2 H; 9-CH_2), 5.01 (br s, 1 H; 4-CH), 5.30 (d, ^3J = 4.2 Hz, 1 H; 1-CH), 8.52 (s, 1 H; 6-CH), 8.61 (s, 1 H; 11-CH), 9.40 (s, 1 H; 16-CH), 9.66 ppm (s, 1 H; 21-CH); IR (KBr): $\tilde{\nu}$ = 2238 (CN), 1742 (C=O), 1724 cm^{-1} (C=O); UV/Vis ($CHCl_3$): λ_{max} (ε) = 620 (37802), 579 (4880), 502 (3816), 401 (103971), 294 nm (10892 mol^{-1} dm^3 cm^{-1}); MS (ESI, CH_2Cl_2/MeOH 1:1000, positive): 690 [M^+], 713 [M+Na$^+$], 792 [M+K$^+$]; MS (ESI, CH_2Cl_2/MeOH 1:1000, negative): 592 [$M - C_4H_4NO_2$], 689 [M−H$^+$], 725 [M+Cl$^-$]. Compound **21** was used for the next reaction step without further characterisation because of its sensitivity.

{Methyl-[(1*S*,2*S*,3*S*,4*R*)-3-(aminomethyl)-1,2,3,4,8,9-hexahydro-8,8,13,14,18,19-hexamethyl-1,4-methano-23*H*,25*H*-benzo[*b*]porphin-2-carboxylato]}zinc(II) (23): A solution of cobalt dichloride hexahydrate (3.8 mg, 16 μmol, 10 equiv) in water (0.3 mL) was added to a solution of **21** (1.1 mg, 1.6 μmol) in THF (0.6 mL). The deep-blue solution was cooled to 0 °C and sodium borohydride (3.9 mg, 96 μmol, 60 equiv) was added in small portions under a hydrogen atmosphere. After 20 min, the cooling bath was removed and the reaction mixture was stirred for an additional 2 h at room temperature. To increase the yield, the black cobalt boride residue was treated with ultrasound every 20 min. The free amine **23** was obtained by addition of some drops of a concentrated ammonium solution. After stirring for 15 min, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried by filtration over cotton wool. After evaporation of the solvent, the residue was dried in vacuo to give **23** as a green solid. Yield: 0.6–0.8 mg (1–1.3 μmol, 60–80 %); R_f = 0.01 (silica gel, CH_2Cl_2/EtOAc 15:1), 0.42 (Alox, CH_2Cl_2/MeOH/Et_3N 20:1:0.5); MS (ESI MS/MS, CH_2Cl_2/MeOH 1:100, positive): 612 [M+H$^+$], 595 [$M - NH_2^+$], 583 [$M - CH_2NH^+$], 580 [$M - CH_3OH^+$], 496 [$M - C_5H_9NO_2^+$]; MS (ESI, CH_2Cl_2/MeOH 1:50, negative): 646 [M+Cl$^-$]. Compound **23** was used for the next reaction step without further characterisation because of its sensitivity.

Chlorin dyad 24: A solution of **22** (1.5 mg, 2.1 μmol), **23** (5.2 mg, 8.5 μmol, 4 equiv) and a catalytic amount of DMAP in dry THF (2 mL) was stirred for 4 h under an argon atmosphere. The solvent was then evaporated and the resultant mixture was dried in vacuo with an oil pump and purified by column chromatography on silica gel with CH_2Cl_2/EtOAc 15:1 as the eluent to afford **24** as a green solid. Yield: 1.9 mg (1.6 μmol, 76 %); $R_f \approx$ 0.4–0.6 (silica gel, CH_2Cl_2/EtOAc 15:1); ^{1}H NMR (360 MHz, CD_2Cl_2): δ = 1.91, 1.97 (2 s, 6 H; 2 × 22-CH_3), 2.04, 2.05 (2 s, 6 H; 2 × 2-CH_3), 2.2 (s, 1 H; 63-CH), 2.29, 2.57 (m, 2 H; 61-CH_2), 2.86, 2.95 (m, 2 H; 48-CH_2), 2.93, 3.29 (m, 2 H; 65-CH_2), 3.19 (s, 3 H; 27-CH_3), 3.24 (s, 3 H; 7-CH_3), 3.27 (m, 1 H; 50-CH), 3.29 (m, 1 H; 64-CH), 3.32 (s, 3 H; 28-CH_3), 3.35 (s, 6 H; 8-CH_3, 32-CH_3), 3.37 (s, 9 H; 12-CH_3, 13-CH_3, 64-CH_3), 3.39 (s, 3 H; 33-CH_3), 3.87 (s, 1 H; 51-CH), 4.02 (s, 1 H; 62-CH), 4.48 (s, 2 H; 23-CH_2), 4.56 (s, 2 H; 3-CH_2), 4.87 (s, 2 H; 47-CH, 60-CH), 4.91 (s, 1 H; 49-CH), 6.69 (s, 1 H; NH), 8.45 (s, 1 H; 40-CH), 8.59 (s, 1 H; 25-CH), 8.61 (s, 1 H; 20-CH), 8.66 (s, 1 H; 5-CH), 9.33 (s, 1 H; 15-CH), 9.41 (s, 1 H; 30-CH), 9.45 (s, 1 H; 10-CH), 9.51 ppm (s, 1 H; 35-CH); ^{13}C NMR (90 MHz, CD_2Cl_2): δ = 11.6 (7-CH_3, 27-CH_3), 11.7 (8-CH_3, 28-CH_3), 11.8 (12-CH_3, 13-CH_3), 31.2 (2 × 22-CH_3), 31.3, 31.4 (2 × 2-CH_3), 33.5 (50-CH), 44.7 (62-CH), 45.3 (65-CH_2), 45.4 (22-C), 45.5 (2-C), 45.8 (60-CH), 47.0 (63-CH), 47.7 (49-CH), 47.8 (47-CH), 51.5 (23-CH_2), 51.6 (3-CH_2), 52.0 (32-CH_3, 33-CH_3, 64-CH_3), 53.0 (61-CH_2), 53.5 (64-CH), 54.5 (51-CH), 55.1 (48-CH_2), 93.4 (20-CH, 40-CH), 93.5 (5-CH), 99.3 (25-CH), 99.8 (10-CH), 99.9 (30-CH), 103.5 (15-CH), 104.1 (35-CH), 123.4 (52-CN), 133.2 (27-C), 133.7 (7-C), 134.1 (32-C), 134.4 (12-C), 135.0 (13-C, 33-C), 137.0 (16-NC), 137.5 (36-NC), 138.1 (28-C), 138.4 (8-C), 143.1 (19-NC), 143.3 (39-NC), 144.66 (14-NC), 144.7 (34-NC), 146.0 (18-C), 146.4 (29-NC), 146.6 (31-NC), 147.1 (11-NC), 149.0 (9-NC), 149.8 (17-C), 149.8 (38-C), 151.6 (37-C), 152.9 (26-NC), 153.3 (6-NC), 159.8 (24-NC), 160.3 (4-NC), 169.4 (21-NC), 169.5 (1-NC), 170.0 (53-CO), 175.0 ppm (64-COO); UV/Vis (CH_2Cl_2): λ_{max} (ε) = 618 (87915), 574 (23119), 5023 (24501), 395 nm (217921 mol^{-1} dm^3 cm^{-1}); CD (CH_2Cl_2, c = 4.2 × 10^{-6} mol L^{-1}): λ_{max} ($[\Theta]_m$) = 617 (64052), 587 (−46906), 569 (−37155), 554 (29471), 542 (−18515), 528 (45942), 489 (−10648), 473 (10363), 458 (−6648), 429 (−12030), 398 (−25610), 379 nm (−45076 deg cm^2 dmol^{-1}); MS (ESI, CH_2Cl_2/MeOH 1:100, positive): 1187 ([M+H$^+$], 1209 [M+Na$^+$], 1225 [M+K$^+$]; MS (ESI, CH_2Cl_2/MeOH 1:100, negative): 1185 [M−H$^+$], 1221 [M+Cl$^-$]; HRMS (ESI, positive): calcd for $C_{67}H_{66}N_{10}O_3Zn_2$: 1186.33968 [$M^+$]; found: 1186.33968.

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