Synthesis of a Novel Enantiomerically Pure Chlorin as a Potential Subunit for an Artificial Photosynthetic Reaction Center

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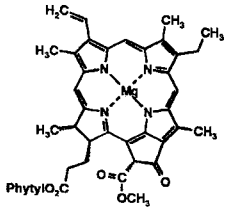
Abstract: The total synthesis of an enantiomerically pure chlorin with two different functional groups as a potential subunit for the construction of artificial photosynthetic reaction centers was achieved.

The essence of photosynthesis is the conversion of sunlight into ATP and reducing equivalents. The key step of this process is the formation of charge-separated supramolecular arrangements by light-induced electron transfer in the photosynthetic reaction center (RC) containing chlorophyll pigments **1**.[1] The present knowledge of photosynthesis is based on studies of the naturally occurring photosynthetic reaction center as well as on artificial photosynthetic model systems.[2] With few exceptions which make use of natural chlorophyll derivatives the large number of the model systems known so far are based on porphyrin subunits with slightly different photophysical properties compared to the "natural" chlorin chromophore **2**.

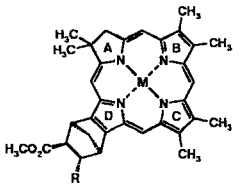


chlorophyll a

1

chlorin

2



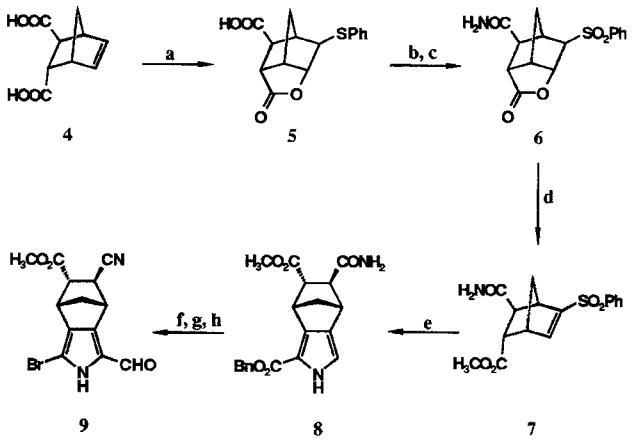
bisfunctionalized chlorin

3a M = 2H, R = CN
3b M = Zn, R = CN
3c M = 2H, R = CH_2NH_2

To obtain chlorin based photosynthetic models we aimed at the synthesis of enantiomerically pure chlorins **3a,b** with two different functional groups at ring D. The functional groups should allow covalent linking of the chlorin thus forming oligomers or supramolecular chlorin donor acceptor arrangements which mimic the photosynthetic reaction center. Enantiomerically pure subunits are required to obtain stereochemically homogenous oligomeric systems. The specific rigid geometry of the ring D structural part of the chlorin should influence the spacial orientation of the subunits in the envisaged oligomers. The target chlorin **3a,b** can be constructed according to a synthetic concept which we had developed earlier for the synthesis of chlorins and corrins.[3,4] An intermediate in the previous syntheses was the nickel tricycle **10** which is also useful for the synthesis of the desired chlorin **3**.[3]

A new ring D building block required for the synthetic route to chlorins **3a,b** could be obtained starting from the enantiomerically pure norbornene dicarboxylic acid **4** (Scheme 1).

The first step along the reaction sequence toward to pyrrole **9** was a sulfeno lactonisation[5] which rendered the necessary differentiation of the carboxylic acid functions and introduced a phenyl sulfide substituent which was further used to form an α,β unsaturated sulfone moiety at the norbornane framework. After transformation of the free carboxylic group of **5** into an amide function, the sulfide was oxidized to sulfone **6**. Among several methods applied cleavage of lactone **6** could only be achieved by a S_N2 type reaction with sodium phenyl selenide.[6] This method had also the advantage that the selenide residue was



Scheme 1.[9] a) CH_2Cl_2, 3 eq. NEt_3, -78 °C, 1.7 eq. $PhSCl/CH_2Cl_2$, 30 min → rt (86 %). b) 1. CH_2Cl_2, 1.5 eq. NEt_3, 2 eq. 1-propanephosphonic acid anhydride, 0 °C; 2. NH_3, 5 min, 0 °C (93 %). c) H_2O/MeOH, 2.05 eq. Oxone®, 2 h, rt (97 %). d) 1. 1 eq. Ph_2Se_2, 2.1 eq. Na, THF, 24 h, rfl.; 2. 0.1 eq. 18-crown-6, **6**, THF, 24 h, rt; 3. 1.2 eq. PPh_3, CCl_4, MeOH, 18 h, rt (71 %). e) 1. 3 eq. KO-*t*Bu, THF; 2. 3 eq. benzyl isocyano acetate/THF; 3. **7**, THF, 1 h, rt (89 %). f) 1. DMF, 5 eq. $POCl_3$, 15 °C, 15 min; 2. 5 °C, **8**/DMF, 90 °C, 45 min; 3. $NaOAc/H_2O$, 90 °C, 15 min (79 %). g) THF/NEt_3, Pd/C/H_2, 30 min, rt (100 %). h) 1.5 eq. pyridine•HBr_3, CH_2Cl_2/pyridine, 18 h, rt (45 %).

subsequently eliminated under the same reaction conditions to yield the α,β unsaturated sulfone moiety directly. Esterification of the carboxylic acid formed during the lactone cleavage according Appel's method[7] gave the final sulfone **7**. The reaction of **7** with benzyl isocyano acetate in the presence of base according to a procedure developed in our laboratory[8] led to the pyrrole **8** which was then functionalized at the α positions by Vilsmeier formylation and debenzylation followed by decarboxylative bromination to yield the bromopyrrole aldehyde **9**.

With the ring D building block at hand, the synthesis of the target chlorin could be achieved (Scheme 2).

Therefore the ester function of the nickel tricycle **10** was hydrolyzed and the carboxylic acid condensed with the bromopyrrole aldehyde **9** in the presence of acid to yield under decarboxylation and decomplexation the deep blue tetrapyrrole **11**. To exercise a template effect in the final cyclisation step, tetrapyrrole **11** was transformed into the zinc complex **12**. The cyclisation was initiated by base-induced elimination of HCN from ring A followed by attack of the formed enamine structure at C 22. Elimination of HBr completed the formation of the 21 methine bridge and yielded the target chlorin **3b**.

The selective reduction of the cyano function in **3b** is under investigation and should lead to the chlorin **3c** which is then ready as a subunit for the formation of dimeric artifical photosynthetic models.

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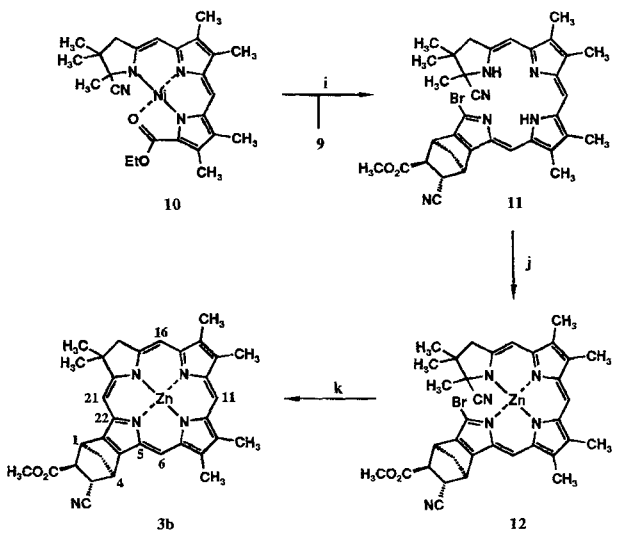

Scheme 2.[9] i) 1. 5 N KOH, MeOH/H_2O (9/1), THF, 45 min, rfl.; 2. 1.5 eq. **9**, 10 eq. 0.4 N *p*-TsOH, $CHCl_3$, 20 min, rfl.. j) 5 eq. $Zn(OAc)_2$, 5 eq. NaOAc, CH_2Cl_2, MeOH, 20 min, rt (52 % over steps i and j).[10] k) 200 eq. DBU, sulfolane, 2 h, 60 °C (40 %).

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(9) All compounds show correct spectroscopic and analytic data. The formula pictures represent the enantiomerically pure compounds. Selected spectroscopic data of **8**, **9**, **3b**: **8:** **^{1}H- NMR** (360 MHz, ([D_6]DMSO): δ = 1.72 (d, ^2J = -8.64 Hz, 1H, CH_2, pyrrole side), 2.08 (d, ^2J = -8.64 Hz, 1H, CH_2), 2.50 (m, 1H, 5-H), 3.25 (s, 3H, OCH_3), 3.32 (m, 1H, 7-H), 3.53 (t, ^3J = 4.32 Hz, 1H, 6-H), 3.74 (m, ^3J = 4.03 Hz, 1H, 4-H), 5.23 (AB spin system, ^2J = -12.67 Hz, 2H, CH_2Ph), 6.66 (d, ^3J = 2.88 Hz, 1H, 3-H), 6.95 (s, br., 1H, NH), 7.34 (m, 1H, *p*-aryl-H), 7.41 (m, 2H, *o*-aryl-H), 7.48 (m, 2H, *m*-aryl-H), 7.57 (s, br., 1H, NH), 11.11 (s, br., 1H, 2-H). **MS** (70 eV, 174 °C), *m/z* (%): 368 (21) [M^+], 337 (3) [M^+ - OCH_3], 130 (100).$[\alpha]_D^{20}$ = -85.8 ° (c = 3.74 in CH_2Cl_2). **9:** **^{1}H-NMR** (360 MHz, $CDCl_3$): δ = 2.23 (dq, ^2J = -10.08 Hz, ^4J = 1.77 Hz, 1H, 8-CH_2, pyrrole side), 2.32 (dm, ^2J = -10.08 Hz, 1H, 8-CH_2), 3.02 (dd, ^3J = 4.25 Hz, ^4J = 1.77 Hz, 1H, 6-H), 3.51 (t, ^3J = 4.25 Hz, 1H, 5-H), 3.69 (s, 3H, OCH_3), 3.78 (dm, ^3J = 4.25 Hz, 1H, 7-H), 3.99 (m, 1H, 4- H), 9.15 [s, br., 1H, 2-H (NH)], 9.42 (s, 1H, 1-CHO). **MS** (70 eV, 140°C), *m/z* (%): 324 (42) [$C_{13}H_{11}{}^{81}BrN_2O_3{}^+$], 322 (41) [$C_{13}H_{11}{}^{79}Br\,N_2O_3{}^+$], 291 (6) [$C_{13}H_{11}{}^{79}BrN_2O_3{}^+$ - OCH_3], 263 (7) [$C_{13}H_{11}{}^{79}BrN_2O_3{}^+$ - CO_2CH_3], 243 (5) [M^+ - Br], 211 (94) [$C_{13}H_{11}{}^{79}BrN_2O_3{}^+$ - H_3CO_2C-CH=CH-CN]. $[\alpha]_D^{20}$ = -4.9 ° (c = 0.58 in CH_2Cl_2). **3b:** **^{1}H-NMR** (360 MHz, $CDCl_3$, 20 µl [D_5]pyridine): δ = 1.75 (s, 3H, 19-CH_3), 1.95 (s, 3H, 19-CH_3), 2.85 (m, 1H, 27-CH_2, chlorin side), 2.92 (m, 1H, 27-CH_2), 3.08 (s, 3H, OCH_3), 3.25 (s, 3H, 14-CH_3), 3.25 (s, 1H, 3-H), 3.32, 3.33 (2 s, 6H, 9-, 13-CH_3), 3.37 (s, 3H, 8-CH_3), 3.98 [dd, ^3J = 3.88 Hz (2x), 1H, 2-H)], 4.41 (AB spin system, ^2J = -16.37 Hz, 2H, 18-CH_2), 4.99 (2 s, 2H, 1-, 4-H), 8.30 (s, 1H, 21-H), 8.53 (s, 1H, 16-H), 9.43 (s, 1H, 11-H), 9.50 (s, 1H, 6-H), nomenclature according Chem. Abstr. **MS** (70 eV, 257°C), *m/z* (%):607 (23) [$C_{34}H_{33}N_5O_2{}^{64}Zn^+$], 496 (47) [$C_{34}H_{33}N_5O_2{}^{64}Zn^+$ - H_3CO_2C-CH=CH-CN], 466 (17), 451 (8). **UV/Vis** ($CHCl_3$): λ_{max} (lg ε) = 400 nm (4.983), 502 (3.578), 577 (3.757), 621 (4.540), 653 (3.720).

(10) Preparation of **12**:
step i) 1. 31.2 mg (65.44 µmol) of tricycle **10** were dissolved in 6 ml of THF and then 4 ml of a 5 N solution (20 mmol) of KOH in methanol / water was added. The mixture was refluxed with stirring under an argon atmosphere for 45 min. After cooling to rt the reaction mixture was diluted with 20 ml of dichloromethane and transfered into a separatory funnel which contained 20 ml of an aqueous solution saturated with sodium bicarbonate. The organic layer was separated and the aqueous layer was exhaustively extracted with small portions of dichloromethane. The combined dichloromethane extracts were dried by filtration through cotton wool and the solvent completely removed by evaporation.
2. To the so formed crude carboxylic acid of **10** was added under an argon atmosphere a solution of 31.7 mg (98.17 µmol, 1.5 equiv.) bromopyrrole aldehyde **9** in 4 ml of degassed dry chloroform, followed by 1.64 ml (654.4 µmol, 10 equiv.) of a 0.4 N solution of anhydrous *p*-toluene sulfonic acid in chloroform. The mixture was refluxed for 20 min and then cooled to rt. The reaction mixture was transfered with 10 ml of dichloromethane in a separatory funnel and extracted with 20 ml of an aqueous solution saturated with sodium bicarbonate. The aqueous layer was again exhaustively extracted with small portions of dichloromethane. The combined organic extracts were passed through dry cotton wool and the solvent was completely evaporated to yield the crude tetracycle **11** which was reacted without further purification in the next reaction step j).
step j) The crude product was dissolved in 6 ml of dichloromethane and a solution of 60 mg (327 µmol, 5 equiv.) of anhydrous zinc(II) acetate and 27 mg (327 µmol, 5 equiv.) of sodium acetate in 3 ml of methanol was added and stirred under argon with exclusion of light at rt for 20 min. The mixture was poured into a separatory funnel and extracted with 10 ml of an aqueous solution saturated with sodium carbonate. The aqueous layer was exhaustively extracted with small portions of dichloromethane and the organic extracts were combined and dried by passing through cotton wool. After evaporation the obtained residue was chromatographed on 15 g silica gel 32-63 µm 60 Å (ICN Biomedicals) with dichloromethane/ethyl acetate (9/1) containing 0.5 % of triethylamine. The chromatography yielded 24.4 mg (52 %) of the green product **12**.