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Simple Approach to "Locked" Chlorins

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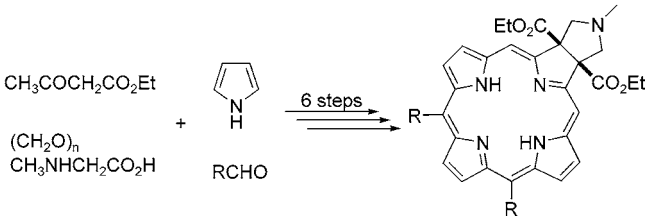
ABSTRACT



A novel synthetic approach to diversely functionalized "locked" chlorins is described. A suitably substituted 2,5-diformylpyrrole undergoes the macrocyclization reaction with tripyrranes, thereby generating porphyrins. Upon the reaction with 1,3-dipoles these porphyrins regioselectively furnish pyrrolidine-fused chlorins, which cannot oxidize to the corresponding porphyrins. In the process involving just six steps from commercially available and cheap materials we are able to obtain ∼200 mg of pure stable chlorins (the overall yield is 1.5–2.8%).

Recently, many studies have been focused on the use of artificial photosynthesis to develop light-energy conversion systems.[1] The natural photosynthetic system is regarded as one of the most elaborate nanobiological machines, with chlorophyll playing one of the important roles.[2] Although porphyrins lack some crucial photophysical features they are often used instead of chlorins in the energy and electron-transfer studies. The perspective of the use of chlorins is hampered by the lack of a reasonable methodology to construct suitable chlorin building blocks. Furthermore photodynamic therapy (PDT), a method utilizing visible or ultraviolet light in combination with a photosensitizing agent to induce a phototoxic reaction that results in cell damage or death, is now an established modality for the treatment of a number of diseases involving hyperproliferation of cells, including cancer, psoriasis, and hypervascularization of the retina.[3] With a growing importance of PDT, which seems to be endowed with several favorable features also for the treatment of localized microbial[4] and fungi infections,[5] there is a need for the development of new agents. Among these, chlorins appear to be the most promising because of the red shift of the longest wavelength Q-band along with the increased molar extinction of this band, which enables lower energy light to be used, with concomitant increased penetration through tissues. Most major second generation PDT sensitizers are chlorins.[6−8] Routes to chlorins for materials and biological chemistry applications typically employ one of three strategies: (1) derivatization of naturally occurring chlorins, (2) transformation of synthetic porphyrins,[9,10] or (3) total syntheses. The first route has access to large quantities of starting material but restricts control over the

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(8) One chlorin is already approved by EMEA (European Medicines Agency) (*m*-tetra(hydroxyphenyl)chlorin, Foscan), for use in head squamous cell carcinomas.

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pattern of substituents. The transformation of synthetic porphyrins is compatible with diverse substituents yet often suffers from adventitious dehydrogenation that regenerates the porphyrin.[9,11] In total syntheses it is possible to incorporate quaternary carbon atoms in the reduced ring to lock in the chlorin reduction level, thereby precluding adventitious dehydrogenation. However, the total syntheses of such stable chlorins are rare and lengthy. Total yields for representative examples are as follows: Battersby (14 steps, 0.04%),[12] Lindsey (11 steps, 0.3%),[13] Montforts (17 steps, 0.3%),[14] and Jacobi (17 steps, 1.1% yield).[15] The preparation of required monocyclic precursors is lengthy and not trivial, and furthermore the amounts of final chlorins obtained are always very small. The current synthetic needs of chlorin chemistry are thus only partially satisfied by these methodologies. This fact provided us with the motivation to develop a simpler procedure for the synthesis of inherently stable chlorins.

We have considered a variety of strategies that seemed to hold promise for particularly concise total syntheses of "locked" chlorins and finally we have chosen an approach based on Cavailero's discovery that simple *meso*-substituted A_4-porphyrins could act as dienophiles in the Diels−Alder reaction and as dipolarophiles in the 1,3-dipolar cycloaddition.[16] In these reactions chlorins were formed as the main product but were accompanied with bacteriochlorins and isobacteriochlorins. These interesting results were not intensively explored[17] because of the following reasons: (1) the reaction was not regioselective, (2) chlorins (and bacteriochlorins) formed were intrinsically unstable and could easily oxidize back to porphyrins, and (3) separation often could be done only by preparative TLC. Despite these drawbacks we saw a great potential in this approach. We envisioned that if two electron-withdrawing groups were placed in vicinal positions at the perimeter of the porphyrins, two problems could be solved at the same time. First, the reaction might take place regioselectively, on the bond activated by two EWG groups.[18] Second, chlorins formed would be "locked" as a result of the presence of two quaternary carbon atoms. We speculated that this approach would offer a number of advantages including ease of synthesis and an inherent stability of products. Such chlorins would be very interesting candidates for various studies providing that (1) the synthesis of respective porphyrins is straightforward and (2) potentially a broad variety of functional groups could be introduced.

To verify this concept, porphyrins bearing two *meso* and two β substituents at designated places at the perimeter of the macrocycle were required (Scheme 1). Porphyrins with such a pattern of substituents were not broadly known before and we had to devise a method for their synthesis. We selected porphyrins **6** and **7** bearing pentafluorophenyl and *p*-cyanophenyl substituents as our primary targets for the synthesis since Cavaleiro and co-workers[16] showed that the presence of electron-withdrawing groups at *meso* positions increases yields of the cycloaddition reaction to porphyrins. In addition, we resolved to prepare porphyrin **8**, bearing electron-donating groups at *meso* positions, to study if porphyrins of such type can also undergo cycloaddition. Simple retrosynthetic analysis revealed that required porphyrins could be synthesized via a [3 + 1] approach[19] from tripyrranes and aldehyde **2**. Respective tripyrranes **3**, **4**, and **5** were synthesized according to the known procedure with slight modifications and used as a mixture of diastereoisomers.[20]

Dialdehyde **2** was a more problematic synthesis. The presence of four electron-withdrawing groups excluded most of the simple routes based on the electrophilic substitution. Finally dialdehyde **2** was prepared from the respective diester **1** (easily accessed by Knorr methodology in two steps from ethyl acetoacetate)[21] via oxidation with cerium ammonium nitrate (CAN) in 50% yield. Other oxidizing agents (PbO_2/$Pb(CH_3COO)_4$,[22] $Pb(CH_3COO)_4$,[23] 2-iodoxybenzoic acid (IBX), and PCC) were also examined in this reaction, but only CAN[24] gave positive results, though extensive changes

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(18) A single example of such an idea has been published.[17c] Reaction of β-nitroTPP with diazomethane gave one regioisomer of locked chlorin. This approach, however, is very unpractical for the following reasons: (a) a very long reaction time (30 days), (b) the formation of a mixture of enantiomers, (c) the preparation of starting porphyrins via nitration cannot be regioselectively done for more complex *meso*-substituted porprhyrins, thereby precluding the possibility of the construction of chlorin building blocks, (d) work with diazomethane.

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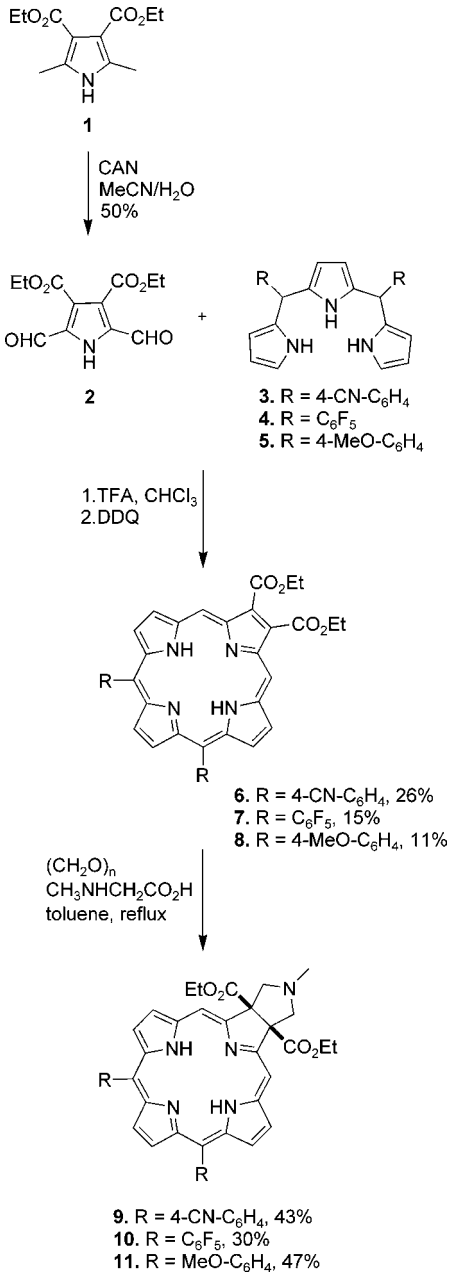
Scheme 1



had to be done to the existing procedure in order to obtain a reasonable yield.

The next stage of the synthesis involved the construction of the porphyrin ring in such a way that the acid-catalyzed decomposition of starting tripyrranes (scrambling) was minimal. The synthesis of porphyrins and core-modified porphyrins via a [3 + 1] route was extensively studied by Lash,[25] but there are almost no examples for the use of β-unsubstituted tripyrranes in this reaction. Therefore the condensation of tripyrrane **4** with aldehyde **2** was initially performed using the reaction conditions that were developed during our study on the condensation of 5-pentafluorophenyldipyrromethane and aldehydes. It was proved that under these conditions corroles were formed without detectable scrambling.[26] Because the yield of porphyrin **7** was low, we have tried to modify the reaction conditions by changing the concentration of TFA and reagents, time, etc. We found that the yield strongly depended on the concentration of reagents. Moreover, we found that much higher concentration of acid was beneficial ([TFA] = 1.00 M). ESI-MS analysis of the crude reaction mixture showed a single porphyrin peak with no detectable scrambled porphyrins byproducts. The optimized conditions differ from typical ones used for β-substituted tripyrranes in that the concentration of TFA is much higher. Eventually, porphyrins **6**, **7**, and **8** were obtained in 26%, 15%, and 11% yields, respectively (Scheme 1).

The stage was set for the pivotal cycloaddition reaction, which we approached with some trepidation because of the regioselectivity issue. In this final step, we chose 1,3-dipolar cycloaddition rather that the Diels−Alder reaction for the following reasons: (1) substrates are commercially available and cheap (1,3-dipoles are generated in situ by thermal decarboxylation of immonium salts obtained from condensation of *N*-methylglycine and paraformaldehyde, in contrast to reactive diene precursors used to date in Diels−Alder reaction with porphyrins), (2) the presence of the pyrrolidine ring in the product imparts some polarity, which should facilitate purification. Our first model, porphyrin **7**, gave the excellent result of a 100% conversion and an isolated purified product yield of 30%, utilizing slightly modified Cavaleiro's conditions (Scheme 1). To achieve full conversion of porphyrin **7** we had to increase the reaction time and amounts of dipole precursors. Though in principle three regioisomeric chlorins could be formed in this reaction, we have obtained only one. The structure of chlorin **10** was confirmed by the analysis of ^{1}H NMR spectrum and mass spectrometry. Results revealed that the desired chlorin **10** formed with full regioselectivity. The formation of bacteriochlorin and isobacteriochlorin was not observed. Chlorins **9** and **11** were obtained under the same conditions in 43% and 47% yields, respectively (Scheme 1). The latter example proves that if electron-withdrawing groups are introduced at β positions, the presence of electron-withdrawing groups at the *meso* position is no longer necessary for successful 1,3-dipolar cycloaddition. It allows for significant expansion of the scope of the presented approach.

To establish the preparative value of the presented methodology, we performed the whole synthesis on a large scale (see Supporting Information). 1,3-Dipolar cycloaddition was performed on 0.8 mmol scale for two exemplary porphyrins. The yields of the last two steps were a little bit lower (porphyrin **6**, 21%; porphyrin **7**, 15%; chlorin **9**, 36%; chlorin **10**, 26%), as compared to small-scale experiments. However, it has to be strongly underlined that our methodology made it possible to obtain 200 mg of each chlorin within just 2 weeks.

Naked-eye observations revealed that chlorin **10** was green, whereas chlorins **9** and **11** were distinctly violet-green. To

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the best of our knowledge such dependence of the electronic spectrum on substituents present at *meso* positions of chlorins was not described in the literature to date. UV−vis spectra (see Supporting Information) provided an explanation of this phenomenon. The absorption spectrum of **10** shows a strong Soret band at 408 nm and at longer wavelength four weak Q-bands at 503, 589, and 641 nm, respectively (Figure 1). The last Q-band is significantly stronger than in the case of chlorins **9** and **11**.

This paper establishes the foundation for the first truly short pathway leading to inherently stable ("locked") chlorins. By using this extensively optimized sequence, chlorins could be prepared from commercially available reagents in just six steps in 1.5−2.8% overall yield (higher than any previous approach based on total synthesis). The methodology is potentially diversity-tolerant, facilitating the introduction of aryl, hetero-aryl, alkyl, cyano, and nitro substituents in both *meso* and β positions around the chlorin scaffold, thus allowing for fine-tuning of properties for energy transfer and PDT. The utilization of this synthetic methodology for the preparation of other chlorins for various applications is currently underway.

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Supporting Information Available: Full experimental procedures for the synthesis of compounds **2** and **6**−**11**, ^{1}H NMR spectra for compounds **6**−**11**, ^{13}C NMR spectra for compounds **9**−**11**, and UV−vis spectra of all chlorins. This material is available free of charge via the Internet at http://pubs.acs.org.

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