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Tetrahedron Letters 44 (2003) 7793–7797

TETRAHEDRON LETTERS

meso-Tetraaryl-7,8-dihydroxydithiachlorins: first examples of heterochlorins

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Received 9 August 2003; accepted 19 August 2003

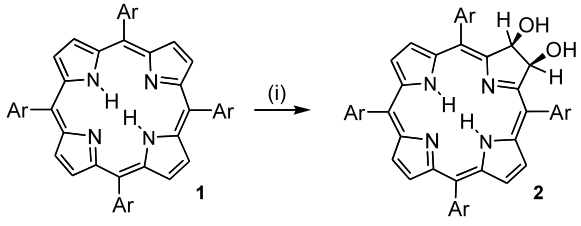
Abstract—Osmium tetraoxide-mediated dihydroxylation of *meso*-tetraaryldithiaporphyrins generates the corresponding *meso*-tetraaryldithia-7,8-dihydroxychlorins and *meso*-tetraaryldithia-7,8,17,18-tetrahydroxybacteriochlorins. The products are spectroscopically characterized and the substitution positions were unequivocally determined. The UV–vis of the heterochlorins and heterobacteriochlorins are chlorin- and bacteriochlorin-like, respectively. However, the chlorin spectra are surprisingly hypsochromically shifted as compared to the corresponding all-aza chlorins, whereas the bacteriochlorin is bathochromically shifted. *meso*-Tetraaryldithia-7,8-dihydroxychlorins are susceptible to oxidative ring-opening reactions to form the corresponding *meso*-tetraaryldithia-7-oxo-8-oxa-dithiaporphyrin (dithiaporpholactone). These derivatives are the first examples of heterochlorins and β-modified dithiaporphyrins.

One of the main driving forces in contemporary porphyrin chemistry is the generation of long-wavelength absorbing and fluorescing molecules with potential use as fluorescence imaging[1] or phototherapeutic agents.[2] With respect to their longest wavelengths of absorption, porphyrins do not fulfill the ideal photophysical requirements for these applications. They generally do not absorb light within the 'photo-therapeutic window' of tissue, i.e. the range of ~680–850 nm in which tissue has minimal absorbance. This has led to extensive efforts to convert porphyrins to chlorins (β,β′-dihydroporphyrins),[3] as chlorins generally have a longer wavelength of absorbance. The search for alternative long-wavelength absorbing chromophores has led to the synthesis of porphyrin isomers,[4] heteroporphyrins,[5–7] expanded porphyrins[4] and pyrrole-modified porphyrins.[8–11]

5,10,15,20 - Tetraaryl - 21,23 - dithiaporphyrins, porphyrins in which the two pyrrole-type nitrogens were formally replaced by sulfur atoms, possess longer wavelengths of absorption (λ_{max} (log ε) = 699 (3.67) nm)[12] as compared to porphyrins (λ_{max} (log ε) = 647 (3.59) nm).[13] Their phototherapeutic efficacy was demonstrated.[6,7] The *meso*-aryl groups allow for the introduction of a wide variety of substituents to allow the adjustment of the solubility and biodistribution properties of the potential drug.

We have reported the OsO_4-mediated dihydroxylation of *meso*-tetraarylporphyrin (**1**) to generate diol chlorin **2**[14] and the corresponding tetraolbacteriochlorins[15] (Scheme 1). The dihydroxylation of porphyrins is also a well known reaction for the modification of β-octaalkylporphyrins.[16] Diol chlorins **2** possesses chlorin-type UV–vis spectra, although λ_{max} is not bathochromically shifted compared to porphyrin **1**. This electronic effect of the diol moiety appears to be general.[17] We have also shown the utilization of diolchlorins in the synthesis of a number of pyrrole-modified chromophores, some of which posses significantly bathochromically shifted optical spectra.[9]

Several questions arise: Is the OsO_4-mediated dihydroxylation of dithiaporphyrins possible? What are the pho-



Scheme 1. *Reaction conditions*: (i) OsO_4/pyridine; (ii) 1. H_2S 2. chromatography.[9]

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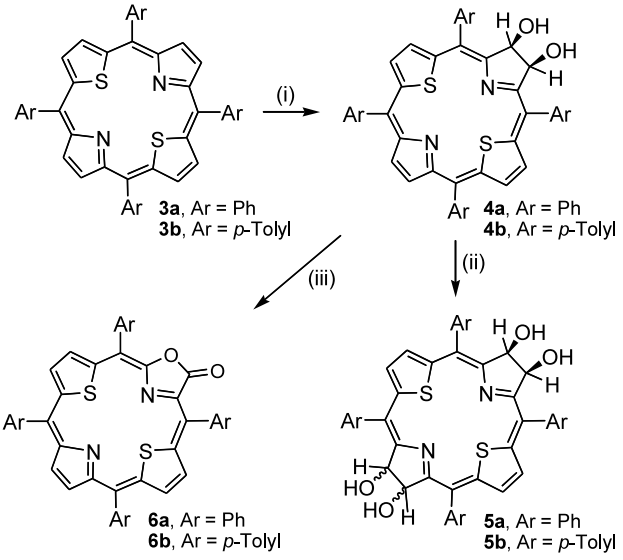
doi:10.1016/j.tetlet.2003.08.070

tophysical properties of the resulting dithiachlorins? The answer to this question is particularly interesting as we are not aware of any examples of heterochlorins. Are the diolheterochlorins also susceptible to further modifications of the dihydroxylated β,β′-bond? This contribution will investigate these questions.

Two dithiaporphyrins, **3a** and **3b**, were synthesized following the 3+1 procedure described by Detty and co-workers.[7] Reaction of the bright orange dithiaporphyrins (**3b**: $R_f = 0.93$, silica/3% MeOH in $CHCl_3$) with 1.2 equiv. OsO_4 in $CHCl_3$/pyridine generated, over the course of 24 h, one more polar dark orange product (**4b**: $R_f = 0.85$, silica/3% MeOH in $CHCl_3$) and, to a much lesser degree, two more polar pink products (**5b**: $R_f = 0.74$ and 0.18, silica/3% MeOH in $CHCl_3$) (Scheme 2).[18] Quenching of the reaction mixture with H_2S, followed by filtration and chromatographic separation of the products, recovered ~60 % of the starting material and produced the orange major product in 20 % and the two minor products in low yields (<5 %). The high resolution mass spectrum of **4b** indicated that the expected diol chlorin had formed (**4b**: $m/z = 739.2453$ (MH^+, FAB-PEG), corresponding to **3b**+2×OH). The mass spectra for the two high polarity products **5** were identical and proved their composition to correspond to that of the bacteriochlorins **5** (**5b**: $m/z = 772.2524$ (M^+, FAB-PEG), i.e. to **3b**+4×OH). The two *vic*-diol moieties in the bacteriochlorin can be arranged on the same side of the plane of the porphyrin or on opposite sides, giving rise to two isomeric products.[15]

OsO_4 reacts with the double bond which, once removed, results in the least loss of resonance energy.[19] This implies that dihydroxylation will take place on the pyrrolic peripheral positions of the porphyrin because this does not destroy the porphyrinic inner 18 π system. The ^1H NMR spectra of the diol heterochlorins provide clear indications for the location of the diol moiety (Fig. 1). In general, the NMR spectrum of dioldithiachlorin **4a** is similar to that of diolchlorin **2**.[9] The presence of the pyrrolidine protons (6.26 ppm, d, ^3J= 5.5. Hz, 1H) which couple with a signal attributed to the alcohol functionalities (5.41 ppm, $^3J = 5.5$ Hz, 1H, exchangeable with D_2O) and the face- and side-differentiation of the *o*-phenyl protons (8.21 ppm, d, $^3J = 6.7$ Hz, 1H; 8.14 ppm, br d, $^3J = 7.0$ Hz, 2H; 7.97 ppm, d, $^3J = 6.5$ Hz, 1H) indicate the presence of the *vic*-*cis*-diol moiety. The β-proton region of the spectrum shows the expected d (9.46 ppm, $^3J = 5.0$ Hz, 1H), d (9.10 ppm, $^3J = 5.0$ Hz, 1H), s (8.40 ppm) pattern expected for the two-fold symmetric product. Again, the peak positions are diagnostic for the determination of the position of the diol moiety. The two doublets are found above 9.0 ppm, the region of the thiophene hydrogens,[7] whereas the singlet for the protons opposite of the site of modification is found at 8.40 ppm. The latter number compares well to the corresponding s at 8.48 ppm and the doublets at 8.63 and 8.33 ppm, $^3J = 4.5$ Hz found in the all-aza diolchlorin **2**.[9]

The UV–vis spectrum of the diol heterochlorin **4b** in comparison to that of the starting material **3a** is shown in Figure 2. In some aspects, the spectrum is diolchlorin-like, i.e. it is characterized by a broadened Soret band and an increased second side band (at 547 nm).



Scheme 2. *Reaction conditions*: (i) 1. 1.2 equiv. OsO_4/pyridine, 2. H_2S, 3. chromatography; (ii) as in (i) with a larger excess of OsO_4; (iii) 1. $KMnO_4$/18-crown-6, THF, 2. chromatography.

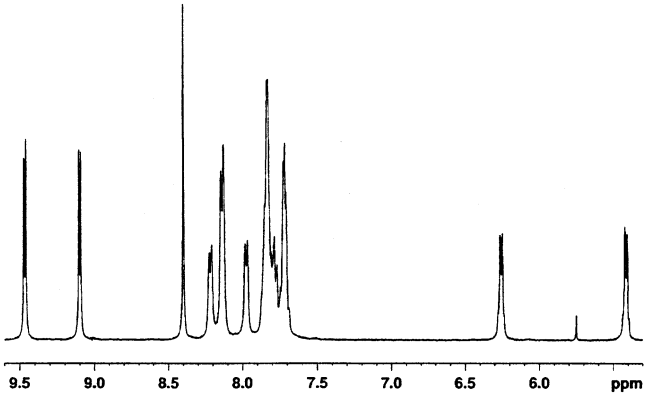


Figure 1. ^1H NMR (400 MHz, DMSO-d_6, 25°C) of **4a**.

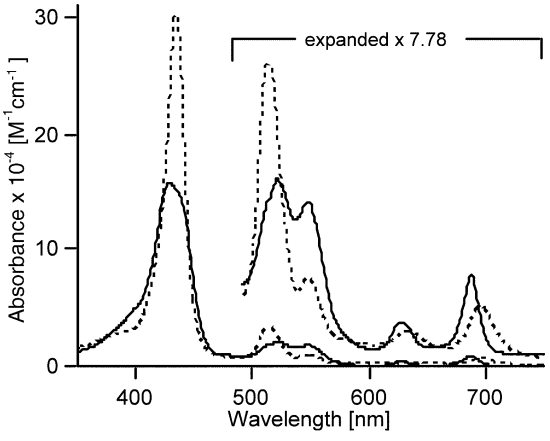


Figure 2. UV–vis spectra (CH_2Cl_2) of **3a** (···) and **4b** (—). The UV–vis spectra of **4a** and **4b** are identical.

However, the longest wavelengths absorption (λ_{max} = 687 nm) is only minimally more intensified and 13 nm hypsochromically shifted compared to the starting porphyrin. The spectrum is, however, bathochromically shifted as compared to that of the diolchlorin **2** (λ_{max} = 648 nm).[9] This shift parallels the bathochromic shift of the spectrum of the dithiaporphyrins as compared to that of the all-aza porphyrin **1** (λ_{max} = 650 nm), delineating the electronic influence the sulfurs have on the porphyrinoid π-system.

The UV–vis spectrum of the bacteriochlorins **5**, on the other hand, shows the expected three-band pattern of a bacteriochlorin chromophore (Fig. 3). The spectra of both isomers of **5** are identical and also significantly red-shifted (λ_{max} = 734 nm) as compared to the corresponding tetraolbacteriochlorins (λ_{max} = 708 nm).

The NMR spectral data for the tetraoldithiabacteriochlorins **5** are largely as found for the bacteriochlorin analogs, save for the larger low-field shifts characteristic for the thiophene units.[18] The NMR spectroscopical characterization of the two isomeric products does not allow the distinction between the *trans*- and *cis*-*vic*-diol isomers. However, the two isomers display vastly different polarity. We rationalize that the compound of lower polarity is the *trans*-isomer as it is unlikely that this compound can interact with the stationary phase concurrently with both diol moieties, whereby the *cis*-isomer could, resulting in much higher polarity.

Porpholactones are porphyrin-like derivatives in which one peripheral double bond of a porphyrin was replaced with a lactone moiety.[20] Porpholactones are generated by oxidation of β-activated porphyrins or chlorins.[20] We recently introduced the synthesis of porpholactone by MnO_4^--induced cleavage of diol **2** under phase transfer catalysis.[10] This reaction is also applicable to dioldithiachlorin **3b**.[21] Thus, reaction of a $CHCl_3$ solution of **2b** with an aq solution of $KMnO_4$ in the presence of the phase transfer catalysts 18-crown-6 produced within minutes one main non-polar (R_f = 0.80, silica/$CHCl_3$) dark orange product. Its HR-MS (FAB+, PEG) showed the expected composition $C_{47}H_{34}N_2O_2S_2$ for dithiaporpholactone **6b**. This composition indicated the characteristic loss of one framework carbon and four hydrogens from the diol dithiachlorin **4b**. A $\nu_{C=O}$ band at 1773 cm^{-1} in the IR spectrum of **6b** identified the functional group (cf. to $\nu_{C=O}$ = 1760 cm^{-1} for porpholactone).[20] The UV–vis spectra of **6a** is shown in Figure 4. Analogous to the similarity of the spectra of porpholactone and **1**,[20] the UV–vis of **6** is, save for slight shifts of the relative intensities of the side bands, similar to that of the dithiaporphyrin **3**. Thus, the lactone moiety closely mimicks the electronic influence of the β,β′-double bond.

The ^1H NMR of **6a** is shown in Figure 5. The β-region of the spectrum displays six doublets corresponding to the expected six non-equivalent peripheral protons. The six signals can be distinguished into two groups, the two doublets at 8.51 ppm (^3J = 4.5 Hz) and 8.58 ppm (^3J = 4.5 Hz) belonging to the pyrrolic protons and the four (partially overlaying doublets) in the region above 9.3 ppm are assigned to the thiophene protons. In comparison, all β-signals for the all-aza porpholactone are found between 8.5 and 8.8 ppm. Again, the low-field shift of the signals found in **6** unambiguously locates the ring modification.

In summary, dioldithiachlorins **4** and tetraoldithiabacteriochlorins **5** are accessible from dithiaporphyrins **3** by means of an OsO_4-mediated dihydroxylation reaction. The UV–vis spectrum of the heterochlorin is surprisingly blue-shifted as compared to the heteroporphyrin, while that of the bacteriochlorin **5** fulfills expectations. This underlines the unique properties of the heteroanalogs of porphyrins. Diolhete-

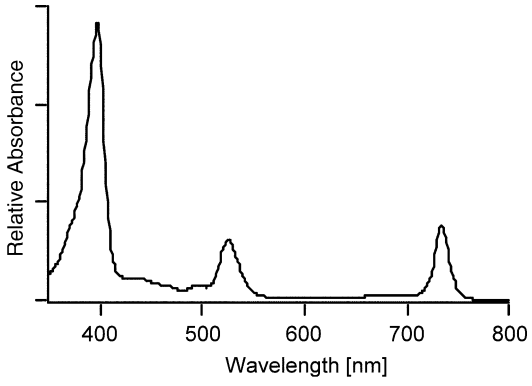


Figure 3. UV–vis spectrum (CH_2Cl_2) of **5a**.

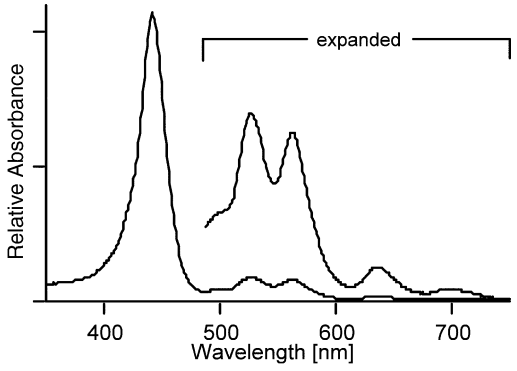


Figure 4. UV–vis spectrum (CH_2Cl_2) of **6b**.

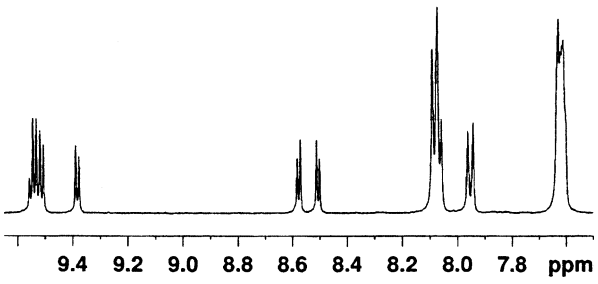


Figure 5. ^1H NMR of **6a** (400 MHz, $CDCl_3$, 25°C). No further signals below 7.6 ppm are observed.

rochlorin **4** is susceptible to an oxidative diol cleavage, providing dithiaporpholactone **6**. The novel chromophores **4**–**6**, while paralleling the chemistry *meso*-arylporphyrins, are unprecedented in the chemistry of heteroporphyrins.

Acknowledgements

C.R. thanks the National Science Foundation for an NSF-REU summer research stipend. We thank Michael R. Detty (State University of New York at Buffalo) for kindly having provided us with dithiaporphyrin samples.

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17. For examples of the hypsochromic effect of hydroxy groups in a benzylic position to the porphyrinic chromophore, see: Refs. 13–15.
18. *General procedure for the synthesis of dithia-7,8-dihydroxychlorins* ***4***: 5,10,15,20-*meso*-Tetraaryl-21,23-dithiaporphyrin **3** (0.424 mmol) was dissolved/suspended in freshly distilled, EtOH-stabilized $CHCl_3$:pyridine (1:3, 100 mL) and was treated with OsO_4 (1.2 equiv.) (**CAUTION**: Fumehood and eye protection!). The reaction flask was stoppered and stirred at ambient temperature for 3 d and shielded from light with aluminum foil. The reaction was then quenched by purging with H_2S for 5 min (**CAUTION**: Fumehood, trapping of excess H_2S!). The solution was then filtered through a plug of Celite to remove the precipitated OsS. The filtrate was evaporated to dryness by a stream of N_2 or in vacuo. The resulting residue was loaded onto a silica gel column (20×5 cm) and eluted with CH_2Cl_2. The first fraction was starting material. 1% MeOH in CH_2Cl_2 then eluted **4**. Increasing the polarity of the solvent to 3% MeOH in CH_2Cl_2 then eluted the low polarity isomer of **5**, followed by the high polarity isomer. All products were recrystallized by slow solvent exchange from CH_2Cl_2 to MeOH. Select spectroscopic data: (**4a**) ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.9, 153.2, 150.3, 141.3, 140.7, 140.4, 135.7, 135.2, 133.5, 133.3, 133.0, 132.1, 131.2, 128.4, 127.8, 127.6, 127.5, 73.5 ppm; (**5b**, high polarity isomer) ^1H NMR (400 MHz, DMSO-d_6): δ 8.78 (s, 1H), 7.91 (d, J=7.0 Hz, 1H), 7.72 (d, J=7.1 Hz, 1H), 7.50 (d, J=6.9 Hz, 1H), 7.43 (d, J=7.0 Hz, 1H), 6.05 (d, J=4.5 Hz, 1H), 5.14 (d, J=4.5 Hz, 1H), 2.53 (s, 3H), 2.46 (s, 3H); HR-MS (M^+, FAB-PEG,) calcd for $C_{48}H_{40}N_2O_4S_2$: 772.2429; found: 772.2469.
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21. *Procedure for the synthesis of* ***6*** *by oxidation of* ***4***: To a stirring solution of **4b** (17.5 mg, 2.4×10^{-2} mmol) in THF (15 mL) was added 18-crown-6 ($\sim$2 mg, 7.8×10^{-3} mmol, 0.33 equiv.). $KMnO_4$ (18.7 mg, 0.12 mmol, 5 equiv.) was added to the solution, and the mixture was allowed to react for 12 h at ambient temperature. The solution was

filtered through a short plug of silica gel. The filter cake was washed with CH_2Cl_2 until the filtrate was colorless. The resulting solution was evaporated to dryness. The product was isolated by column chromatography eluted with $CHCl_3$ to provide, after recrystallization by solvent exchange into EtOH, **6b** in 54 % yield (9.2 mg). $R_f = 0.8$ (silica/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (m, 3H), 9.38 (d, $J = 4.9$ Hz, 1H), 8.58 (d, $J = 4.5$ Hz, 1H), 8.51 (d, $J = 4.5$ Hz, 1H), 8.07 (m, 6H), 7.95 (d, $J = 7.8$ Hz, 2H), 7.62 (m, 8H), 2.71 (s, 6H), 2.68 (s, 3H), 2.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8,158.7, 155.6, 155.4, 152.2, 150.6, 146.2, 146.0, 138.9, 138.8, 138.6, 138.5, 138.1, 137.8, 136.3, 135.7, 134.93, 134.9, 134.7, 134.4, 134.4, 134.1, 134.0, 132.7, 132.6, 132.2, 129.6, 129.4, 128.9, 128.8, 118.3, 22.2, 22.03, 22.02, 22.0, 21.98 ppm.