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SYNTHESES AND UNUSUAL SPECTROSCOPIC PROPERTIES OF NOVEL KETOBACTERIOPURPURINS

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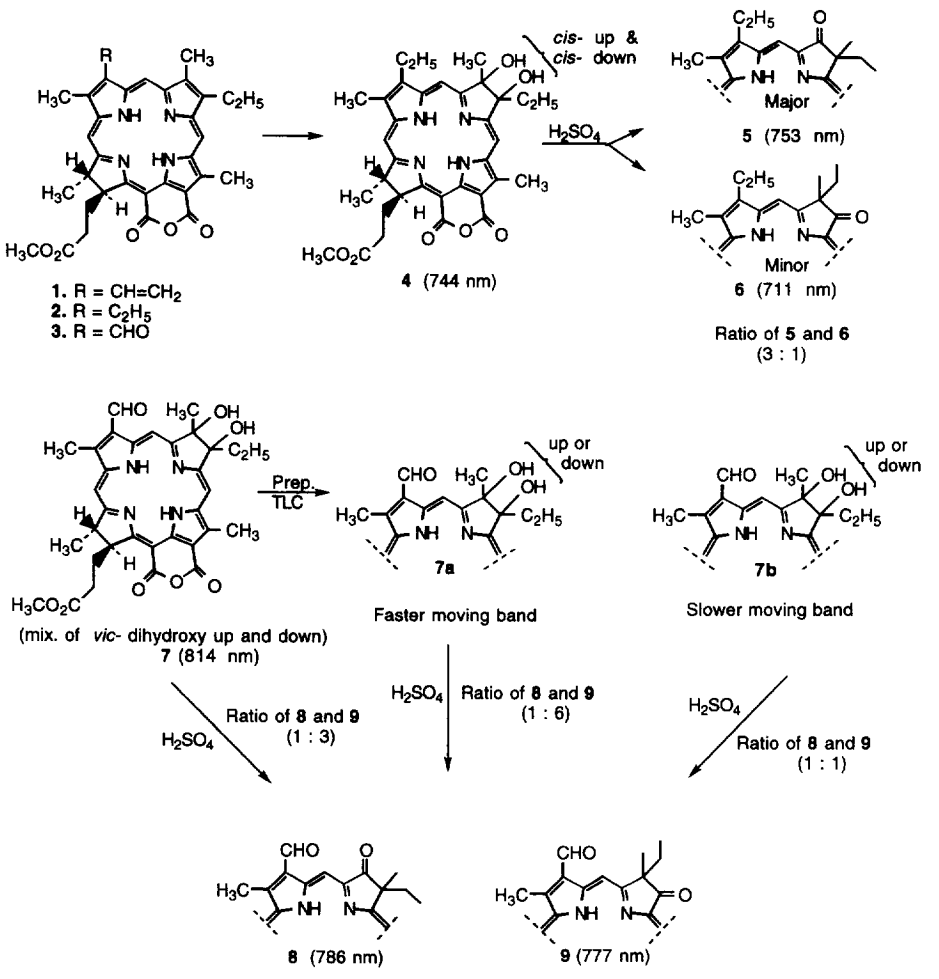
Abstract: Nuclear Overhauser enhancement experiments show that migratory aptitudes of alkyl groups in various *vic*-dihydroxybacteriopurpurins are different for individual stereoisomers. Long wavelength absorption maxima of ketobacteriopurpurins obtained from pinacol-pinacolone rearrangements of the corresponding diols are influenced by the position of the keto group in the macrocycle; differences in these maxima are diminished by introduction of electron-withdrawing substituents.

Osmium tetroxide reactions of porphyrins have been investigated in depth by various investigators.[1] Mechanistic details of the formation of ketochlorin from β,β-dihydroxychlorin were confirmed by Bonnett and coworkers.[2] Chang et al.[3] later studied the migratory aptitudes of several types of substituent in acid catalyzed reactions of β,β-dihydroxyporphyrins. The regiochemistry of OsO_4 oxidation of various metalated or free base chlorins to give either isobacteriochlorins or bacteriochlorins has also been established.[4] Our own initial studies utilized porphyrin systems in which electron-withdrawing substituents were regioselectively placed either at peripheral position(s) or at the meso position(s). Using such substrates we showed that electron-withdrawing or electron-donating substituents induce significant regiospecificity with regard to the pyrrole subunit which undergoes OsO_4 oxidation.[5] This approach was extended to pheophorbide-a and chlorin-e_6 esters, and it was shown that the migration of alkyl groups in *vic*-hydroxybacteriochlorins is also influenced by the number of the electron-withdrawing groups.[5,6] Due to their stable nature and long wavelength absorptions (λ_{max} 645-760 nm) some of the *vic*-dihydroxychlorins, ketochlorins and bacteriochlorins have since been evaluated for photodynamic efficacy in photodynamic therapy (PDT).[7]

In recent years long-wavelength photosensitizers (λ_{max} 660-800 nm) have generated great interest due to their ability to use low energy light and sensitize at deeper tissue penetration distances in PDT.[8] In our approach for the synthesis of such compounds, we reported the preparation, from purpurin-18 methyl ester **1**, of some *vic* -dihydroxybacteriochlorins bearing anhydride or imide rings (λ_{max} 813-816 nm).[9,10] Some of these compounds were found to be effective in PDT if the mice were treated with light of an appropriate wavelength at 3 h post injection of the sensitizer.[9] No activity was observed at 24h post injection. In another series of bacteriochlorins, obtained from 9-deoxypyropheophorbide-a, it was generally observed that the keto-analogues were much more effective PDT sensitizers than were the corresponding *vic* -dihydroxy-derivatives.[7] This might be due to their more hydrophobic nature, which possibly helps them to be retained in tumor cells for longer times. Keeping this in mind, we thought it worth while to convert the *vic*-dihydroxybacteriopurpurins into the related keto-derivatives and to investigate their photosensitizing activity.



Scheme 1: Purpurin synthetic transformations.

In our initial studies, mesopurpurin-18 methyl ester **2** was used as a substrate; it was obtained from methyl pheophorbide-a. Reaction of **2** with OsO_4/pyridine/H_2S produced *vic*- dihydroxybacteriopurpurin **4**, in 60% yield, as a diastereomeric mixture (*vic* -dihydroxy groups up or down compared to pyrrolic ring D) with long-wavelength absorption at 744 nm. Treatment of **4** with H_2SO_4 under pinacol-pinacolone conditions gave 3-ketobacteriopurpurin **5** (via methyl group migration) and 4-keto-bacteriopurpurin **6** (via ethyl group migration) in a 3:1 ratio. The structures of **5** and **6** were confirmed by nuclear Overhauser enhancement (nOe) experiments, as shown in Scheme 2. This pinacol-pinacolone migratory pattern is in sharp contrast to that previously observed in porphyrins and pyropheophorbides, (in which the ethyl invariably migrated preferentially over the methyl group).[4,5] The most unexpected feature among isomeric compounds **5** and **6** is the large difference ($\Delta\lambda$ 42 nm) in the electronic absorption maxima. As shown in Figure 1, the 3-keto- analogue has a strong absorption at λ_{max} 753 nm, compared with the 4-keto- derivative (at only 711 nm). In general, transformation of *vic*-dihydroxychlorin (if porphyrin is the OsO_4 substrate) or *vic*-dihydroxy-bacteriochlorin (if chlorin is the substrate) into the corresponding keto-derivative results in blue-shifts in the optical spectra.[6] Surprisingly, compared with *vic*-dihydroxybacteriopurpurins, isomers **5** was red shifted while isomer **6** was blue shifted.

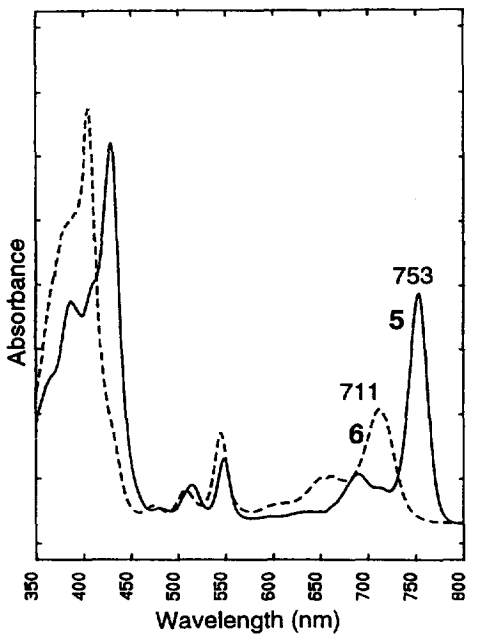


Figure 1: Optical spectra (in CH_2Cl_2) of **5** [λ_{max} 387 nm (ε 53,000), 426 (86,000), 521 (7000), 546 (14,000) and 753 (53,000)] and **6** [λ_{max} 389 nm (ε 71,000), 402 (108,000), 518 (6000), 545 (18,000) and 711 (27,000)].

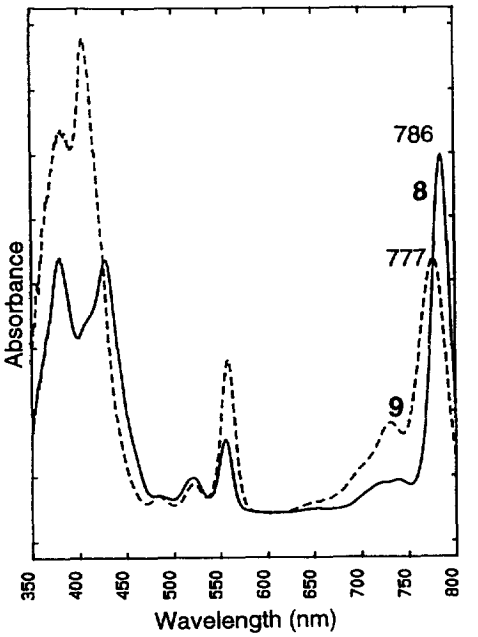
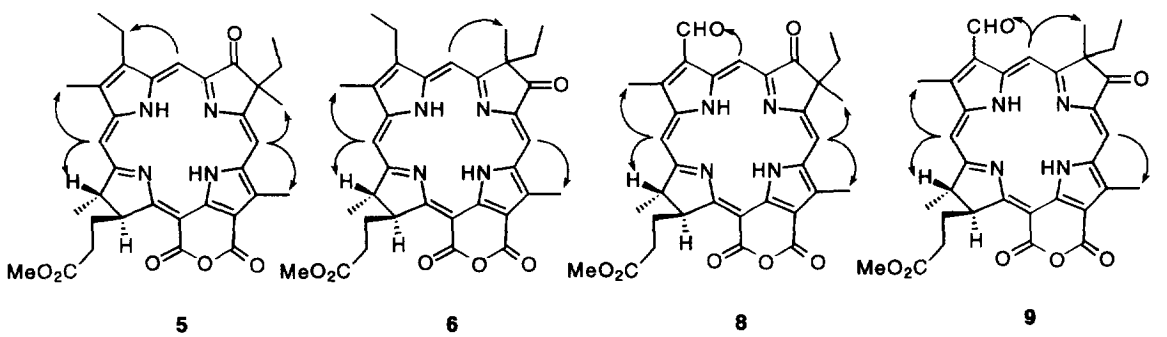


Figure 2: Optical spectra (in CH_2Cl_2) of **8** [λ_{max} 378 nm (ε 52,000), 429 (51,000), 520 (6500), 555 (13,000) and 786 (64,000)] and **9** [λ_{max} 381 nm (ε 82,000), 405 (104,000), 521 (5500), 558 (21,000) and 777 (38,000)].

To investigate the effect of electron-withdrawing groups in the migration of alkyl substituents under pinacol-pinacolone reaction conditions, 2-formyl-*vic*- dihydroxy-bacteriochlorin **7** (λ_{max} 815 nm), (HPLC[11] retention times 23.5 and 26.3 min), was prepared from **3**.[9] The diastereomeric mixture was separated into the individual isomers **7a** (λ_{max} 813 nm) and **7b** (818 nm) (*cis*- up or *cis*- down) by preparative column chromatography. As expected, under acidic conditions, the diastereomeric mixture gave keto-derivatives **8** and **9** (1:3 ratio). The structures of **8** and **9** were confirmed by proton NMR and nOe studies (Scheme 2). Surprisingly, under similar reaction conditions, the two individual isomers **7a** and **7b** gave a different ratio of keto derivatives **8** and **9** (1:6 from **7a**; 1:1 from **7b**). The absolutestereochemistries of **7a** and **7b** have yet to be determined. In the electronic absorption spectra, compared to keto-



Scheme 2: Nuclear Overhauser enhancements seen for compounds **5**, **6**, **8**, and **9**.

mesobacteriochlorins **5** and **6** (in which a difference of 45 nm shift was observed at long-wavelength absorptions), the 2-formyl-ketobacteriopurpurins **8** and **9** did not show such a remarkable difference. Isomers **8** and **9** have long wavelength absorptions at λ_{max} 786 nm and 777 nm, respectively (Figure 2), which are both blue-shifted compared with the diol-precursors.

This is the first occasion in which the *vic*- dihydroxybacteriochlorins from OsO_4 oxidation of a tetrapyrrole were separated into their individual diastereoisomers, and in which the migratory aptitudes of the alkyl groups (Me vs Et) in each was investigated under pinacol-pinacolone reaction conditions. From this study it is clear that presence of electron-donating or -withdrawing substituents profoundly affects the mechanistic pathway which regulates the migration of one substituent over the other. Once the stereochemistry of the individual *vic*- dihydroxybacteriochlorins is known, it may be easier to explain the preferential migration of methyl and ethyl substituents, which in the present work is unexpectedly different for each individual isomer. We believe that the new compounds described herein serve as good models for further mechanistic and theoretical studies of the pinacol-pinacolone reaction in cyclic tetrapyrrole systems.

These newly synthesized long-wavelength absorbing stable bacteriopurpurins are currently being evaluated for their *in vivo* PDT efficacy.

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