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Tunable *meso*-Tetraphenyl-alkyloxazolo-chlorins and -bacteriochlorins†

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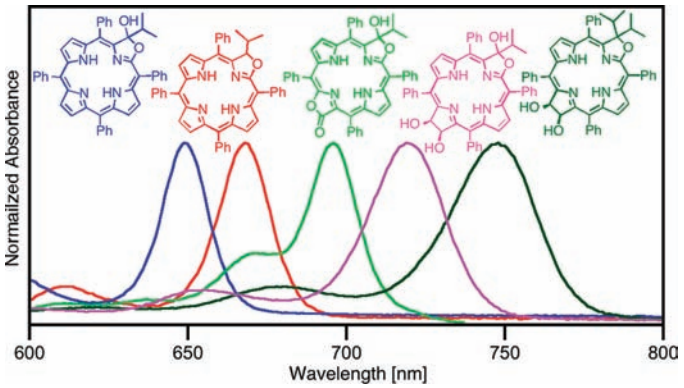
ABSTRACT



Alkyl-Grignard addition to *meso*-tetraphenylporpholactone generates monoalkyl- and *gem*-bis-alkyloxazolochlorins. Together with compounds made by further synthetic manipulations of these derivatives, a series of chlorin-type chromophores with modulated optical properties is generated. Furthermore, their OsO_4-mediated dihydroxylations and subsequent functional group transformations generate a family of bacteriochlorins that possess substituent-dependent optical properties. Thus, the formal replacement of a pyrrolidine moiety in chlorins and bacteriochlorins by variously substituted oxazoles is a flexible methodology to generate novel and stable chromophores that are tunable over a considerable range of the optical spectrum.

For porphyrinoid chromophores to find utility as, for instance, photosensitizers, imaging agents in tissue, or in light-harvesting systems, their optical properties need to be tuned to the particular application. This frequently means shifting the maximum wavelength of absorbance (λ_{max}) of the prototypical porphyrin *meso*-tetraphenylporphyrin from 648 nm bathochromically into the 'optical window' of tissue, while preferably also increasing the absorbance at λ_{max}.[1] In addition, a considerable portion of sun light is in the region above 650 nm. Chromophores absorbing strongly in these regions can potentially increase their light harvest efficiency.[2] In nature, chlorins (2,3-dihydroporphyrins) and bacteriochlorins (2,3,12,13-tetrahydroporphyrins) fullfill these optical requirements.[3]

Many principal approaches can be taken to achieve the synthesis of red-absorbing porphyrinoids. Among them are the synthesis of ring expanded systems[4] and annulated porphyrins[5,6] as well as the development of methods to convert porphyrins to chlorins and bacteriochlorins.[7] Representative of the latter approach is the addition of

† Oxazolochlorins **4**. Oxazolochlorins **3**: Khalil, G. E.; Daddario, P.; Lau, K. S. F.; Imtiaz, S.; King, M.; Gouterman, M.; Sidelev, A.; Ghandehari, M.; Brückner, C. *Analyst* **2010**, *135*, 2125–2131.

(1) The 'optical window' is between 600 and 1300 nm; the wavelength of maximum penetration of breast tissue is ~725 nm: Cerussi, A. E.; Berger, A. J.; Bevilacqua, F.; Shah, N.; Jakubowski, D.; Butler, J.; Holcombe, R. F.; Tromberg, B. *J. Acad. Radiol.* **2001**, *8*, 211–218.

(2) For example, see: *Artificial Photosynthesis & Solar Fuels* thematic issue of *Acc. Chem. Res.* **2009**, *42*, 1859–2029.

(3) *Chlorophylls*; Scheer, H., Ed.; CRC: Boca Raton, FL, 1991.

(4) (a) Sessler, J. L.; Weghorn, S. *Expanded, Contracted & Isomeric Porphyrins*; Pergamon Press: New York, NY, 1997. (b) *The Porphyrin Handbook, Vol. 2 - Heteroporphyrins, Expanded Porphyrins and Related Macrocycles*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 2.

(5) Fox, S.; Boyle, R. W. *Tetrahedron* **2006**, *62*, 10039–10054.

(6) For recent examples, see: (a) Jiao, C. J.; Huang, K. W.; Guan, Z. P.; Xu, Q. H.; Wu, J. S. *Org. Lett.* **2010**, *12*, 4046–4049. (b) Diev, V. V.; Hanson, K.; Zimmerman, J. D.; Forrest, S. R.; Thompson, M. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5523–5526. (c) Davis, N. K. S.; Thompson, A. L.; Anderson, H. L. *J. Am. Chem. Soc.* **2011**, *133*, 30–31. (d) Akhigbe, J.; Zeller, M.; Brückner, C. *Org. Lett.* **2011**, *13*, 1322–1325.

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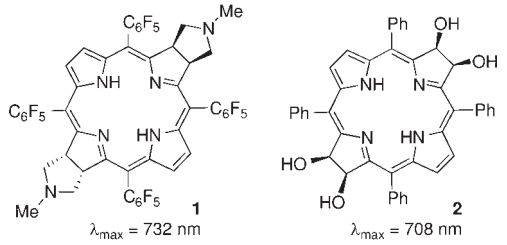
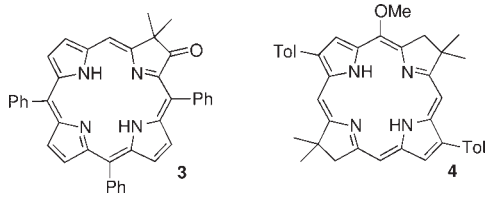
azomethine ylide to *meso*-tetraarylporphyrin to produce a chlorin and bacteriochlorin **1**.[8] Multiple other porphyrin-to-chlorin conversion reactions have become known.[7,9]



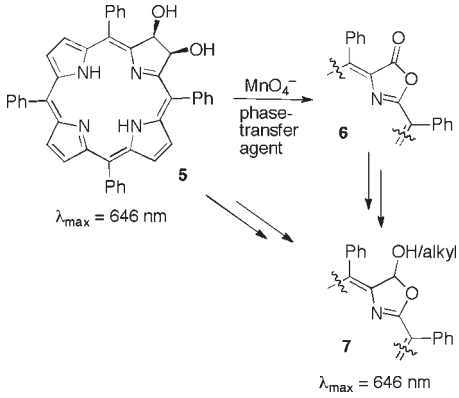
(only one of two stereoisomers shown)

An alternative strategy toward the synthesis of novel *meso*-aryl- and *β*-alkyl-chorins and bacteriochlorins of general structures **3** and **4** is their total synthesis, as impressively demonstrated by Lindsey and co-workers.[10] Their studies also delineated the structural requirements that result in high extinction coefficients in these chromophores.[10]



We established the OsO_4-mediated dihydroxylation of *meso*-tetrarylporphyrins to generate dihydroxychlorin **5** and tetrahydroxybacteriochlorin **2**.[11,12] Functional group manipulation of the diol functionality of chlorin **5** allowed the synthesis of a range of chromophores carrying a nonpyrrolic moiety.[11,13−15] For instance, oxidation of diol

Scheme 1. Literature-Known Syntheses of the *meso*-Tetraphenylporpholactone **6** and *meso*-Tetraphenyloxazolochlorin **7**



5 using MnO_4^- leads to formation of porphyrin-like porpholactone **6** (Scheme 1).[13,16] This chromophore, previously discovered by others,[17] could be reduced to the chlorin-like hydroxy-/alkoxy-modified oxazolochlorin **7**.[18,19] However, hemiacetals of type **7** possess a relatively low chemical stability and *O*-alkylation does not modulate their optical properties.[18,19]

We report here the addition of alkyl-Grignard reagents to the carbonyl group in porpholactone, generating a family of alkyloxazolochlorins that can also be converted to bacteriochlorins. Most significantly, their optical properties can be tuned.

Thus, reaction of the zinc complex of porpholactone, **6Zn**, with a 15-fold molar excess of *i*-PrMgCl in THF at ambient temperature, followed by an acid workup procedure that also removes the Zn(II), converts the green, higher polarity (R_f = 0.38, silica/CH_2Cl_2) starting material in good yield (~80%, 0.72 mmol scale) to the purple lower polarity (R_f = 0.5, silica/CH_2Cl_2) product **8** (Scheme 2) that possesses a chlorin-like UV−vis spectrum (Figure 1; for a detailed discussion of the electronic spectra of the chromophores prepared, see below). The use of the Zn(II) 'protecting group' in **6** prevents any NH deprotonation and subsequent inactivation toward nucleophilic attack.

Reaction of hemiketal **8** with a stoichiometric excess of Et_3SiH under Lewis acid catalysis ($BF_3 \cdot OEt_2$) affects its hydrodehydroxylation to isopropyloxazolochlorin **9** in acceptable yields (76%, 0.15 mmol scale). A diagnostic peak in its ^{1}H NMR is the oxazole proton signal (d, 6.9 ppm, ^3J = 2.3 Hz, 1H) that is coupled to the isopropyl C<u>H</u>Me_2 proton. Unlike hemiacetal **7**, hemiketal **8** and oxazolochlorin **9** are chemically robust with respect to oxidation back to porpholactone **6**, or other undesirable spontaneous oxidations.

Reaction of **6Zn** with excess *i*-PrMgCl in the presence of $BF_3 \cdot OEt_2$ resulted in the formation of bis-adduct **10** as the

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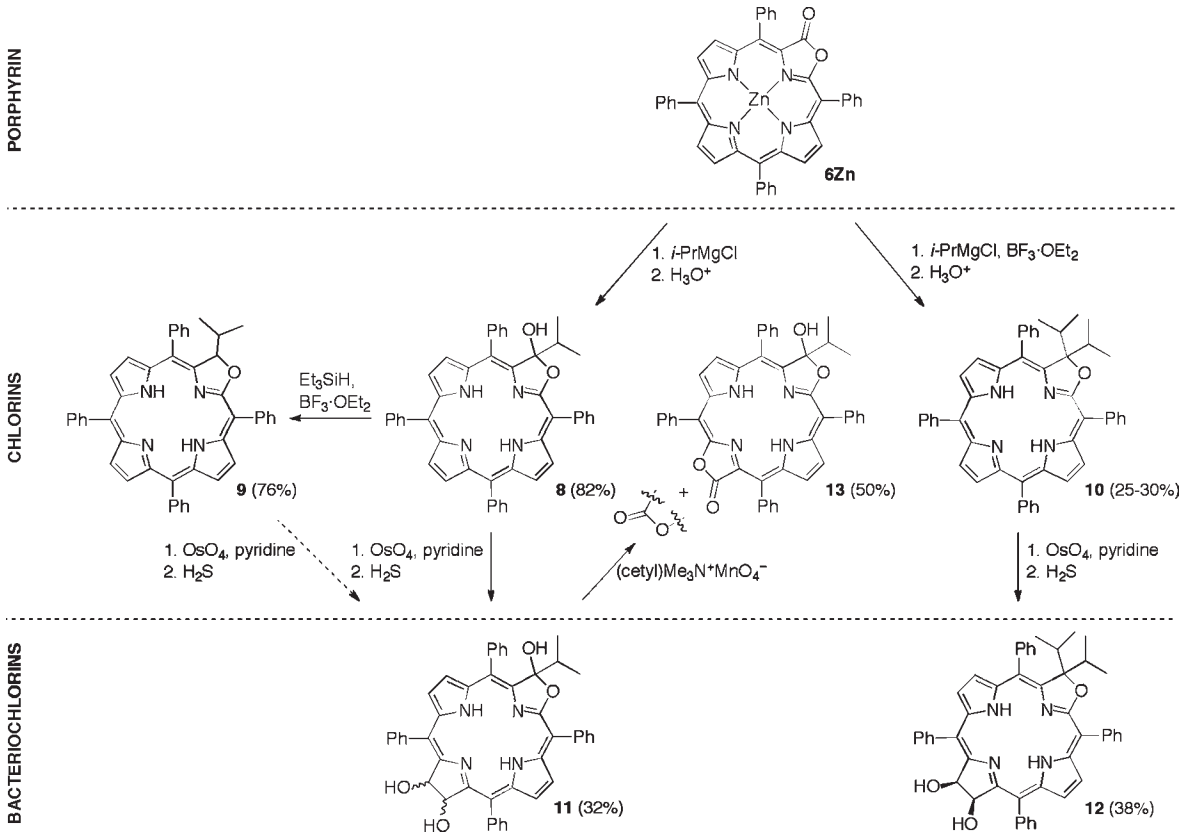
Scheme 2. Synthesis of the *meso*-Tetraphenylalkyl-oxazolochlorins and -bacteriochlorins



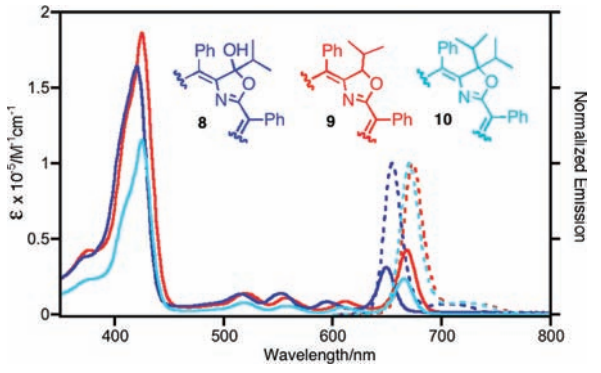


Figure 1. UV−vis (solid traces) spectra and fluorescence emission (broken traces) spectra (CH_2Cl_2) of the novel oxazolochlorins **8** (blue trace), **9** (red trace), and **10** (light blue trace). Florescence spectra were recorded by excitation at the respective λ_{Soret}.

sole low-polarity product in ~30% yield. This unoptimized reaction is accompanied by extensive side reactions. The double alkylation is confirmed by NMR spectroscopy and mass spectrometry. Importantly, bis-isopropyl-substituted oxazolochlorin **10** is, unlike monoadduct **8**, devoid of stereoisomers that complicate further manipulations.

Oxazolochlorins **8**, **9**, and **10** all possess chlorin-type UV−vis absorption and fluorescence emission spectra, but alkylation and dehydroxylation modulate λ_{max} of the spectra significantly (Figure 1). The optical spectra of the parent hemiacetal **7** (not shown) and its alkylated analogue **8** are essentially identical. Removal of the hydroxy group, however, results in an ~20 nm bathochromic shift. We noted the strong influence of the β-hydroxy groups on the porphyrinic chromophore before,[12] but this shift is unusually pronounced. *gem*-Alkylation of the oxazolochlorins results in an ~30% reduction of the extinction coefficients but otherwise only in a minor (> 5 nm) hypochromic shift of λ_{max}.

Because of their absorbance at wavelengths above 700 nm, bacteriochlorin-type chromophores are particularly appealing. An OsO_4-mediated dihydroxylation of oxazolochlorin **8**, followed by a reductive workup, produced triol **11** as an inseparable mixture of two diasteromers (all hydroxy group on the same side of the plane defined by the macrocycle, or *cis*-diol and quaternary alcohol functionalities on opposite sides).[20] Surprisingly, the corresponding oxidation of alkyloxazolochlorin **9** also generates triol **11**, albeit in lower yields. This unintended oxidation of the oxazole moiety defines the limits of the stability of these oxaolochlorins in the presence of strong oxidants.

Triol **11** possesses a typical bacteriochlorin-like optical spectrum (Figure 2). The spectrum is significantly red-shifted

(20) Each diastereomer is chiral; thus they are each expected to exist as a racemic pair.

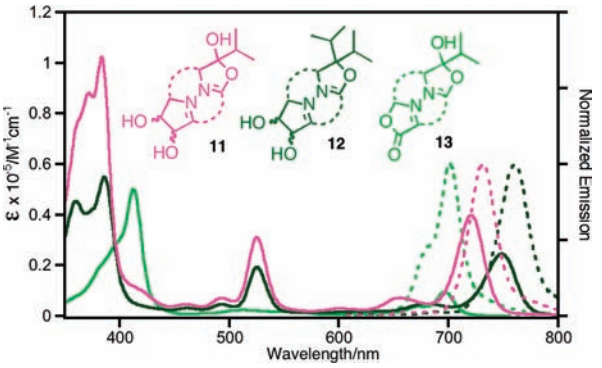


Figure 2. UV−vis (solid traces) spectra and fluorescence emission (broken traces) spectra (CH_2Cl_2) of the novel oxazolobacteriochlorins **11** (purple trace) and **12** (dark green trace), and bisoxazolochlorin **13** (lime-green trace). Florescence spectra were recorded by excitation at the respective λ_{Soret}.

compared to the spectrum of the corresponding tetrahydroxybacteriochlorin isomers.[12] This is unexpected since the optical spectra of parent oxazolochlorin **8** are not shifted compared to those of dihydroxychlorin **5**.[18]

The dihydroxylation reaction is also applicable to *gem*-dialkyloxazolochlorin **10**, generating dihydroxyoxazolobacteriochlorin **12**, with the added benefit that this reaction does not form a diasteromeric mixture (alas, it forms as a racemic mixture of the enantiomers differentiated by the *vic*-diol moiety pointing up or down). Parallel to the observations made for their parent chlorins (**8** and **10**), the bacteriochlorin-type absorbance and emission spectra of **12** are also red-shifted compared to those of triol **11**.

Application of the MnO_4^--mediated diol oxidation reaction to triol **11** converts it to the bisoxazolochlorin **13**, the first porphyrin analogue containing two oxazole moieties. The optical spectra of bisoxazolochlorin **13** are chlorin-like; i.e., the lactone moiety acts spectroscopically akin to a β,β-double bond, albeit the spectra are significantly red-shifted compared to those of the parent chlorin **8**. Thus, the lactone moiety exhibits here a significant influence on the electronic structure of these chromophores.

The fluorescence quantum yields ϕ of the chlorins (**8**, $\phi = 0.35$; **9** $\phi = 0.26$; **10**, $\phi = 0.31$; **13**, $\phi = 0.29$) were relatively high but those of the two most red-shifted bacteriochlorins **11** and **12** were lower ($\phi = 0.14$ and 0.07 respectively). These findings are in line with earlier reports of the ground state photophysical properties of chlorins and bacteriochlorins.[12]

In conclusion, we have shown that alkyl-Grignard additions to porpholactone and functional group manipulations of the resulting oxazolochlorins result in the formation of chemically stable chlorin and bacteriochlorin analogues. Significantly, the substituents of the oxazolochlorins and bacteriochlorins can be chosen to allow a tuning of λ_{max} in the range from 650 to 750 nm, in 20–30 nm increments. This synthetic methodology offers a novel tool for the synthetic manipulation of the porphyrinic chromophore. The conversion of *meso*-tetraphenylporphyrin into oxazolo-chlorins and -bacteriochlorins presents an alternative to the total synthesis of chlorins and bacteriochlorins.[10] Our method does not allow the exquisite control of the β-substituents and resulting electronic properties of the chromophores the total synthesis methods offer. However, only a few steps from readily available starting materials are required to generate intriguing chromophores. Detailed structural and spectroscopic studies and investigations of the biological activity of the alkylozazolochlorins as photosensitizers in photodynamic therapy are ongoing.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.