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# Effect of Substituents in Directing the Formation of Benzochlorins and Isobacteriochlorins in Porphyrin and Chlorin Systems

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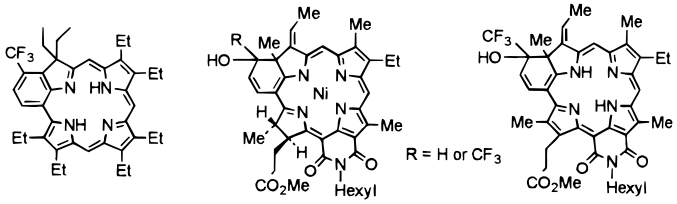
## ABSTRACT




**A first synthesis of free-base fluorinated benzochlorins by acid-catalyzed cyclization of 20-(2-trisiloxy-trifluoromethylvinyl)octaethylporphyrin is achieved. Under similar reaction conditions, the purpurin-18-*N*-hexylimide analogues produced the corresponding fluorinated and nonfluorinated ethylidene-substituted isobacteriochlorins and fluorinated chlorin, respectively. The structure of the porphyrin based fluorinated benzochlorin was also confirmed by X-ray analysis.**

Clinical results of photodynamic therapy (PDT) continue to show promise for the treatment of various solid malignancies.[1] In this therapy, the properties of tumor localization of porphyrin based analogues and photochemical generation of reactive oxygen species are combined with precise delivery of laser-generated light to produce a treatment that offers selective tumorcidal action.[2] So far, Photofrin (a hematoporphyrin derivative), is the only drug that has been approved worldwide for the treatment of a variety of cancers. Besides its wide application, it suffers from certain disadvantages due to its complex chemical nature,[3] and retention of the drug in skin that leads to potential cutaneous photosensitization of extended duration.

The ability to obtain deeper tissue penetration at longer wavelengths of light (>630 nm for Photofrin) and the recent introduction of low-cost reliable solid-state lasers that emit light from 660 to 800 nm has stimulated the development of compounds absorbing in this region of the electromagnetic spectrum. Such photosensitizers mainly include chlorins,

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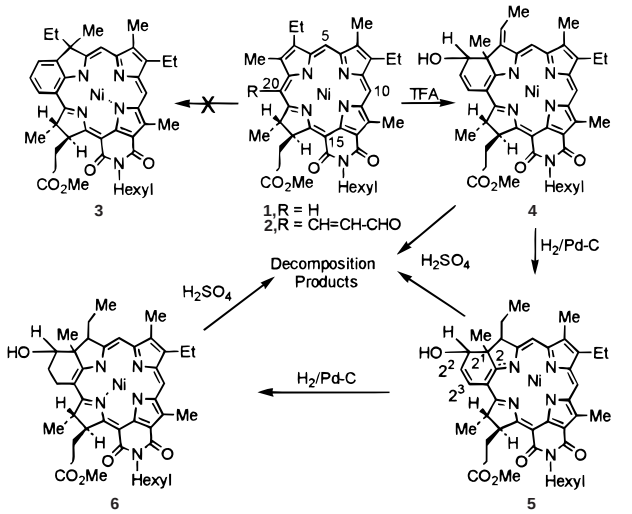
bacteriochlorins, texaphyrins, phthalocyanines, and naphthalocyanines.[2−5]

We have previously shown that free-base benzochlorin **5** can be obtained from the related nickel(II) 20-(2-formylvinyl)-9-deoxypyropheophorbide in good yield.[6] These results were in contrast to those obtained from nickel(II) mesochlorin-$e_6$ (a chlorophyll a derivative),[7] and suggest that the presence of the five-membered isocyclic ring fused at the *meso*-position slightly distorts the macrocycle which possibly helps in demetalation under acidic conditions. Unfortunately, these compounds as free bases or as the related metal analogues did not produce any significant PDT efficacy.

For a number of years, one of the objectives of our laboratory has been to establish the general structural requirements for effective photosensitizers. In our efforts, among certain photosensitizers related to pheophorbide *a*, pyropheophorbide *a*, 9-deoxypyropheophorbide *a*, chlorin $e_6$, purpurin-imides, and benzoporphyrin derivatives (BPD), we have shown that overall lipophilicity of the molecule plays a major role in tumor localization and PDT efficacy.[8,9] The lipophilic characteristics of these molecules can easily be altered by varying the length of the carbon chain of the alkyl substituents. These results prompted us to prepare a series of *N*-alkylated purpurin-imide based benzochlorins and evaluate them for PDT efficacy. For our studies, purpurin-imide **1** was selected as a substrate for the following reasons: (a) the distortion caused by the presence of a fused imide ring system would help in demetalation at the final step of the synthesis, (b) the inherent ability of the molecule to change the overall lipophilicity by varying the length of the *N*-alkyl chain, (c) the electron-withdrawing nature of the imide ring, fused at the *meso*-position of the resulting benzochlorins should exhibit longer wavelength absorptions than those obtained from OEP or pyropheophorbides, thus possibly allowing deeper seated tumors to be treated by PDT.

For the preparation of the desired photosensitizers, purpurin-18 methyl ester, which in turn was obtained from methylpheophorbide *a*, was converted into nickel(II) meso-purpurin-*N*-hexylimide **1** by following methodology developed in our laboratory.[10] Reaction of **1** with the Vilsmeier reagent obtained by treating 3-*N*,*N*′-dimethylaminoacrolein with $POCl_3$ regioselectively introduced a 2-formylvinyl substituent at position 20 of the macrocycle and purpurin **2** was isolated in 42% yield. This compound was then subjected to intramolecular cyclization under various acidic conditions. The best result was obtained when trifluoroacetic acid was used as a cyclizing reagent. Under stronger acidic conditions decomposition products were mainly obtained. The mass spectral analysis of the TFA-induced cyclized product showed a molecular ion peak, *m*/*z* at 774.2, an increase of 18 Da more than expected for a benzochlorin with a fused benzene ring. On the basis of detailed NMR (decoupling and 2D experiments), the structure for the cyclized product was assigned as 3-deethyl-3-ethylideneisobacteriochlorin **4**, obtained as a diastereomeric mixture. The next step was to remove the metal ion before treatment with DDQ to generate the desired benzochlorin **3**. Unfortunately, the isobacteriochlorin **4**, under strong acidic conditions was found to be unstable. These results are in agreement with those obtained by reacting metalated porphyrin based compounds containing the vinyl or olefinic groups with strong acids. Hence, prior to demetalation, isobacteriochlorin **4** was hydrogenated using 10% Pd/C as a catalyst, and as can be seen from Scheme 1, resulted two products, **5** (*m*/*z* 776.1) and **6** (*m*/*z* 778.2), in which either the ethylidene group or both the ethylidene and double bond between $2^2$ and $2^3$ carbon units of the newly formed exocyclic ring were reduced. These results were in contrast to those reported by Dolphin and co-workers[11] in fused nitrogen-containing ring chlorins. Unfortunately, our efforts to demetalate these isobenzochlorins under variable conditions were unsuccessful. In any event, to the best of our knowledge, this is the first example in benzochlorin chemistry for the formation of an isobacteriochlorin with an ethylidene substituent formed via intramolecular cyclization of formylvinyl porphyrin or chlorin systems.

**Scheme 1**




Recently we have shown the utility of Ruppert's reagent for the synthesis of perfluorinated porphyrins, chlorins, and bacteriochlorins.[12] These compounds were prepared so as to determine their utility in investigating the pharmacokinetic profile by $^{19}F$ NMR studies as well as understanding the effects of fluoro analogues on photodynamic therapy. We explored the utility of this reagent for preparing fluorinated benzochlorins. Therefore, in our approach, nickel(II) *meso*-(2-formylvinyl)OEP was reacted with (trifluoromethyl)-trimethylsilane (TMS−$CF_3$) to produce the intermediate

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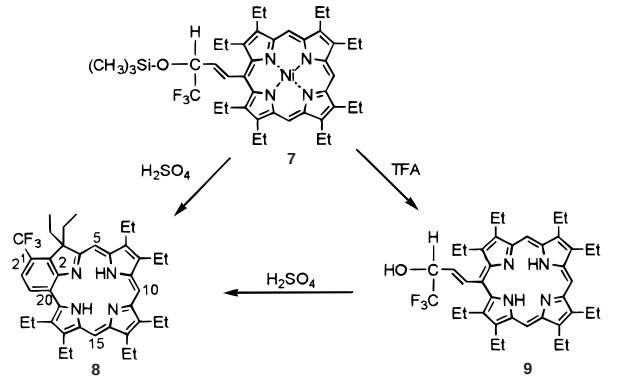
fluorinated trimethylsiloxy porphyrin **7** in 92% yield. To our surprise, cyclization of the intermediate **7** under strong acidic conditions (concentrated $H_2SO_4$, room temperature, 2 h) directly gave free-base benzochlorin **8** in excellent yield (97%), and no sulfonated analogue[5b] as reported for preparing nonfluorinated OEP based benzochlorin was isolated. However, under weaker acidic conditions, porphyrin **7** did not produce the desired free-base or metalated benzochlorin, instead a free-base hydroxyvinyltrifluoromethylporphyrin **9** was obtained in quantitative yield. Further reaction of porphyrin **9** with sulfuric acid produced the desired benzochlorin **8** as a sole product in quantitative yield (Scheme 2). The structure of **8** was confirmed by $^1$HNMR, $^{13}$CNMR, $^{19}$FNMR, mass spectrometry [*m*/*z* calculated 640, found 641 (M + 1)] and X-ray analyses. Figure 1 presents an ORTEP diagram of the trifluoromethyloctaethylbenzochlorin molecule in the crystal. There are two crystallographically independent molecules in the triclinic crystal. In both the molecules the central benzochlorin chromophore is planar. The crystals formed differ in the relative orientation of the trifluoromethyl and the ethyl groups attached to the central benzochlorin molecule.

**Scheme 2**



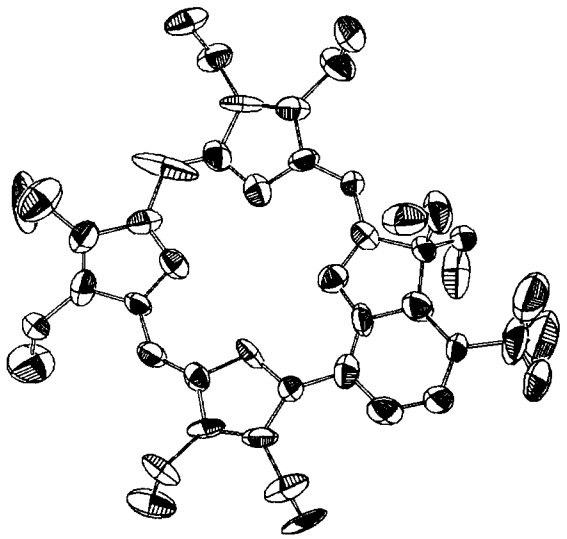
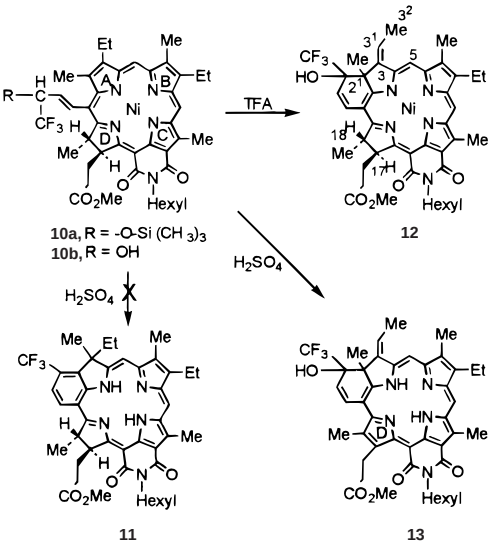



**Figure 1.** Molecular structure of 2$^1$-trifluoromethyloctaethylbenzochlorin.

The efficient methodology developed for the preparation of OEP based free-base fluorinated benzochlorin is very exciting. It suggests that at the intramolecular cyclization step of the synthesis the presence of the metal [Ni(II)] at the core of the macrocycle does not have any effect on the outcome of the reaction product. These results are in contrast to those reported by Arnold et al.,[13] and recently by Dolphin and co-workers for the pyridine fused non-fluorinated OEP based chlorin analogues.[11] These findings prompted us to extend this approach in preparing purpurin-imide based benzochlorins.

For our studies, the trimethylsiloxyfluorinated chlorin **10a** and its related hydroxy analogue **10b** obtained by cleavage of the trimethylsiloxy group were obtained in 56% and 31% yield, respectively, by reacting nickel(II) 20-(2-formylvinyl)-purpurin-imide **2** with TMS−$CF_3$. Reaction of the mixture (**10a** and **10b**) with TFA at room temperature produced fluorinated isobacteriochlorin **12** (62% yield). Several attempts to prepare the corresponding free-base analogue **11** under various acidic conditions were unsuccessful and only unidentified decomposition products were obtained. Replacing TFA with $H_2SO_4$, however, resulted in a mixture. The major component was identified as a free-base chlorin **13** containing an ethylidiene substituent (Scheme 3). The structures of the isobacteriochlorin **12** and chlorin **13** were confirmed by $^1$H,$^{19}$F, 2D NMR (ROESY and COSY) and

**Scheme 3**

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mass spectrometry analyses. The characterization of other products is in progress and will be discussed in our full paper.

As shown in Figure 2, compared to the isobacteriochlorin

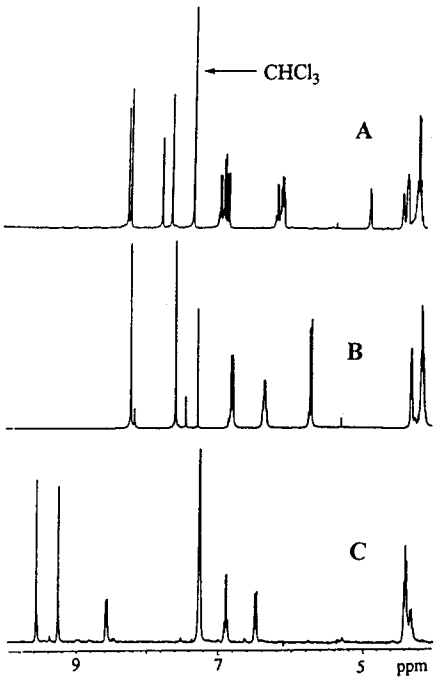


**Figure 2.** $^1$H NMR spectra (Bruker 400 MHz, $CDCl_3$, $\delta$ ppm) of nickel(II) isobacteriochlorin **4** (A), nickel(II) isobacteriochlorin **12** (B), and chlorin **13** (C).

**4**, which consists of a 1:1 mixture of *Z*- and *E*-isomers, the $^1$H NMR spectrum of fluorinated isobacteriochlorin **12** also showed two sets of signals, but in a ratio of 8:1. The $^{19}$F NMR studies also provided similar results. From ROESY experiments, a strong interaction of the methyl protons at $\delta$ 2.30 ppm with the adjacent *meso*-H signal at $\delta$ 7.57 ppm, as well as the interaction of the methyl resonances observed as a singlet at $\delta$ 1.63 ppm with CH resonances (=*CH*—$CH_3$), at $\delta$ 6.35 ppm revealed the presence of a *Z*-isomer. The only structural difference between the nonfluorinated isobacteriochlorin **4** and the related fluorinated analogue **12** is the replacement of the hydrogen at position $2^1$ with a trifluoromethyl substituent. Thus, in isobacteriochlorin **12**, steric hindrance caused by the $CF_3$ group is possibly the only factor directing the formation of the *Z*-isomer. The hydroxy group present at position $2^1$ showed a long-range coupling with H-$2^2$ and H-$2^3$ ($J_{OH,2}{}^2 = 2.5$ Hz, $J_{OH,2}{}^1 = 3.0$ Hz), confirmed by the decoupling experiments (the hydroxy signal at 3.59 ppm, observed as dd for H-$2^2$ and H-$2^3$ on irradiation were simplified as doublets). The presence of two NH signals at −0.38 and −1.50 ppm confirmed the formation of a free-base chlorin. Compared to compound **12**, protons 17 and 18 in chlorin **13** were found to be absent, and the 18-methyl group generally observed at 1.07 ppm showed a significant downfield shift and was observed at 3.19 ppm. α-Methylene protons of the 17-propionic ester side chain (C*H*$_2$CH$_2$CO$_2$CH$_3$) observed at 3.82 and 3.69 ppm (integrating for one proton each) confirmed the oxidation of the reduced pyrrole ring D. Similar to isobacteriochlorin **12** in chlorin **13** the hydroxy group present at position $2^1$ also had long-range coupling with H-$2^2$ and H-$2^3$ ($J_{OH,2}{}^2 = 2.0$ Hz, $J_{OH,2}{}^3 = 2.90$ Hz). On the basis of the ROESY and COSY experiments, the assignments of all protons were achieved. Compared to isobacteriochlorin **4** and **12**, chlorin **13** exhibited a remarkable red shift of 120 nm with long absorption at $\lambda_{max}$ 751 nm. The characteristic Soret band also showed a significant shift from $\lambda_{max}$ 415 nm to $\lambda_{max}$ 563 nm (Figure 3).

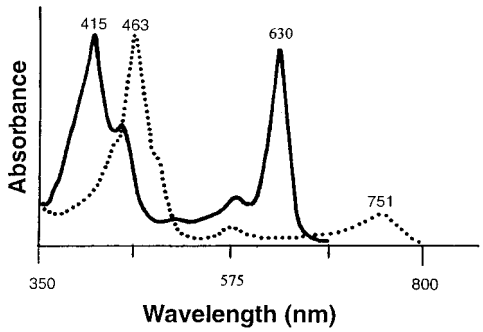


**Figure 3.** Electronic absorption spectra (in $CH_2Cl_2$) of nickel(II) isobacteriochlorin **12** (—) and chlorin **13** (- - -).

In conclusion, we have reported an effective and efficient synthesis of porphyrin based fluorinated benzochlorins. For QSAR and $^{19}$FNMR studies, this methodology provides access to a novel series of long wavelength absorbing fluorinated and nonfluorinated benzochlorins with variable lipophilicity. Our work also demonstrates that the formation of the cyclized products resulting from an acid-catalyzed cyclization of the *meso*-substituted 2-formylvinyl analogue entirely depends on the nature of the substituents present at the peripheral positions. Our efforts to improve the yield of chlorins containing imide ring systems, selectivity of this reaction, and the ability to extend this methodology in other porphyrin based compounds will be reported in due course.

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**Supporting Information Available:** The full characterization of new compounds by NMR, mass, and X-ray analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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