ORGANIC LETTERS

2008
Vol. 10, No. 10
1931−1934

# Swallowtail Bacteriochlorins. Lipophilic Absorbers for the Near-Infrared

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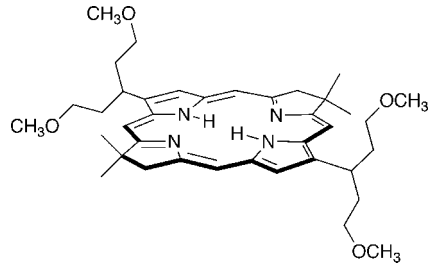
**Received February 26, 2008**

## ABSTRACT




**Bacteriochlorins absorb strongly in the near-infrared spectral region and hence are ideally suited for diverse photomedical applications, yet naturally occurring bacteriochlorins have limited stability and synthetic malleability. A de novo route has been exploited to prepare synthetic bacteriochlorins that bear a geminal dimethyl group in each pyrroline ring for stability and a symmetrically branched 1,5-dimethoxypentyl group attached to each pyrrole ring for solubility in lipophilic media.**

The ability to tailor photoactive molecules that absorb near-infrared (NIR) light is expected to open a number of diagnostic and therapeutic opportunities in photomedicine, namely, optical imaging[1] and photodynamic therapy (PDT),[2] respectively.[3] The benefit of NIR light, particularly in the 700−900 nm region, stems from the deep penetration of soft tissue afforded by light of this frequency.[4] Bacteriochlorophylls have been regarded as ideal for PDT given their strong absorption in this spectral region; indeed, the palladium chelate of a derivative of bacteriochlorophyll *a* (Tookad, or WST09) has been used in a variety of studies (Figure 1).[5] A taurine conjugate of a bacteriochlorophyll *a* derivative also has been prepared upon opening of the isocyclic ring.[6] However, more extensive modifications of naturally occurring bacteriochlorophylls have proven difficult given their susceptibility toward adventitious dehydrogenation (giving the chlorin or porphyrin)[7] and the nearly full complement of substituents about the perimeter of the macrocycle.[8] We recently developed a de novo synthesis of bacteriochlorins

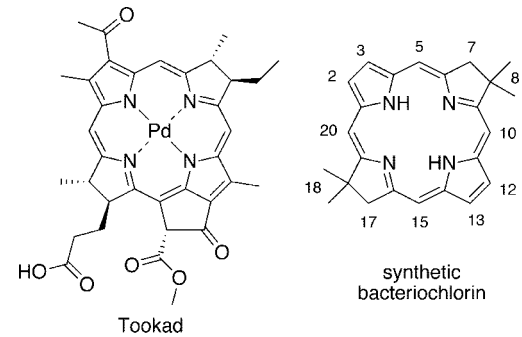



**Figure 1.** Naturally derived versus synthetic bacteriochlorins.

(1) Licha, K. *Top. Curr. Chem.* **2002**, *222*, 1–29.
(2) Juzeniene, A.; Peng, Q.; Moan, J. *Photochem. Photobiol. Sci.* **2007**, *6*, 1234–1245.
(3) Taniguchi, M.; Cramer, D. L.; Bhise, A. D.; Kee, H. L.; Bocian, D. F.; Holten, D.; Lindsey, J. S. *New J. Chem.* Published online. DOI: 10.1039/b717803d.
(4) Dawson, J. B.; Barker, D. J.; Ellis, D. J.; Grassam, E.; Cotterill, J. A.; Fisher, G. W.; Feather, J. W. *Phys. Med. Biol.* **1980**, *25*, 695–709.
(5) (a) Chen, Q.; Huang, Z.; Luck, D.; Beckers, J.; Brún, P.-H.; Wilson, B. C.; Scherz, A.; Salomon, Y.; Hetzel, F. W. *Photochem. Photobiol.* **2002**, *76*, 438–445. (b) Weersink, R. A.; Forbes, J.; Bisland, S.; Trachtenberg, J.; Elhilali, M.; Brún, P. H.; Wilson, B. C. *Photochem. Photobiol.* **2005**, *81*, 106–113.

10.1021/ol800436u CCC: $40.75 
**Published on Web 04/18/2008**

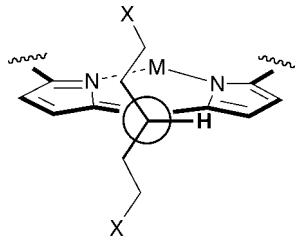



**Figure 2.** Newman projection showing the swallowtail alkyl chains above and below the plane of a tetrapyrrole macrocycle.

that are stable by virtue of the presence of a geminal dimethyl group in each reduced ring.[9] The bacteriochlorins prepared previously also contained *p*-tolyl groups at the 2- and 12-positions,[9,10] or bromo groups at the 3- and 13-positions.[3] The latter provided a versatile scaffold for the introduction of auxochromes (e.g., acetyl, ethynyl, vinyl) at the 3- and 13-positions via a variety of Pd-mediated coupling reactions.

For applications in photomedicine, the ability to tailor the bacteriochlorin with groups ranging in polarity from lipophilic to hydrophilic is desirable for selectively targeting biological organisms, organelles, or molecules. For lipophilic architectures, we were drawn to the use of branched alkyl (i.e., "swallowtail")[11] groups attached directly to the bacteriochlorin macrocycle. Swallowtail groups adopt a conformation wherein alkyl moieties project above and below the face of the macrocycle (Figure 2), thereby suppressing aggregation of the macrocycles. The suppression of aggregation is important for retaining photochemical activity (i.e., fluorescence for optical imaging, intersystem crossing, and energy transfer to oxygen for PDT). Swallowtail groups have been employed with porphyrins,[12–16] chlorins,[17] and multiporphyrin arrays.[18] The swallowtail groups include all-hydrocarbon units (pent-3-yl,[12] tridec-7-yl[13,18]) that afford increased solubility in organic media, and polar-terminated analogues (e.g., 1,5-diphosphonopent-3-yl) that afford solubility in aqueous media.[14–17] In each case, the swallowtail substituent was located at a meso position. Here we describe the synthesis of bacteriochlorins bearing lipophilic swallowtail motifs at the 2,12- or 3,13-positions.[19] Such bacteriochlorins are of interest for PDT studies, the results of which will be described elsewhere.

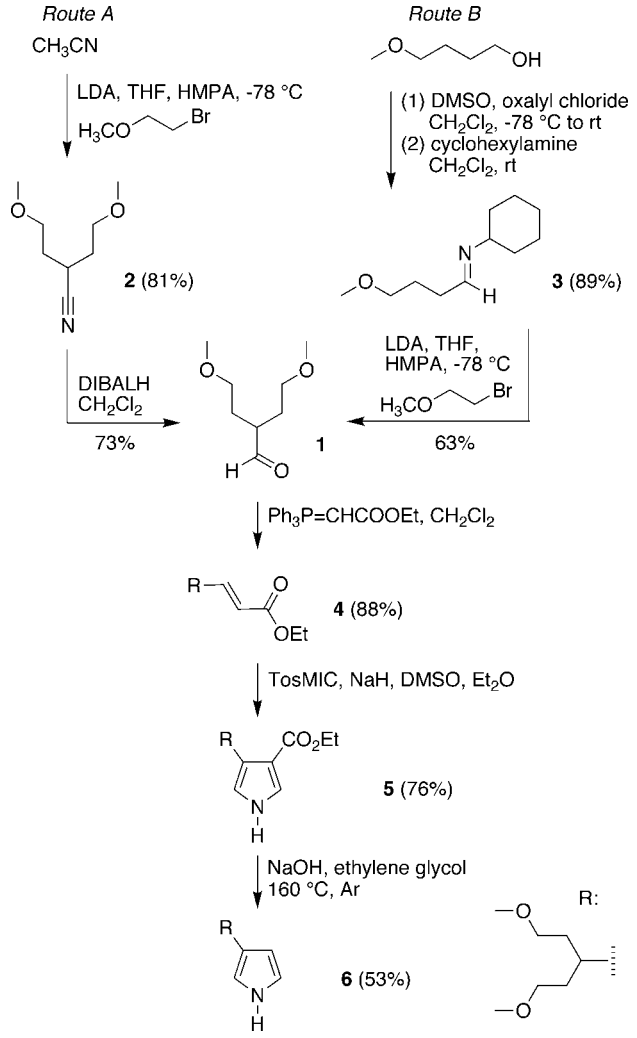
The de novo bacteriochlorin synthesis relies on a dihydrodipyrrin that can undergo self-condensation by virtue of a free α-pyrrole position and an acetal at the α-position of the pyrroline ring.[3,9,20] Introduction of *β*-pyrrole substituents can be achieved via precursors to the pyrrole or by bromination of the pyrrole employed to prepare the dihydrodipyrrin. The route to the swallowtail-substituted dihydrodipyrrin is modeled on the reported synthesis of *p*-tolyl-substituted dihydrodipyrrins, which accordingly required the synthesis of a swallowtail pyrrole.

A swallowtail-substituted pyrrole was prepared via the van Leusen method,[21] which employed swallowtail aldehyde **1** as a precursor. Two aldehydes, bearing methoxy or benzyloxy termini were investigated. The benzyl ether proved unstable to the final Ti(III)-mediated reductive cyclization (Supporting Information). Methyl ether-substituted swallowtail aldehyde **1** was synthesized from commercially available bromoethyl methyl ether via one of the two routes shown in Scheme 1. Aldehyde **1** is a known compound,[22] but the only reported procedure requires five steps and a 20-fold excess of the costly bromoethyl methyl ether. Route A follows reported procedures for the synthesis of symmetrically branched aldehydes[23] and entails deprotonation of acetonitrile with LDA followed by dialkylation with bromoethyl methyl ether. The product after column chromatography contained small amounts of monoalkylated and trialkylated nitriles; reduction of this material with DIBALH followed by chromatography afforded **1** in pure form. Route B employs commercially available 4-methoxybutanol as the starting material. Swern oxidation[24] followed by treatment of the crude product with cyclohexylamine and subsequent Kugelrohr distillation gave imine **3** in 89% yield. The procedure to give **3** was readily carried out at >10 g scale. Deprotonation of the imine with LDA followed by alkylation with bromoethyl methyl ether yielded **1** in 63% yield from **3**, and 56% overall yield from 4-methoxybutanol. Route B was superior owing to cleanliness, avoidance of aluminum salts, and low cost of the starting materials.

Reaction of **1** with (carbethoxymethylene)triphenylphosphorane yielded unsaturated ester **4** in excellent yield. Van Leusen reaction of **4** with TosMIC in $Et_2O$/DMSO (2:1) in the presence of NaH furnished swallowtail carbethoxy-

(6) Brandis, A.; Mazor, O.; Neumark, E.; Rosenbach-Belkin, V.; Salomon, Y.; Scherz, A. *Photochem. Photobiol.* **2005**, *81*, 983–993.
(7) (a) Limantara, L.; Koehler, P.; Wilhelm, B.; Porra, R. J.; Scheer, H. *Photochem. Photobiol.* **2006**, *82*, 770–780. (b) Vakrat-Haglili, Y.; Weiner, L.; Brumfeld, V.; Brandis, A.; Salomon, Y.; McIlroy, B.; Wilson, B. C.; Pawlak, A.; Rozanowska, M.; Sarna, T.; Scherz, A. *J. Am. Chem. Soc.* **2005**, *127*, 6487–6497.
(8) Kozyrev, A. N.; Chen, Y.; Goswami, L. N.; Tabaczynski, W. A.; Pandey, R. K. *J. Org. Chem.* **2006**, *71*, 1949–1960.
(9) Kim, H.-J. Lindsey, J. S. *J. Org. Chem.* **2005**, *70*, 5475–5486.
(10) Fan, D.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2007**, *72*, 5350–5357.
(11) (a) Demmig, S.; Langhals, H. *Chem. Ber.* **1988**, *121*, 225–230. (b) Langhals, H.; Demmig, S.; Potrawa, T. *J. Prakt. Chem.* **1991**, *333*, 733–748.
(12) Wiehe, A.; Stollberg, H.; Runge, S.; Paul, A.; Senge, M. O.; Röder, B. *J. Porphyrins Phthalocyanines* **2001**, *5*, 853–860.
(13) Thamyongkit, P.; Speckbacher, M.; Diers, J. R.; Kee, H. L.; Kirmaier, C.; Holten, D.; Bocian, D. F.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 3700–3710.
(14) Borbas, K. E.; Mroz, P.; Hamblin, M. R.; Lindsey, J. S. *Bioconjugate Chem.* **2006**, *17*, 638–653.
(15) Yao, Z.; Borbas, K. E.; Lindsey, J. S. *New J. Chem.* **2008**, *32*, 436–451.
(16) Borbas, K. E.; Kee, H. L.; Holten, D.; Lindsey, J. S. *Org. Biomol. Chem.* **2008**, *6*, 187–194.
(17) Borbas, K. E.; Chandrashaker, V.; Muthiah, C.; Kee, H. L.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **2008**, *73*, 3145– 3158.
(18) Thamyongkit, P.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 5796–5799.
(19) Preliminary studies concerning the 2,12-disubstituted bacteriochlorins have been described in a patent application: Lindsey, J. S.; Laha, J. K.; Muthiah, C.; Borbas, K. E. WO 2007/064842 A2.
(20) Kim, H.-J.; Dogutan, D. K.; Ptaszek, M.; Lindsey, J. S. *Tetrahedron* **2007**, *63*, 37–55.
(21) van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett.* **1972**, *13*, 5337–5340.
(22) Cheeseman, E. N. *Org. Prep. Proc. Int.* **1990**, *22*, 519–521.
(23) Vader, J.; Sengers, H.; de Groot, A. *Tetrahedron* **1989**, *45*, 2131–2142.
(24) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

**Scheme 1.** Swallowtail Pyrrole Synthesis

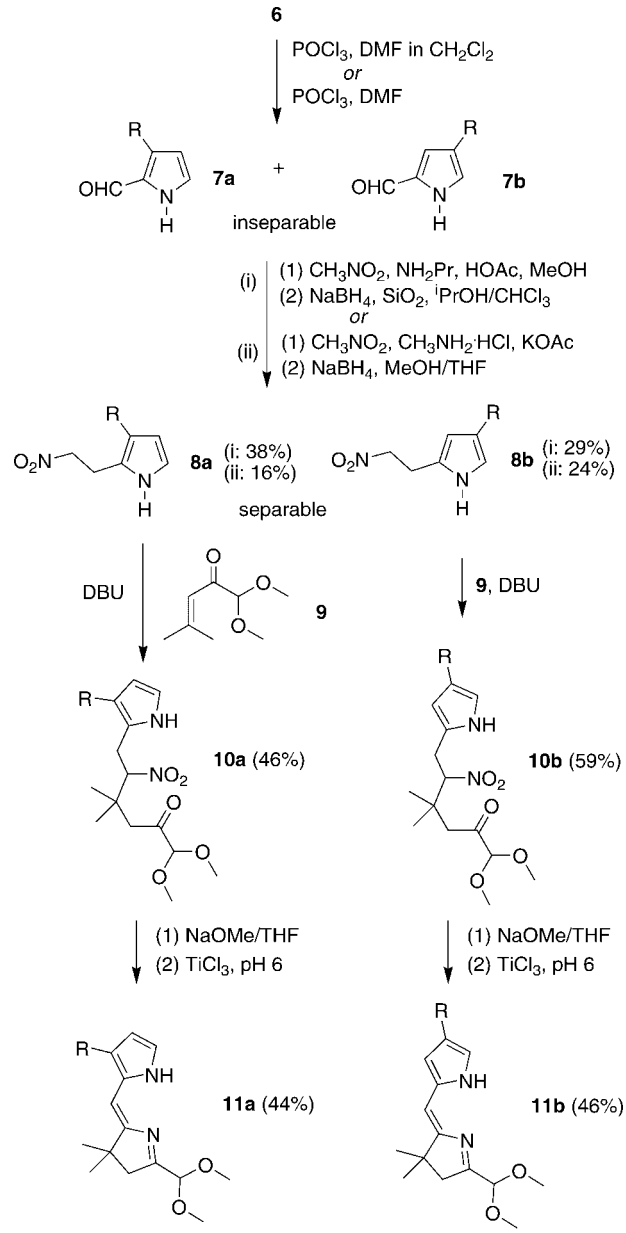



pyrrole **5**. Saponification and decarboxylation was achieved with NaOH in hot ethylene glycol, affording the swallowtail-pyrrole **6**.

Vilsmeier formylation of **6** in $CH_2Cl_2$ yielded two regioisomeric formylpyrroles (2:1 by $^1H$ NMR analysis of the crude product), which were not separable by column chromatography. Carrying out the reaction in DMF reversed the regioselectivity (0.65:1 by $^1H$ NMR analysis of the crude product). Unlike the previous 2-formyl-3-*p*-tolylpyrrole,[9] **7a/b** is an oil and thus not purifiable through crystallization. The mixture **7a/b** was carried forward (Scheme 2).

Two methods were explored for the synthesis of nitroethylpyrroles **8a** and **8b**: (i) the reaction of **7a/b** in a methanolic solution of nitromethane containing propylamine and acetic acid, followed by $NaBH_4$ in $^i$PrOH/$CHCl_3$/silica gel,[10] gave readily separable isomeric nitroethylpyrroles **8a** and **8b** upon silica column chromatography in 38% and 29% yield, respectively (67% overall); (ii) the reaction of **7a/b** in neat nitromethane containing methylamine hydrochloride and potassium acetate, followed by reduction with $NaBH_4$ in MeOH/THF,[9] gave **8a** and **8b** in 16% and 24% yield, respectively (40% overall). Despite the higher yields obtained

**Scheme 2.** Swallowtail Dihydrodipyrrin Syntheses[a]




[a] R = same as in Scheme 1.

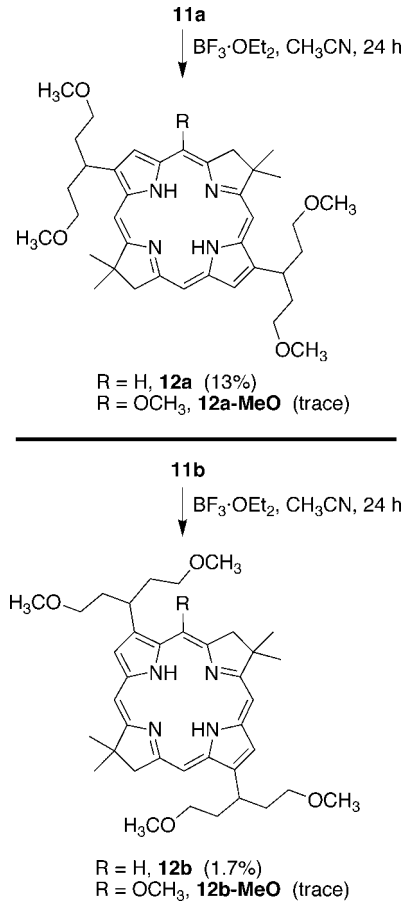
by the first method, the second method is preferred because of its operational simplicity and better reproducibility. The structures of the pure compounds were confirmed by NMR experiments. The identity of regioisomer **8a** was confirmed by $^1H$-$^1H$ gCOSY, $^1H$-$^{13}C$ HSQC, and $^1H$-$^{13}C$ gHMBC experiments, as well as by $^1H$ NMR spectroscopy following deuterium exchange of the pyrrolic NH proton. The sequence **4** → **8** could be performed with only simple aqueous−organic workup of each reaction, without the need to obtain the intermediates in an analytically pure form.

Treatment of **8a** or **8b** with the dimethyl acetal derivative of mesityl oxide[9,25] (**9**, 3 equiv) in the presence of DBU (5 equiv) under solventless conditions[20] yielded hexanone **10a** or **10b** as a yellow oil. Ti(III)-mediated reductive cyclization

of the nitronate anion obtained from **10a** or **10b** upon treatment with NaOMe yielded swallowtail dihydrodipyrrin **11a** or **11b** in 44% or 46% yield, respectively. Yields throughout were comparable to those reported for *p*-tolyl substituted analogues.

The synthesis of swallowtail bacteriochlorins was examined with both **11a** and **11b** (Scheme 3). Employing the

**Scheme 3.** Swallowtail Bacteriochlorin Syntheses




conditions developed for the synthesis of 2,12-di-*p*-tolylbacteriochlorins,[9] self-condensation of dihydrodipyrrin **11a** in $CH_3CN$ in the presence of $BF_3{\cdot}OEt_2$ yielded two bacteriochlorins: **12a** (major) and the 5-methoxy-substituted analogue **12a-MeO** (trace). Bacteriochlorin **12a** was isolated in 13% yield, while **12a-MeO** was observed upon LD-MS analysis of the reaction mixture (*m*/*z* 660.7).

The self-condensation of **11b** proceeded to afford bacteriochlorin **12b** as the major product, albeit in significantly

(25) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *J. Org. Chem.* **1990**, *55*, 4523–4528.

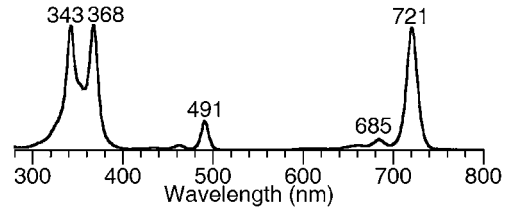



**Figure 3.** Absorption spectrum of swallowtail bacteriochlorin **12a** in $CH_2Cl_2$ at room temperature.

lower yields than that of **12a**, likely because of steric hindrance of the swallowtail substituent on the reactive α-pyrrolic position. The 5-methoxy-substituted bacteriochlorin **MeO-12b** was observed upon LD-MS analysis of the reaction mixture. The product distributions (**12a**/**12a-MeO** and **12b**/**12b-MeO**) were comparable to that reported for the *p*-tolylbacteriochlorins, but the isolated yields were lower. The lower yield may be due to diminished stability of the dihydrodipyrrins **11a** and **11b** under the reaction conditions versus that of the *p*-tolyl-substituted dihydrodipyrrin. Carrying out the condensation of **11b** with lower acid concentration (12.7 mM, 70% of that reported as optimal for the *p*-tolylbacteriochlorin) or longer duration (43 h vs 24 h) did not increase the yield.

The 2,12- and 3,13-substituted bacteriochlorins **12a** and **12b** have absorption spectra that are almost identical to each other ($\lambda_{max}$, ratio of B and Q bands). The spectrum of **12a** is shown in Figure 3. Both **12a** and **12b** display strong absorption bands in the UV (343 and 368 nm), weak bands at 491 and 685 nm, and a strong band at 721 nm (**12a**) or 720 nm (**12b**). The ratio of the intensities of the 368 and 721 (or 720) nm bands was 1.05 for **12a**, and 1.11 for **12b**.

The solubility of bacteriochlorin **12a** was examined in solvents at room temperature without heating and without sonication. The solubility decreased in the following order: $CHCl_3 \approx CH_2Cl_2 \approx$ tetrahydrofuran (BHT free) ≈ *N*,*N*-dimethylacetamide ≈ *N*,*N*-dimethylformamide > acetone > acetonitrile > dimethyl sulfoxide > ethanol. The good solubility in a range of organic solvents, including several that are miscible with water, augurs well for use in optical imaging, PDT, and other biomedical studies.

**Acknowledgment.** This work was supported by the NIH (GM36238).

**Supporting Information Available:** Experimental section and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800436U