JOC Article

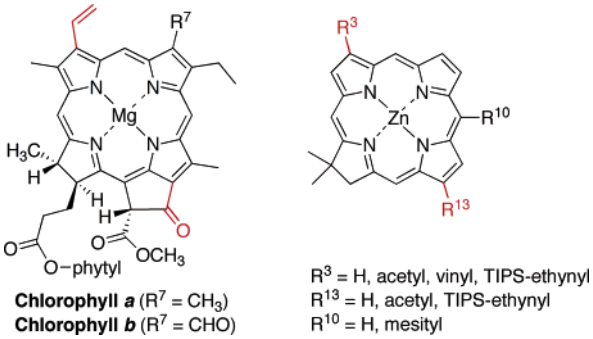
Synthetic Chlorins Bearing Auxochromes at the 3- and 13-Positions

Joydev K. Laha, Chinnasamy Muthiah, Masahiko Taniguchi, Brian E. McDowell, Marcin Ptaszek, and Jonathan S. Lindsey*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

jlindsey@ncsu.edu

Received January 31, 2006



Chlorophyll *a* ($R^7 = CH_3$)
Chlorophyll *b* ($R^7 = CHO$)

Synthetic chlorins bearing diverse auxochromes at the 3- and 13-positions of the macrocycle are valuable targets given their resemblance to chlorophylls *a* and *b*, which bear 3-vinyl and 13-keto groups. A de novo route has been exploited to construct nine zinc chlorins bearing substituents at the 3- and 13-positions and two benchmark zinc chlorins lacking such substituents. The chlorins are sterically uncongested and bear (1) a geminal dimethyl group in the reduced pyrroline ring, (2) a H, an acetyl, a triisopropylsilylethynyl (TIPS-ethynyl), or a vinyl at the 3-position, (3) a H, an acetyl, or TIPS-ethynyl at the 13-position, and (4) a H or a mesityl at the 10-position. The synthesis of the 13-substituted chlorins relied on *p*-TsOH·H_2O-catalyzed condensation of an 8,9-dibromo-1-formyldipyrromethane (eastern half) and 2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin (western half), followed by metal-mediated oxidative cyclization, affording the 13-bromochlorin. Similar use of a bromo- or TIPS-ethynyl-substituted western half provided access to 3-substituted chlorins. A 3-bromo, 13-bromo, or 3,13-dibromochlorin was further transformed by Pd-coupling to introduce the vinyl group (via tributylvinyltin), TIPS-ethynyl group (via TIPS-acetylene), or acetyl group (via tributyl(1-ethoxyvinyl)tin, followed by acidic hydrolysis). In the 10-mesityl-substituted zinc chlorins, the series of substituents, 3-vinyl, 13-TIPS-ethynyl, 3-TIPS-ethynyl, 13-acetyl, 3,13-bis(TIPS-ethynyl), 3-TIPS-ethynyl-13-acetyl, or 3,13-diacetyl, progressively causes (1) a redshift in the absorption maximum of the B band (405−436 nm) and the Q_y band (606−662 nm), (2) a relative increase in the intensity of the Q_y band ($I_B/I_Q = 4.2-1.5$), and (3) an increase in the fluorescence quantum yield Φ_f (0.059−0.29). The zinc chlorins bearing a 3-TIPS-ethynyl-13-acetyl or a 3,13-diacetyl group exhibit a number of spectral properties resembling those of chlorophyll *a* or its zinc analogue. Taken together, this study provides access to finely tuned chlorins for spectroscopic studies and diverse applications.

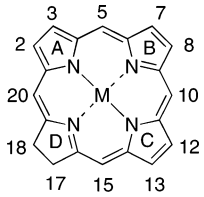
Introduction

The fundamental chromophore of the chlorophylls is a chlorin, which differs from a porphyrin in having one pyrrole ring reduced at the β-positions. Reduction of a porphyrin to give the chlorin enhances the intensity of the long-wavelength absorption (Q_y) band.[1] However, mere reduction does not account for the intensity or redshifted position of the long-wavelength transition exhibited by naturally occurring chlorophylls. Indeed, chlorophyll *a* exhibits a strong Q_y band at 661 nm ($\epsilon_{Q_y} = 78\,200$ $M^{-1}cm^{-1}$),[2] whereas a benchmark compound that contains only the core magnesium chlorin chromophore (**MgChlorin**, Chart 1) exhibits a Q_y band at 610 nm ($\epsilon_{Q_y} = 56\,000$ $M^{-1}cm^{-1}$).[3]

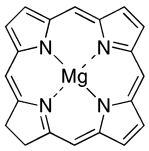
(1) Gouterman, M. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. III, pp 1−165.

10.1021/jo060208o CCC: $33.50
Published on Web 04/26/2006

CHART 1



chlorin nomenclature



MgChlorin

Naturally occurring chlorins typically contain a full complement of substituents at the β-pyrrolic positions of the macrocycle, including alkyl groups (2-, 8-, and 12-positions) and auxochromic groups (3-, 7-, and 13-positions). Chlorophyll *a* and *b* each bear a 3-vinyl group and an isocyclic ring spanning the 13−15 positions.[4] The isocyclic ring contains a 13-keto group, which is conjugated with the π-system of the macrocycle.

Studies to probe the effects of substituents on chlorin spectral properties have generally employed derivatives of the naturally occurring macrocycles. Key findings are that the 3-vinyl substituent redshifts the Q_y transition by ∼12−14 nm (versus that of a 3-ethyl group)[5,6] and the annulated 13-keto substituent imparts a redshift of ∼20−30 nm.[5,7,8] The 3-vinyl group does not appear to cause any change in the intensity of the transition, whereas the 13-keto substituent has a significant hyperchromic effect.[5] The introduction of conjugative substituents on the 3-vinyl group has resulted in a redshift of up to 60 nm.[9] Thus, the presence of auxochromes at the 3- and 13-positions appears essential for realizing strong absorption in the far-red region with chlorin chromophores.

A more thorough examination of substituent effects on chlorin spectral properties requires the ability to prepare stable, sterically uncongested chlorin macrocycles with a defined number and pattern of substituents at the β-pyrrole and meso positions. There are three distinct routes to chlorins, including (1) derivatization of naturally occurring chlorins, (2) reduction of synthetic porphyrins, and (3) de novo syntheses.[10] The derivatization of chlorophylls is constrained by the nearly full complement of substituents present in the naturally occurring macrocycles. The reduction of synthetic chlorins suffers from limited control over the pattern of substituents with respect to the ring that undergoes reduction, and the resulting chlorins often slowly revert via dehydrogenation to the corresponding porphyrin. The de novo routes to chlorins are few in number and have been developed primarily as exercises in natural products synthesis rather than for fundamental studies of chlorin physical properties.

Over the past decade, we have been developing rational de novo routes for preparing chlorins, wherein each chlorin bears a geminal dimethyl group in the reduced pyrroline ring.[11−15] The geminal dimethyl group blocks adventitious dehydrogenation to give the porphyrin, thereby affording a more stable chlorin (i.e., dihydroporphyrin) chromophore. The general synthetic route has entailed the reaction of a 9-bromodipyrromethane-1-carbinol (eastern half) and a 2,3-dihydro-1,3,3-trimethyldipyrrin[11] or 2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin[13] (western half). The use of substituted analogues of the eastern and western halves provided access to chlorins bearing substituents at the 2-, 5-, 8-, 10-, 12-, and 18-positions (Chart 1).[11−13] Subsequent oxidation afforded the 17-oxochlorins.[14] Halogenation of the chlorin or oxochlorin at the 15- or 20-position followed by Pd-mediated coupling reactions enabled the introduction of aryl or ethynyl substituents at these meso sites.[15] Thus, access has been achieved for all sites with the exception of positions 3, 7, and 13. It is ironic that these latter three sites are perhaps the most important for tuning the spectral properties of the chlorins.

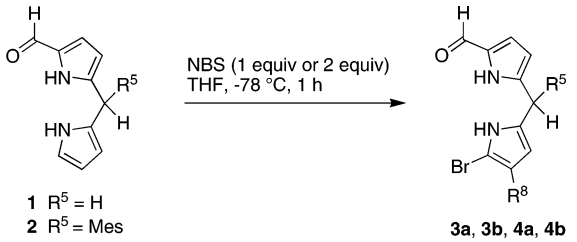
In this paper, we report the synthesis of nine zinc chlorins bearing a variety of potential auxochromic groups at the 3-position (acetyl, TIPS-ethynyl, vinyl) and 13-position (acetyl, TIPS-ethynyl). The chlorins bear a minimum of other substituents so that the effects of the 3- and 13-groups can be clearly delineated. Taken together, this work provides the foundation for tuning the spectral properties of chlorins in a systematic manner and establishes methodology for gaining access to chlorins of potential value in applications ranging from artificial photosynthesis to photomedicine.

Results and Discussion

I. Synthesis. Each of the target chlorins herein lacks a substituent at the 5-position to avoid any possible steric interaction with substituents at the 3-position. Our prior synthetic route to chlorins employed a 9-bromodipyrromethane-1-carbinol as the eastern half, where the substituent at the 1-position of the eastern half becomes the 5-substituent in the chlorin. We recently developed new methodology for chlorin synthesis that employs a 1-formyl-9-bromodipyrromethane and a 2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin, whereupon the chlorin lacks a 5-substituent. The synthesis development and studies of the fundamental properties of stable unsubstituted chlorins will be described elsewhere. The syntheses described herein rely on

(2) Strain, H. H.; Svec, W. A. In *The Chlorophylls*; Vernon, L. P., Seely, G. R., Eds.; Academic Press: New York, 1966; pp 21−66.
(3) Eisner, U.; Linstead, R. P. *J. Chem. Soc.* **1955**, 3742−3749.
(4) Scheer, H. In *Chlorophylls*; Scheer, H., Ed.; CRC Press: Boca Raton, FL, 1991; pp 3−30.
(5) Boldt, N. J.; Donohoe, R. J.; Birge, R. R.; Bocian, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 2284−2298.
(6) Smith, K. M.; Goff, D. A.; Simpson, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 4946−4954.
(7) Tamiaki, H.; Miyatake, T.; Tanikaga, R. *Tetrahedron Lett.* **1997**, *38*, 267−270.
(8) Abraham, R. J.; Rowan, A. E.; Smith, N. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1047−1059.
(9) Tamiaki, H.; Kouroba, M. *Tetrahedron* **1997**, *53*, 10677−10688.
(10) (a) Pavlov, V. Y.; Ponomarev, G. V. *Chem. Heterocycl. Compd.* **2004**, *40*, 393−425. (b) Montforts, F.-P.; Glasenapp-Breiling, M. *Fortschr. Chem. Org. Naturst.* **2002**, *84*, 1−51. (c) Pandey, R. K.; Zheng, G. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 6, pp 157−230. (d) Vicente, M. G. H. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 1, pp 149−199. (e) Jaquinod, L. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 1, pp 201−237. (f) Montforts, F.-P.; Glasenapp-Breiling, M. *Prog. Heterocycl. Chem.* **1998**, *10*, 1−24. (g) Montforts, F.-P.; Gerlach, B.; Höper, F. *Chem. Rev.* **1994**, *94*, 327−347. (h) Smith, K. M. In *Chlorophylls*; Scheer, H., Ed.; CRC Press: Boca Raton, FL, 1991; pp 115−143. (i) Hynninen, P. H. In *Chlorophylls*; Scheer, H., Ed.; CRC Press: Boca Raton, FL, 1991; pp 145−209.
(11) Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160−3172.
(12) Balasubramanian, T.; Strachan, J. P.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7919−7929.
(13) Taniguchi, M.; Ra, D.; Mo, G.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2001**, *66*, 7342−7354.
(14) Taniguchi, M.; Kim, H.-J.; Ra, D.; Schwartz, J. K.; Kirmaier, C.; Hindin, E.; Diers, J. R.; Prathapan, S.; Bocian, D. F.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **2002**, *67*, 7329−7342.
(15) Taniguchi, M.; Kim, M. N.; Ra, D.; Lindsey, J. S. *J. Org. Chem.* **2005**, *70*, 275−285.

TABLE 1. Bromination of 1-Formyldipyrromethanes



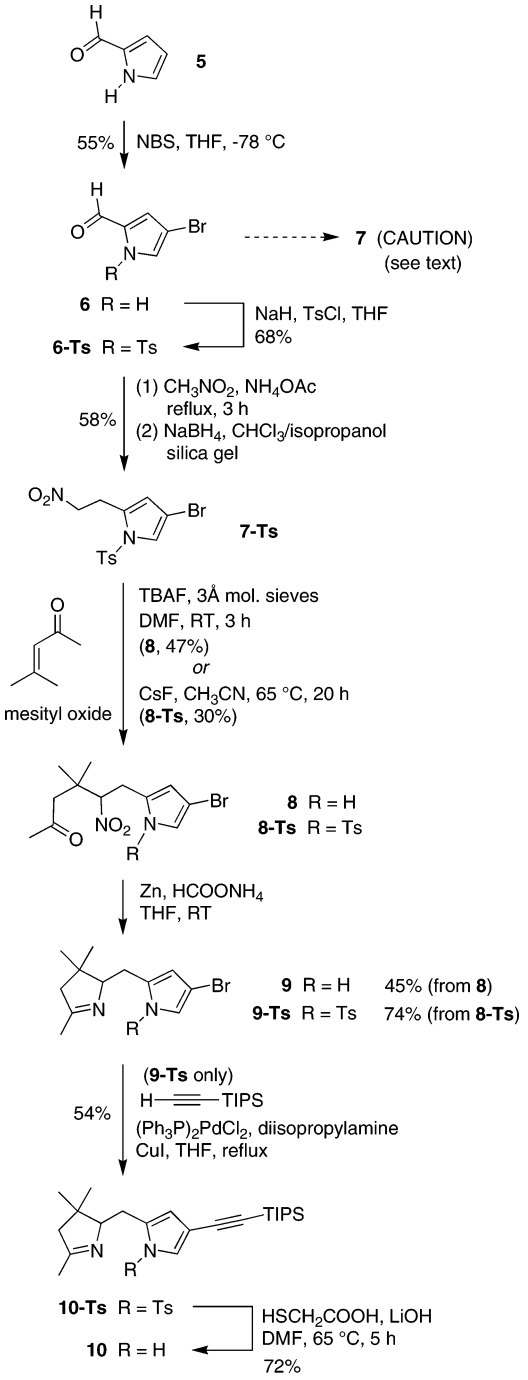
reactant	NBS equiv	product	R^5	R^8	yield (%)
1	1	**3a**	H	H	78
1	2	**3b**	H	Br	56
2	1	**4a**	Mes	H	67
2	2	**4b**	Mes	Br	51

this approach, using an 8-bromo derivative of the eastern half (i.e., an 8,9-dibromo-1-formyldipyrromethane) and an 8-bromo derivative of the western half to gain access to chlorins bearing substituents at the 3- and 13-positions.

A. Eastern and Western Halves. The syntheses of 9-bromo and 8,9-dibromo derivatives of 1-formyldipyrromethanes are shown in Table 1. While the 9-bromo derivatives of 1-acyldipyrromethanes are known,[11−15] 8,9-dibromo derivatives of 1-formyldipyrromethanes have not been previously prepared. In this regard, a number of polyhalogenated pyrroles from marine organisms have been identified and synthesized.[16] Treatment of 1-formyldipyrromethane **1**[17] or **2**[17] with 1 molar equivalent of NBS at −78 °C gave the 9-bromo derivative **3a** or **4a** in 78 or 67% yield, respectively. On the other hand, treatment of **1** or **2** with 2 molar equivalents of NBS at −78 °C gave the 8,9-dibromo derivative **3b** or **4b** in 56 or 51% yield, respectively. The regiochemistry of the 8,9-vicinal substitution pattern in the dibromo derivatives was established by NMR spectroscopy (HH−COSY and NOESY experiments, see Supporting Information). The regioselective formation of the dibromo product (**3b**, **4b**) stems in part from the deactivation of the α-formyl-substituted pyrrole ring. The first bromination occurs at the most active site in the dipyrromethane, which is the α-position of the adjacent pyrrole ring, and the second bromination occurs at the vicinal *β*-pyrrole position.

In some instances, the 8,9-dibromodipyrromethanes **3b** and **4b** were found to have limited stability. A study was carried out to more closely assess the factors that affect handling. A solution of compound **3b** (10 mM) in a solvent such as CH_2Cl_2, ethyl acetate, hexanes, or mixtures thereof changed color from pale yellow to purple over 2 h but without any evidence of decomposition of **3b**, as assessed by ^{1}H NMR spectroscopy. In $CDCl_3$, the compound was stable for 24 h, but

SCHEME 1



was found to have decomposed completely after 30 h. On the other hand, a solution of **3b** in THF-d_8 was very stable for 5 days. The powdered solid **3b** can be stored at −20 °C for 2−3 months without decomposition. Compound **4b** proved to be somewhat less stable, decomposing almost completely in ethyl acetate or chlorinated solvents within 18−20 h, even at 0 °C, but was very stable in THF-d_8 for 5 days. However, compound **4b** also could be stored in the solid form at −20 °C for 2−3 months without decomposition. In general, we have found that removal of the solvent during workup or column chromatography of **3b** or **4b** should be done without heating, and the samples should be stored at low temperature in the solid form.

The synthesis of an 8-bromo-substituted western half is shown in Scheme 1. Treatment of pyrrole-2-carboxaldehyde (**5**) with

(16) (a) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300−1302. (b) Bailey, D. M.; Johnson, R. E.; Salvador, U. J. *J. Med. Chem.* **1973**, *16*, 1298−1300. (c) Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221−2225. (d) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965−2975. (e) Cho, H.; Matsuki, S.; Mizuno, A.; Annoura, H.; Tatsuoka, T. *J. Heterocycl. Chem.* **1997**, *34*, 87−91. (f) Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1998**, *63*, 1248−1253. (g) He, R. H.-Y.; Jiang, X.-K. *J. Chem. Res., Synop.* **1998**, 786−787. (h) Armitt, D. J.; Banwell, M. G.; Freeman, C.; Parish, C. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1743−1745. (i) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783. (j) Patel, J.; Pelloux-Léon, N.; Minassian, F.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 9081−9084.

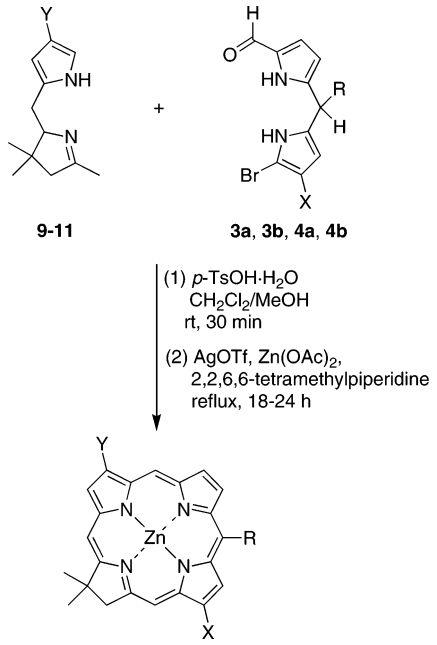
(17) Ptaszek, M.; McDowell, B. E.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 4328−4331.

one molar equivalent of NBS at −78 °C gave 4-bromopyrrole-2-carboxaldehyde **6**[18] in 55% yield after crystallization. This method for brominating pyrrole-2-carboxaldehyde is superior to a reported method that uses Br_2.[18] It should be noted that careful handling of the crude product is required; the off-white solid often turns reddish (irrespective of preparation using Br_2 or NBS), which complicates crystallization. Following a procedure for the synthesis of 2-(2-nitroethyl)pyrroles,[13] treatment of **6** with excess nitromethane, sodium acetate, and methylamine hydrochloride at room temperature for 16 h, followed by the addition of $NaBH_4$, gave 4-bromo-2-(2-nitroethyl)pyrrole (**7**) in variable yield (32−48%). However, **7** was found to explode (CAUTION), which caused us to abandon this intermediate.

We investigated the protection of the pyrrole nitrogen in 4-bromopyrrole-2-carboxaldehyde (**6**) with two purposes: (1) to obtain a stable analogue of 4-bromo-2-(2-nitroethyl)pyrrole (**7**), and (2) to achieve efficient palladium-coupling in the latter part of the 8-ethynyl western half synthesis. Considering the facile conditions for the removal of a *p*-toluenesulfonyl group as well as the crystalline nature of 2-(2-nitroethyl)-*N*-*p*-tosylpyrroles,[19] the *N*-tosylation[20] of compound **6** was carried out. Thus, treatment of **6** with NaH for 1 h, followed by addition of *p*-toluenesulfonyl chloride, gave **6-Ts** as a pale yellow crystalline solid in 68% yield. Following a reported procedure for the synthesis of 2-(2-nitrovinyl)-*N*-*p*-tosylpyrroles,[19] a mixture of **6-Ts**, excess nitromethane, and ammonium acetate was refluxed for 3 h. The crude product was satisfactorily pure (as evidenced by NMR spectroscopy) and was used directly in the next step. Reduction of the crude product with $NaBH_4$ in the presence of Montmorillonite K10[21] or silica gel[22] at room temperature afforded 2-(2-nitroethyl)-*N*-*p*-tosylpyrrole **7-Ts** as a white solid in 40 or 58% yield, respectively. A Michael addition of **7-Ts** with mesityl oxide in the presence of TBAF[23] and 3 Å molecular sieves gave the detosylated pyrrole-hexanone **8** in 47% yield. The *p*-toluenesulfonyl group is known to be cleaved by TBAF.[24] The reduction[22] of **8** with excess zinc dust and $HCOONH_4$ in THF at room temperature afforded the 8-bromo western half **9** in 45% yield.

For the synthesis of 3,13-unsymmetrical chlorins, we considered functionalizing the western half **9** as a means of installing the desired auxochrome prior to the chlorin-forming reaction. The synthesis of a western half bearing a TIPS-ethynyl group at the 8-position is shown in Scheme 1. The Michael addition[13] of **7-Ts** and mesityl oxide was carried out using CsF in anhydrous CH_3CN at 65 °C, affording nitrohexanone **8-Ts** in 30% yield along with a substantial amount of *N*-detosylated product **8** (∼30%). CsF also is known to cause detosylation.[25] A similar reaction at room temperature for 16 h gave a similar product distribution. Commonly used bases[22] for Michael additions such as tetramethylguanidine or DBU did not give any trace of **8-Ts**. The reductive cyclization of **8-Ts** in the presence of excess zinc dust and $HCOONH_4$ in THF at room temperature gave *N*-tosyl western half **9-Ts** in 74% yield. Sonogashira coupling of **9-Ts** with (triisopropylsilyl)acetylene was carried out under conditions that have been used with pyrrolic compounds (20 mol % each of $(PPh_3)_2PdCl_2$ and CuI in THF and diisopropylamine),[26] affording **10-Ts** in 54% yield. The selective detosylation[27] in the presence of the TIPS group was achieved by stirring a mixture of **10-Ts**, $HSCH_2COOH$, and LiOH in anhydrous DMF at 65 °C for 5 h, affording TIPS-ethynyl western half **10** in 72% yield.

TABLE 2. Effects of Substituents on Chlorin-Forming Reactions



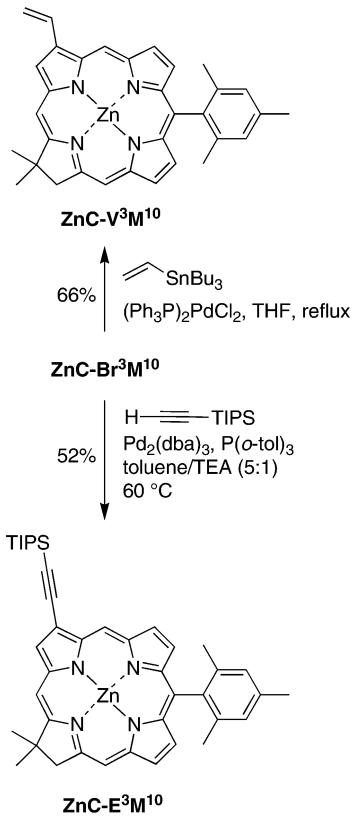
		chlorin substituents[c]				
WH[a]	EH[b]	3	13	10	chlorin	yield[d] (%)
11	**4a**	H	H	Mes	**ZnC-M[10]**	42
9	**4a**	Br	H	Mes	**ZnC-Br[3]M[10]**	37
11	**4b**	H	Br	Mes	**ZnC-M[10]Br[13]**	26
9	**4b**	Br	Br	Mes	**ZnC-Br[3]M[10]Br[13]**	30
10	**4b**	≡—TIPS	Br	Mes	**ZnC-E[3]M[10]Br[13]**	11
11	**3a**	H	H	H	**ZnC**	16
9	**3b**	Br	Br	H	**ZnC-Br[3]Br[13]**	26
10	**3b**	≡—TIPS	Br	H	**ZnC-E[3]Br[13]**	7

[a] Western half with no substituent (**11**, Y = H) or a substituent at the 8-position (**9**, **10**). [b] Eastern half. [c] Numbering of chlorins is shown in Chart 1. [d] Isolated yield.

B. Chlorin Formation. The general chlorin-forming reaction entails an acid-catalyzed condensation of a 9-bromo-1-formyldipyrromethane species (eastern half) and a 2,3,4,5-tetrahydro-1,3,3-trimethyldihydrodipyrrin species (western half), followed by zinc-mediated oxidative cyclization, as shown in Table 2. The conditions were drawn in part from those employed by Battersby in the synthesis of copper chlorins.[23] Thus, a stirred suspension of an eastern half (**3a**, **3b**, **4a**, **4b**, in slight excess) and a western half with a substituent at the 8-position (**9**, **10**) or no substituent (**11**) in anhydrous CH_2Cl_2 was treated with a solution of *p*-$TsOH\cdot H_2O$ in anhydrous MeOH under argon,

(18) Anderson, H. J.; Lee, S.-F. *Can. J. Chem.* **1965**, *43*, 409−414.
(19) Hamdan, A.; Wasley, J. W. F. *Synth. Commun.* **1985**, *15*, 71−74.
(20) Tietze, L. F.; Kettschau, G.; Heitmann, K. *Synthesis* **1996**, 851−857.
(21) Bahulayan, D.; Das, S. K.; Iqbal, J. *J. Org. Chem.* **2003**, *68*, 5735−5738.
(22) Ptaszek, M.; Bhaumik, J.; Kim, H.-J.; Taniguchi, M.; Lindsey, J. S. *Org. Process Res. Dev.* **2005**, *9*, 651−659.
(23) Battersby, A. R.; Fookes, C. J. R.; Snow, R. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2725−2732.
(24) Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595−596.
(25) Eisch, J. J.; Behrooz, M.; Dua, S. K. *J. Organomet. Chem.* **1985**, *285*, 121−136.
(26) (a) Alvarez, A.; Guzmán, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653−1656. (b) Bergauer, M.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1937−1940.
(27) Haskins, C. M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 599−601.

SCHEME 2

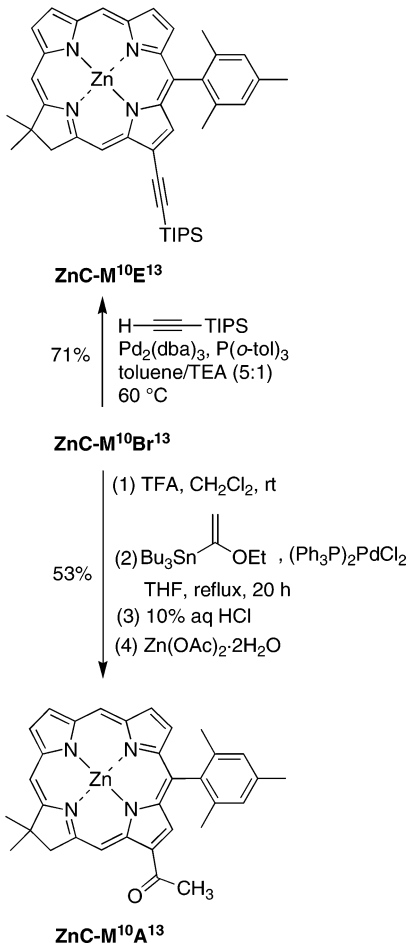


affording a clear reddish-brown solution over 30−45 min. Workup afforded a yellow-brown foamlike solid, which was treated with $Zn(OAc)_2$, 2,2,6,6-tetramethylpiperidine, and AgOTf in CH_3CN at reflux exposed to air for 18−24 h. The chlorin was obtained by silica column chromatography. This route provided access to chlorins bearing H, Br, or TIPS-ethynyl at the 3-position and H or Br at the 13-position in yields ranging from 7 to 42%. In the chlorin-forming reactions with ethynyl western half **10**, two chlorins in ~2:1 ratio were isolated from the crude mixture, of which the major product was the desired chlorin and the minor chlorin was not identified. Each target chlorin was characterized by absorption spectroscopy, ^{1}H NMR spectroscopy, LD-MS, and high-resolution mass spectrometry.

C. Chlorin Derivatization. (i) 3-Substituted Chlorins. The syntheses of 3-vinylchlorin **ZnC-V^{3}M^{10}** and 3-ethynylchlorin **ZnC-E^{3}M^{10}** are shown in Scheme 2. Stille coupling of **ZnC-Br^{3}M^{10}** and tributyl(vinyl)tin was carried out under conditions that have been employed with porphyrin substrates (10 mol % of $(PPh_3)_2PdCl_2$ in THF at reflux),[28] affording **ZnC-V^{3}M^{10}** in 66% yield. Sonogashira coupling of **ZnC-Br^{3}M^{10}** and (triisopropylsilyl)acetylene was carried out under conditions that have been used with chlorins [$Pd_2(dba)_3$ and P(*o*-tol)$_3$ in toluene/TEA (5:1)],[15] affording **ZnC-E^{3}M^{10}** in 52% yield. The latter conditions for Sonogashira coupling proceed under mild conditions and avoid the use of copper altogether, which can transmetalate with the zinc chelate.

(ii) 13-Substituted Chlorins. The syntheses of 13-acetylchlorin **ZnC-M^{10}A^{13}** and 13-ethynylchlorin **ZnC-M^{10}E^{13}** are shown in Scheme 3. The key step entails Pd-mediated coupling of a bromochlorin with tributyl(1-ethoxyvinyl)tin,[29] the product

SCHEME 3



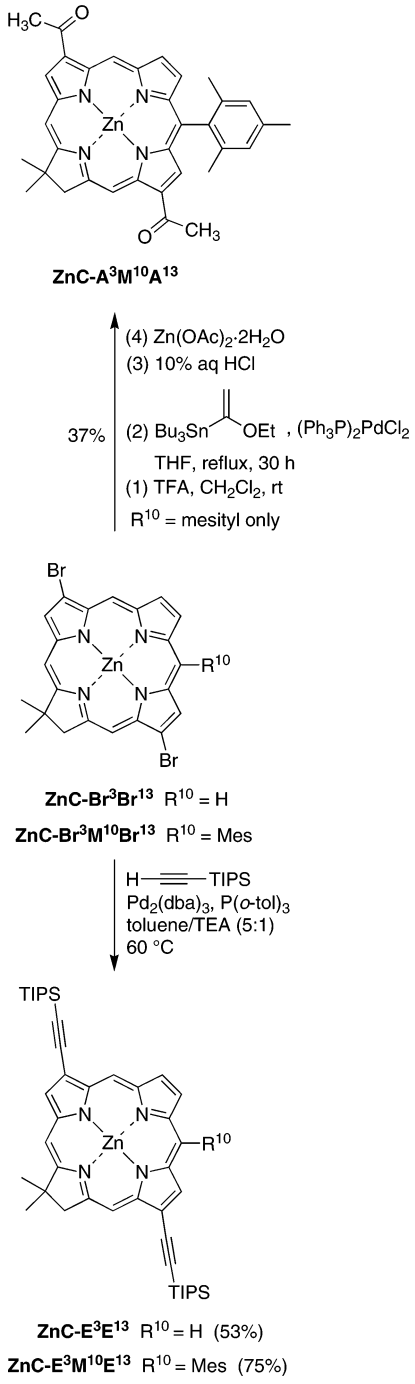
of which upon acidic hydrolysis unveils the acetyl group. Exploratory studies showed that the yield of the coupling step was higher with the free-base chlorin versus the zinc chlorin. Because the acidic hydrolysis would cause demetalation, thereby requiring reinsertion of zinc(II), we went ahead and demetalated the precursor zinc bromochlorins and performed the coupling on the free-base bromochlorin. Thus, chlorin **ZnC-M^{10}Br^{13}** was demetalated with TFA in CH_2Cl_2 at room temperature. The crude free-base chlorin was subjected to Stille coupling with tributyl(1-ethoxyvinyl)tin in the presence of 20 mol % of $(PPh_3)_2PdCl_2$ in THF for 20 h. Subsequent hydrolysis of the reaction mixture with 10% aqueous HCl gave a crude product that on metalation with $Zn(OAc)_2{\cdot}2H_2O$ gave chlorin **ZnC-M^{10}A^{13}** in 53% overall yield. Sonogashira coupling of **ZnC-M^{10}Br^{13}** with (triisopropylsilyl)acetylene in the presence of $Pd_2(dba)_3$ and P(*o*-tol)$_3$ gave 13-ethynylchlorin **ZnC-M^{10}E^{13}** in 71% yield.

(iii) 3,13-Substituted Chlorins. The syntheses of 3,13-diethynylchlorins **ZnC-E^{3}E^{13}** and **ZnC-E^{3}M^{10}E^{13}** are shown in Scheme 4. Sonogashira coupling of **ZnC-Br^{3}M^{10}Br^{13}** with **(**triisopropylsilyl)acetylene in the presence of 20 mol % of $(PPh_3)_2PdCl_2$ and CuI gave 3,13-diethynylchlorin **ZnC-E^{3}M^{10}E^{13}** in 42% yield, along with the formation of an unknown monoethynyl chlorin (~15% yield). The same coupling of **ZnC-Br^{3}Br^{13}** or **ZnC-Br^{3}M^{10}Br^{13}** with (triisopropylsilyl)acetylene, using the superior copper-free conditions [$Pd_2(dba)_3$ and P(*o*-

(28) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Org. Chem.* **1993**, *58*, 5983−5993.

(29) Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 767−768.

SCHEME 4

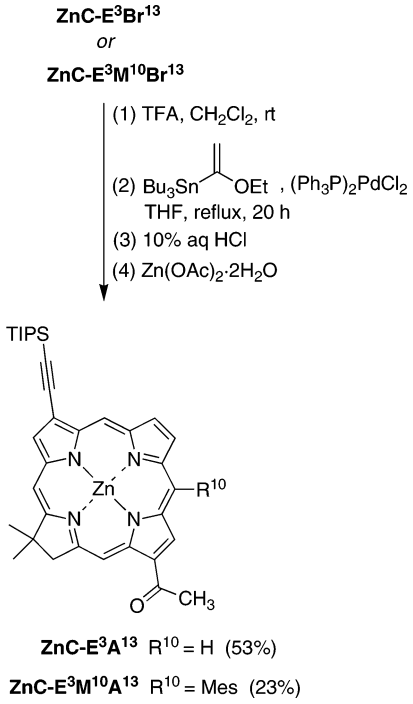


tol)$_3$], gave 3,13-diethynylchlorin **ZnC-E^{3}E^{13}** or **ZnC-E^{3}M^{10}E^{13}** in 53 or 75% yield, respectively.

The synthesis of 3,13-diacetylchlorin **ZnC-A^{3}M^{10}A^{13}** also is shown in Scheme 4. Demetalation of chlorin **ZnC-Br^{3}M^{10}Br^{13}** with TFA in CH_2Cl_2 at room temperature afforded the crude free-base chlorin, which was subjected to Stille coupling with tributyl(1-ethoxyvinyl)tin in the presence of 20 mol % of $(PPh_3)_2PdCl_2$ in THF for 30 h. Hydrolysis of the reaction mixture with 10% aqueous HCl, followed by metalation with $Zn(OAc)_2{\cdot}2H_2O$, gave chlorin **ZnC-A^{3}M^{10}A^{13}** in 37% overall yield.

The syntheses of 3-ethynyl-13-acetylchlorins **ZnC-E^{3}A^{13}** and **ZnC-E^{3}M^{10}A^{13}** were carried out using the protocol described above for the installation of the 13-acetyl group with the 13-bromo-3-ethynylchlorins **ZnC-E^{3}Br^{13}** and **ZnC-E^{3}M^{10}Br^{13}** (Scheme 5). Thus, demetalation of **ZnC-E^{3}Br^{13}** or **ZnC-E^{3}M^{10}Br^{13}**, Stille coupling of the corresponding crude product with tributyl(1-ethoxyvinyl)tin, acidic workup, and zinc metalation gave **ZnC-E^{3}A^{13}** or **ZnC-E^{3}M^{10}A^{13}** in 53 or 23% overall yield, respectively.

SCHEME 5



II. Spectroscopy. A. NMR Spectroscopy. ^{1}H NMR spectroscopy provides valuable information about the chlorin substitution patterns. A general description of chlorin spectral features, and complete spectral assignments for the meso and β-pyrrole protons of selected 3- and 13-substituted chlorins are shown in the Supporting Information.

B. Absorption and Fluorescence Spectroscopy. The spectral properties of interest in the chlorins include the position, intensity, and full-width at half-maximum (fwhm) of both the short-wavelength absorption band (B) and the long-wavelength absorption band (Q_y), the fluorescence emission spectrum and fluorescence quantum yield (Φ_f), and the Stokes shift ($\Delta\nu$) between absorption and emission. The intensities of the B and Q_y transitions can be assessed by the measured molar absorption coefficients; however, comparisons of such values often are somewhat unreliable given the experimental variability encountered upon handling small quantities of materials. A traditional method in the chlorophyll field employs the ratio of the intensities of the B and Q_y bands for a given compound (I_B/I_Q ratio), which obviates reliance on molar absorption coefficients.[30] For a wide variety of applications, bathochromic and hyperchromic shifts of the Q_y band are desired (i.e., shifted to longer wavelength and increased in intensity), given that the position and intensity of the long-wavelength transition plays a dominant role in determining photochemical properties.

The spectral properties of the zinc chlorins are listed in Table 3. The spectral properties of the nine new substituted chlorins can be compared with those of chlorophyll *a* (**Chl *a***),[30−33] its

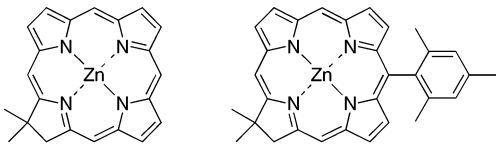
(30) Strain, H. H.; Thomas, M. R.; Katz, J. J. *Biochim. Biophys. Acta* **1963**, *75*, 306−311.

TABLE 3. Spectral Properties of Chlorins[a]

compound	λ_B (fwhm) in nm	log ϵ_B	λ_{Qy} (fwhm) in nm	log ϵ_{Q_y}	$\Delta\nu_{Q_y}$[b] (cm^{-1})	I_B/I_Q[c]	λ_{em}[d] (nm)	$\Delta\upsilon$[e] (cm^{-1})	Φ_f[f]
ZnC-M^{10}	405 (13)	5.45	606 (12)	4.81	0	4.2	609	80	0.059
ZnC-V^{3}M^{10}	413 (18)	5.18	621 (16)	4.66	400	3.3	625	100	0.078
ZnC-M^{10}E^{13}	413 (16)	5.26	626 (11)	4.92	530	2.2	628[g]	50	0.16
ZnC-E^{3}M^{10}	416 (16)	5.14	627 (12)	4.73	550	2.6	630	80	0.11
ZnC-M^{10}A^{13}	418 (18)	5.17	632 (14)	4.84	680	2.1	636	100	0.22
ZnC-E^{3}M^{10}E^{13}	423 (18)	4.97	646 (12)	4.76	1020	1.6	649	70	0.24
ZnC-E^{3}M^{10}A^{13}	428 (21)	4.79	652 (16)	4.62	1160	1.5	656	90	0.25
ZnC-A^{3}M^{10}A^{13}	436 (21)	4.72	662 (18)	4.54	1400	1.5	668	110	0.29
ZnC	399 (14)	5.38	603 (13)	4.84	0	3.2	605	50	0.062
ZnC-E^{3}E^{13}	420 (19)	5.08	645 (12)	4.93	1080	1.4	648[h]	70	0.18
ZnC-E^{3}A^{13}	428 (31)	4.81	655 (17)	4.75	1320	1.2	660	120	0.22
Zn-Pheo *a* [i,j]	423 (38)	5.09	653 (18)	4.96		1.38	657[k]	90[k]	0.23[k]
Chl *a* [i,l]	429 (39)[m]	5.05	661 (17)[m]	4.93		1.3	666[n]	110[m]	0.32[o]
Chl *a* [p,q]	433 (39)[m]	5.01	666 (19)[m]	4.89		1.294	671[m]	110[m]	0.325[o]

[a] In toluene at room temperature, unless noted otherwise. [b] The redshift of the Q_y band relative to that of the parent chlorin (**ZnC-M^{10}** or **ZnC**). [c] Ratio of the intensities of the B and Q_y bands. [d] Excitation was performed at the λ_{max} of the B band. [e] Stokes shift. [f] Determined in toluene at room temperature with λ_{exc} at the B-band maximum using chlorophyll *a* as a standard ($\Phi_f = 0.322$), unless noted otherwise (see Supporting Information). [g] Shoulder at 689 nm. [h] Shoulder at 705 nm. [i] In diethyl ether. [j] Absorption data from ref 35. The absorption spectrum is essentially identical in $CHCl_3$.[34] [k] Reference 37. We calculated the Φ_f value using data from ref 37 and chlorophyll *a* as a standard. A value of $\Phi_f = 0.17$ in diethyl ether/petroleum ether has been reported.[36] [l] Absorption data from ref 30. [m] This work. [n] Data from PhotochemCAD version 2.[33] [o] Reference 31. [p] In benzene. [q] Absorption data from ref 32.

zinc analogue (**Zn-Pheo *a***),[34−37] as well as two benchmark zinc chlorins lacking 3- and 13-substituents (**ZnC-M^{10}** and **ZnC**). Each benchmark, **ZnC** or **ZnC-M^{10}**, exhibits a B band at 399 or 405 nm, a Q_y band at 603 or 606 nm, and I_B/I_Q ratio of 3.2 or 4.2, respectively. Inspection of the table shows the progressive redshift in absorption properties upon introduction of vinyl, TIPS-ethynyl, and/or acetyl groups. Indeed, each chlorin with a single 3- or 13-substituent (vinyl, TIPS-ethynyl, or acetyl) exhibits a B band in the region of 413−418 nm and a Q_y band in the range from 621 to 632 nm. Thus, a single substituent at the 3- or 13-position redshifts the Q_y band by 400−680 cm^{-1} (∼15−26 nm), compared to the benchmark chlorin **ZnC-M^{10}**. The presence of substituents at both 3- and 13-positions results in a B band in the region 423−436 nm, and a Q_y band in the range from 646 to 662 nm; the total redshift of the Q_y band is 1000−1400 cm^{-1} (∼40−56 nm). The largest effect of a single substituent was observed with the acetyl group (**ZnC-M^{10}A^{13}**), and the most pronounced redshift with two substituents was observed with two acetyl groups (**ZnC-A^{3}M^{10}A^{13}**).



ZnC **ZnC-M^{10}**

The redshift of absorption maxima is accompanied by a relative increase in the intensity of the Q_y band versus that of the B band. Thus, the band intensity ratio changed from 4.2 in the unsubstituted parent compound **ZnC-M^{10}** to 1.5 in **ZnC-A^{3}M^{10}A^{13}**. The redshift and changing band intensities (I_B/I_Q ratio) are displayed in the normalized absorption spectra of chlorins in the 10-mesityl-substituted family (Figure 1, upper panel). Note that **ZnC-E^{3}M^{10}** and **ZnC-M^{10}E^{13}** exhibit nearly identical spectra; only the data for the former are displayed. Analogous redshifts and changing band intensities were observed in the 10-unsubstituted family of chlorins (Figure 1, lower panel). It is noteworthy that the measured molar absorption coefficient for the B band tends to decline upon substitution with groups affording redshifted spectra, but is not fully compensated by a commensurate increase in the intensity of the Q_y band. For example, the spectrum of **ZnC-A^{3}M^{10}A^{13}** closely resembles that of chlorophyll *a* in terms of shape and position, but is ∼2-fold weaker in intensity. We have no explanation for this apparent discrepancy. A more full discussion concerning absorption intensity is provided in the Supporting Information, including a figure showing overlaid absorption spectra plotted on the basis of measured molar absorption coefficients.

The fluorescence emission spectra are typical of chlorins, with strong (0,0) bands and much weaker (0,1) and (0,2) emission bands. The fluorescence quantum yields were measured in degassed toluene at room temperature, using chlorophyll *a* as a standard ($\Phi_f = 0.322$). The values increased from 0.059 or 0.062 for **ZnC-M^{10}** or **ZnC**, respectively, to 0.25 or 0.22 for the 3-TIPS-ethynyl-13-acetylchlorins **ZnC-E^{3}M^{10}A^{13}** or **ZnC-E^{3}A^{13}**. The most emissive chlorin was the 3,13-diacetylchlorin **ZnC-A^{3}M^{10}A^{13}**, which exhibited $\Phi_f = 0.29$. The increase in fluorescence quantum yield generally paralleled the redshift and relative intensification of the Q_y band. In general, the rate constant for radiative emission is directly proportional to the oscillator strength of the transition. It should be noted, however, that the oscillator strength of the Q_y band is given by the integrated band area[38] (approximated by the product of ϵ_{Q_y} × fwhm) rather than the molar absorption coefficient. This is pertinent here given the variation in fwhm of the Q_y bands, which ranges from 11 to 18 nm across the series of chlorins. A deeper understanding of the effect of auxochromic groups on the fluorescence yield requires knowledge of the excited-state

(31) Weber, G.; Teale, F. W. J. *Trans. Faraday Soc.* **1957**, *53*, 646−655.
(32) Seely, G. R.; Jensen, R. G. *Spectrochim. Acta* **1965**, *21*, 1835−1845.
(33) Dixon, J. M.; Taniguchi, M.; Lindsey, J. S. *Photochem. Photobiol.* **2005**, *81*, 212−213.
(34) Boucher, L. J.; Katz, J. J. *J. Am. Chem. Soc*. **1967**, *89*, 4703−4708.
(35) Jones, I. D.; White, R. C.; Gibbs, E.; Denard, C. D. *J. Agric. Food Chem.* **1968**, *16*, 80−83.
(36) Dvornikov, S. S.; Knyukshto, V. N.; Solovev, K. N.; Tsvirko, M. P. *Opt. Spektrosk.* **1979**, *46*, 385−388.
(37) Agostiano, A.; Catucci, L.; Colafemmina, G.; Scheer, H. *J. Phys. Chem. B* **2002**, *106*, 1446−1454.
(38) Strickler, S. J.; Berg, R. A. *J. Chem. Phys*. **1962**, *37*, 814−822.

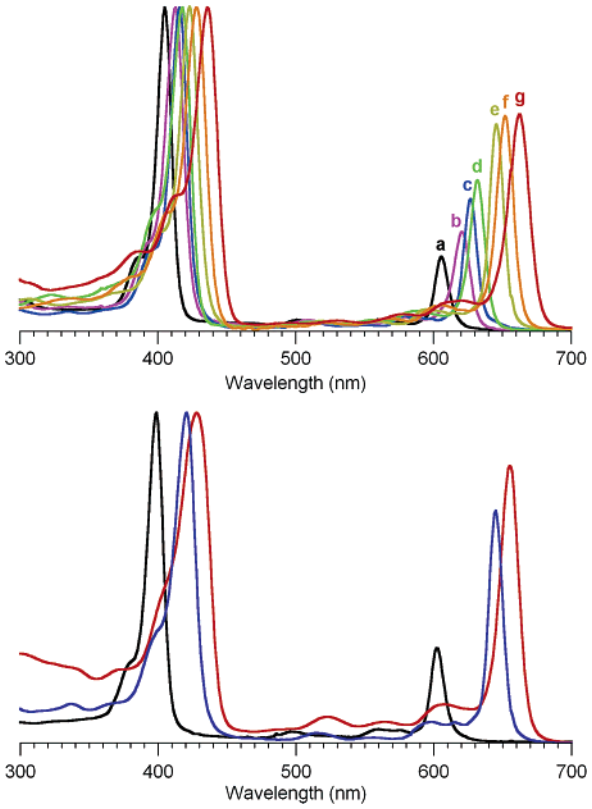


FIGURE 1. Absorption spectra in toluene at room temperature of zinc chlorins (normalized at the B bands). Upper panel: The 10-mesityl-chlorins (label, color in graph) and their Q_y bands include **ZnC-M^{10}** (a, black), 606 nm; **ZnC-V^{3}M^{10}** (b, violet), 621 nm; **ZnC-E^{3}M^{10}** (c, blue), 627 nm; **ZnC-M^{10}A^{13}** (d, green), 632 nm; **ZnC-E^{3}M^{10}E^{13}** (e, lime), 646 nm; **ZnC-E^{3}M^{10}A^{13}** (f, orange), 652 nm; and **ZnC-A^{3}M^{10}A^{13}** (g, red), 662 nm. The I_B/I_Q ratio decreases from 4.2 to 1.5 in the series. Lower panel: The 10-unsubstituted chlorins (color in graph) and their Q_y bands include **ZnC** (black), 603 nm; **ZnC-E^{3}E^{13}** (blue), 645 nm; and **ZnC-E^{3}A^{13}** (red), 655 nm. The I_B/I_Q ratio decreases from 3.2 in **ZnC** to 1.2 in **ZnC-E^{3}A^{13}**.

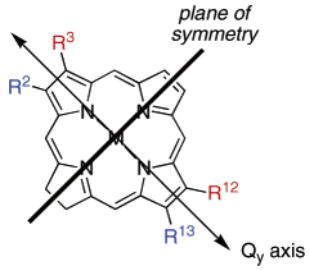


FIGURE 2. The Q_y axis in chlorins.

dynamics, including excited singlet-state lifetimes. Regardless, the absorption spectral properties (shape and position) and fluorescence spectral properties of the 3,13-bis(TIPS-ethynyl)-chlorins (**ZnC-E^{3}M^{10}E^{13}**, **ZnC-E^{3}E^{13}**), 3-TIPS-ethynyl-13-acetylchlorins (**ZnC-E^{3}M^{10}A^{13}**, **ZnC-E^{3}A^{13}**), and 3,13-diacetylchlorin **ZnC-A^{3}M^{10}A^{13}** resemble those of chlorophyll *a* or its zinc analogue **Zn-Pheo *a***.

A final point concerns the effect of auxochromes substituted in ring A versus ring C. In chlorins, the Q_y band is polarized along the N−N axis containing pyrrole rings A and C (Chart 1 and Figure 2).[1] A chlorin nominally has C_{2v} symmetry,[1] in which case the 2- and 13-positions are symmetrically equivalent, and the 3- and 12-positions are symmetrically equivalent. In practice, the presence of the geminal dimethyl group in the pyrroline ring of the synthetic chlorins prepared herein lowers the symmetry, but the geminal dimethyl group is not expected to perturb the π-system and, hence, should have little effect on the spectral properties. The 3- and 13-positions each reside in a pyrrole ring aligned along the Q_y axis; the former is distal, whereas the latter is proximal to the pyrroline ring. In one case where a comparison could be made, the magnitude of the effect caused by a substituent at the 3-position was found to be quite similar to that at the 13-position: **ZnC-E^{3}M^{10}** and **ZnC-M^{10}E^{13}** exhibited nearly identical Q_y band positions (627 nm, 626 nm). Additional comparisons are required to more fully understand the effects of auxochromes at the two locations proximal (2 and 13) versus distal (3 and 12) to the pyrroline ring. Such comparisons are now possible with the synthetic methodology described herein for preparing substituted chlorins.

Conclusions

A new route has been established for the de novo synthesis of sterically uncongested, stable chlorins bearing substituents at the 3- and 13-positions. The motivation for introducing auxochromes at the 3- and 13-positions stems from chlorophylls *a* and *b*, which bear 3-vinyl and 13-keto groups. This work complements studies of derivatives of naturally occurring chlorins, which typically contain a full set of β-pyrrolic substituents and are less malleable synthetically. The use of one or two acetyl, TIPS-ethynyl, or vinyl groups at these positions enables fine-tuning of the absorption and fluorescence properties of the chlorins. The spectral redshift imparted by a single group is substantial [3-vinyl (400 cm^{-1}), 3- or 13-TIPS-ethynyl (∼540 cm^{-1}), 13-acetyl (680 cm^{-1})], and the effect of two such groups is nearly additive [3,13-bis(TIPS-ethynyl) (1020 cm^{-1}), 3-TIPS-ethynyl-13-acetyl (1160 cm^{-1}), 3,13-diacetyl (1400 cm^{-1})]. The redshift is accompanied by (1) a relative increase in the Q_y band intensity versus the B band intensity, and (2) an increase in the fluorescence quantum yield. The use of 3,13-bis(TIPS-ethynyl), 3-TIPS-ethynyl-13-acetyl, or 3,13-diacetyl groups affords chlorins with absorption spectral (shape and position, but not intensity) properties and fluorescence properties that rival those of chlorophyll *a*. It is noteworthy that ethynes do not occur in natural chlorophylls; however, ethynes are particularly attractive in their ease of introduction, potent auxochromic effect, and amenability toward synthetic elaboration. Ethynes have been employed extensively in porphyrin chemistry,[28,39] but have been relatively little examined with hydroporphyrins.[15,40] The synthetic approaches described herein should enable a much broader examination of substituents for tuning the spectral and photochemical properties of chlorins. The ability to prepare 3,13-substituted chlorins also complements the work of Balaban *et al.*, who have employed synthetic porphyrins or derivatives of chlorophylls in exploring the effects of substituents on porphyrinic self-assembly processes leading to light-harvesting architectures.[41]

Experimental Section

Monobromination: 9-Bromo-1-formyl-5-mesityldipyrromethane (4a). Following a reported procedure,[11] a solution of **2** (43.5

(39) Lin, V. S.-Y.; DiMagno, S. G.; Therien, M. J. *Science* **1994**, *264*, 1105−1111.

(40) Hindin, E.; Kirmaier, C.; Diers, J. R.; Tomizaki, K.-Y.; Taniguchi, M.; Lindsey, J. S.; Bocian, D. F.; Holten, D. *J. Phys. Chem. B* **2004**, *108*, 8190−8200.

mg, 0.149 mmol) in dry THF (4 mL) at −78 °C under argon was treated with NBS (26.5 mg, 0.149 mmol) and stirred for 30 min. Hexanes (4 mL) and water (4 mL) were added, and the cooling bath was removed. The mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and filtered. The filtrate was concentrated to give a brown solid that was chromatographed [silica, hexanes/ethyl acetate (9:1 → 3:1)]. The product was recrystallized (EtOH/H_2O, 4:1) to afford light brown crystals (37 mg, 67%): mp 159 °C (dec); ^{1}H NMR (THF-d_8) δ 2.05 (s, 6H), 2.22 (s, 3H), 5.49−5.52 (m, 1H), 5.74 (s, 1H), 5.80−5.85 (m, 1H), 5.89−5.92 (m, 1H), 6.76−6.78 (m, 1H), 6.80 (s, 2H), 9.38 (s, 1H), 10.45 (br s, 1H), 11.09 (br s, 1H); ^{13}C NMR δ 22.2, 31.9, 41.5, 98.4, 110.7, 111.4, 112.2, 121.9, 131.9, 134.5, 135.3, 136.2, 138.0, 139.2, 143.6, 179.2; FAB-MS obsd, 370.0664; calcd, 370.0681 ($C_{19}H_{19}BrN_2O$).

Dibromination: 8,9-Dibromo-1-formyldipyrromethane (3b). A solution of **1** (270 mg, 1.55 mmol) in dry THF (15.5 mL) at −78 °C under argon was treated with NBS (552 mg, 3.17 mmol). The reaction mixture was stirred for 1 h at −78 °C. Hexanes and water were added at −20 °C, and the mixture was allowed to warm to 0 °C. The organic layer was separated, dried (K_2CO_3), and concentrated at ambient temperature. The resulting brown solid was purified by column chromatography [silica, hexanes/CH_2Cl_2/ethyl acetate (7:2:1)], affording a purple solid (290 mg, 56%): mp 109−111 °C (dec); ^{1}H NMR (THF-d_8) δ 3.93 (s, 2H), 5.89 (s, 1H), 6.05−6.07 (m, 1H), 6.78−6.79 (m, 1H), 9.37 (s, 1H), 10.81 (br s, 1H), 11.16 (br s, 1H); ^{13}C NMR (THF-d_8) δ 26.0, 96.3, 98.0, 110.1, 112.7, 121.7, 128.9, 134.3, 139.0, 178.5. Anal. Calcd for $C_{10}H_8Br_2N_2O$: C, 36.18; H, 2.43; N, 8.44. Found: C, 36.58; H, 2.50; N, 8.11. Note: A significant amount (∼30%) of the starting 1-formyldipyrromethane **1** was recovered in this reaction. Compound **3b** can be stored in solid form at −20 °C for 2−3 months without decomposition but is susceptible to decomposition in solution, particularly in $CDCl_3$. All handling in solution, including during solvent removal, should be done without heating.

4-Bromopyrrole-2-carboxaldehyde (6). A solution of pyrrole-2-carboxaldehyde (**5**, 4.75 g, 50.0 mmol) in dry THF (200 mL) was cooled to −78 °C under argon. NBS (8.90 g, 50.0 mmol) was added, and the reaction mixture was stirred for 1 h at −78 °C. Hexanes and water were added, and the reaction mixture was allowed to warm to 0 °C. The organic phase was extracted with hexanes and dried (Na_2SO_4). Crystallization of the crude mixture using hexanes/THF afforded white crystals (4.83 g, 55%): mp 120−121 °C [lit.[18] 122−123 °C]; ^{1}H NMR δ 6.95 (m, 1H), 7.12 (m, 1H), 9.45 (s, 1H), 9.65−9.85 (br s, 1H); ^{13}C NMR δ 99.0, 123.0, 127.0, 132.8, 179.3. Anal. Calcd for C_5H_4BrNO: C, 34.51; H, 2.32; N, 8.05. Found: C, 34.50; H, 2.26; N, 7.75. Note: Careful handling of the crude mixture is required. Evaporation of the solvent during workup should be done without heating. The use of ethyl acetate or any chlorinated solvent was avoided during workup or crystallization. The crystallization of the crude mixture was carried out by dissolving the off-white solid in THF by warming (40−50 °C), followed by addition of hexanes. The crude off-white solid very often turns a reddish color, which subsequently prevents crystallization. In that case, a small silica-pad filtration of the crude mixture is required before crystallization.

4-Bromo-2-formyl-*N*-*p*-tosylpyrrole (6-Ts). Following a reported procedure,[20] a stirred suspension of NaH (865 mg, 36.0 mmol) in THF (200 mL) was treated with **6** (5.22 g, 30.0 mmol) at room temperature. When the evolution of gas had ceased, the mixture was stirred for 1 h before treating with *p*-toluenesulfonyl chloride (6.30 g, 33.0 mmol). After 16 h, the conversion was complete, as monitored by TLC. The reaction mixture was quenched by adding saturated aqueous NH_4Cl. Ethyl acetate was added, and the organic layer was separated. The organic layer was washed (water and brine) and dried (Na_2SO_4). Concentration followed by crystallization (ethyl acetate/hexanes) afforded pale yellow crystals (6.75 g, 68%): mp 83−85 °C; ^{1}H NMR δ 2.43 (s, 3H), 7.09 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 8.3 Hz, 2H), 9.94 (s, 1H); ^{13}C NMR δ 22.0, 101.8, 125.4, 127.8, 127.9, 130.6, 133.5, 134.7, 146.7, 178.5. Anal. Calcd for $C_{12}H_{10}BrNO_3S$: C, 43.92; H, 3.07; N, 4.27; S, 9.77. Found: C, 43.92; H, 3.02; N, 4.26; S, 9.84.

4-Bromo-2-(2-nitroethyl)-*N*-*p*-tosylpyrrole (7-Ts). Following a reported procedure,[19] a mixture of **6-Ts** (7.50 g, 22.8 mmol), nitromethane (21.6 mL, 405 mmol), and ammonium acetate (1.18 g, 15.3 mmol) was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with aqueous $NaHCO_3$, water, and brine and then dried (Na_2SO_4). Removal of the solvent gave a brown solid that was used directly in the next step. Following a published procedure,[22] a solution of the crude product in $CHCl_3$ (195 mL) and 2-propanol (65 mL) was treated with silica (26.3 g). The resulting suspension was treated in three portions with $NaBH_4$ (1.65 g, 45.6 mmol) under vigorous stirring at room temperature. The reaction mixture was stirred for ∼1.5 h and monitored by TLC. The reaction mixture was filtered. The filter cake was washed several times with CH_2Cl_2. The organic solution was washed with water and brine. The organic layer was dried ($NaSO_4$), concentrated, and subjected to high vacuum to remove traces of 2-propanol. The resulting residue was subjected to column chromatography [silica, hexanes/CH_2Cl_2/ethyl acetate (8:1:1)] to afford a pale yellow solid (4.95 g, 58%): mp 126−128 °C; ^{1}H NMR (300 MHz) δ 2.44 (s, 3H), 3.38 (t, J = 7.0 Hz, 2H), 4.60 (t, J = 7.0 Hz, 2H), 6.09 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 21.9, 25.3, 74.3, 100.9, 117.3, 122.5, 127.0, 129.5, 130.7, 135.4, 146.2. Anal. Calcd for $C_{13}H_{13}BrN_2O_4S$: C, 41.84; H, 3.51; N, 7.51. Found: C, 41.88; H, 3.50; N, 7.29. An alternative preparation using Montmorillonite K10 is described in the Supporting Information.

6-(4-Bromo-1*H*-pyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one (8). Following a reported procedure,[23] a solution of TBAF·$3H_2O$ (2.64 g, 8.36 mmol) in anhydrous DMF (25 mL) was stirred in the presence of 3 Å molecular sieves (8 g) for 30 min at room temperature under argon. The stirred suspension was treated with a solution of **7-Ts** (1.56 g, 4.18 mmol) and mesityl oxide (4.80 mL, 42.0 mmol) in anhydrous DMF (15 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through filter paper. The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate. The organic solution was washed with water, dried (Na_2SO_4), and chromatographed [silica, CH_2Cl_2] to give a viscous liquid (623 mg, 47%): ^{1}H NMR (300 MHz) δ 1.09 (s, 3H), 1.22 (s, 3H), 2.14 (s, 3H), 2.40 (d, J = 17.6 Hz, 1H), 2.58 (d, J = 17.6 Hz, 1H), 2.97 (AB, J = 15.2 Hz, 1H), 3.28 (ABX, ^2J = 15.2 Hz, ^3J = 11.6 Hz, 1H), 5.11 (ABX, ^2J = 11.6 Hz, ^3J = 3.5 Hz, 1H), 5.97−5.99 (m, 1H), 6.62−6.64 (m, 1H), 8.10−8.18 (br s, 1H); ^{13}C NMR δ 24.3, 24.5, 26.8, 32.0. 36.9, 51.6, 94.4, 96.2, 110.0, 117.8, 127.3, 207.7; FAB-MS obsd, 316.0432; calcd, 316.0423 ($C_{12}H_{17}BrN_2O_3$). Note: Compound **8** (neat or in solution) changes color from yellow to black over time (1−2 days) at room temperature, indicating partial decomposition.

6-(4-Bromo-*N*-*p*-tosylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one (8-Ts). Following a reported procedure,[13] CsF (3.17 g, 20.9 mmol) was freshly dried by heating at 100 °C under vacuum for 1 h and then cooled to room temperature under argon. A solution of **7-Ts** (2.60 g, 6.96 mmol) and mesityl oxide (8.16 mL, 71.0 mmol, 10 molar equiv) in dry acetonitrile (61 mL) was transferred by cannula to the flask containing CsF. The mixture was stirred at 65 °C for 18 h. The reaction mixture was filtered through a pad of silica, and the filter cake was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. Column chromatography [silica, hexanes/CH_2Cl_2/ethyl acetate (7:2:1)] of the crude product

(41) Balaban, T. S.; Tamiaki, H.; Holzwarth, A. R. *Top. Curr. Chem.* **2005**, *258*, 1−38.

afforded a brown solid (0.980 g, 30%): mp 103−104 °C; ^{1}H NMR δ 1.11 (s, 3H), 1.24 (s, 3H), 2.13 (s, 3H), 2.40 (AB, J = 17.8 Hz, 1H), 2.43 (s, 3H), 2.55 (AB, J = 17.8 Hz, 1H), 3.18 (AB, J = 16.2 Hz, 1H), 3.36 (ABX, ^3J = 16.2 Hz, ^2J = 11.8 Hz, 1H), 5.14 (AB, J = 11.8 Hz, 1H), 6.00−6.02 (m, 1H), 7.22−7.24 (m, 1H), 7.34 (AB, J = 8.2 Hz, 2H), 7.64 (AB, J = 8.2 Hz, 2H); ^{13}C NMR δ 21.9, 23.7, 24.4, 26.4, 31.8. 36.9, 51.0, 93.5, 101.0, 117.0, 122.4, 126.8, 130.2, 130.6, 135.6, 146.0, 206.3; FAB-MS obsd, 471.0596; calcd, 471.0589 ($C_{19}H_{23}BrN_2O_5S$).

Western Half Formation: 8-Bromo-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin (9). Following a refined procedure,[22] a stirred suspension of **8** (350 mg, 1.10 mmol) and $HCOONH_4$ (1.04 g, 16.5 mmol) in THF (4.4 mL) was treated portionwise with Zn dust (1.07 g, 16.5 mmol) for 15 min. The reaction mixture was stirred vigorously for 3 h at room temperature. Ethyl acetate was added, and the reaction mixture was filtered through filter paper. The filtrate was washed (half saturated aqueous $NaHCO_3$, water, brine), dried (Na_2SO_4), and chromatographed (silica, ethyl acetate), affording a yellow solid (135 mg, 45%): mp 83−84 °C; ^{1}H NMR δ 0.92 (s, 3H), 1.11 (s, 3H), 2.03 (s, 3H), 2.28 (AB, J = 16.8 Hz, 1H), 2.38 (AB, J = 16.8 Hz, 1H), 2.54 (ABX, ^2J = 14.9 Hz, ^3J = 11.8 Hz, 1H), 2.69 (ABX, ^2J = 11.8 Hz, ^3J = 2.5 Hz, 1H), 3.56−3.62 (m, 1H), 5.85−5.94 (m, 1H), 6.63−6.69 (m, 1H), 9.72−10.01 (br s, 1H); ^{13}C NMR δ 20.7, 23.0, 27.3, 27.8, 42.0, 54.4, 80.2, 95.2, 108.2, 116.5, 132.8, 175.1. Anal. Calcd for $C_{12}H_{17}BrN_2$: C, 53.54; H, 6.37; N, 10.41. Found: C, 53.15; H, 6.32; N, 10.11. Note: Continued reaction for ≥5 h often results in the significant formation of a side product.

8-[2-(Triisopropylsilyl)ethynyl]-2,3,4,5-tetrahydro-1,3,3-trimethyl-*N*^{11}-*p*-tosyldipyrrin (10-Ts). A mixture of **9-Ts** (0.560 g, 1.32 mmol), (triisopropylsilyl)acetylene (0.590 mL, 2.65 mmol), $(PPh_3)_2PdCl_2$ (186 mg, 0.265 mmol), diisopropylamine (0.930 mL, 6.63 mmol), and CuI (50.0 mg, 0.262 mmol) was refluxed in THF (6 mL) for 20 h using a Schlenk line. The reaction mixture was concentrated and chromatographed [silica, hexanes/ethyl acetate (1:1)], affording a viscous liquid (375 mg, 54%): ^{1}H NMR (300 MHz) δ 0.87 (s, 3H), 1.05−1.07 (m, 24H), 1.97 (s, 3H), 2.26 (AB, J = 16.8 Hz, 1H), 2.35 (AB, J = 16.8 Hz, 1H), 2.40 (s, 3H), 2.60 (ABX, ^2J = 16.2 Hz, ^3J = 10.1 Hz, 1H), 2.86 (ABX, ^2J = 16.2 Hz, ^3J = 3.8 Hz, 1H), 3.68−3.70 (m, 1H), 6.28−6.30 (m, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.46−7.47 (m, 1H), 7.68 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 11.5, 18.8, 20.7, 21.8, 23.0, 27.2, 28.0, 42.4, 54.6, 77.9, 91.1, 100.5, 108.6, 116.2, 125.9, 127.3, 130.3, 134.1, 136.0, 145.4, 175.2. FAB-MS obsd, 525.2966; calcd, 525.2971 [$(M + H)^+$, $M = C_{30}H_{45}N_2O_2SSi$].

8-[2-(Triisopropylsilyl)ethynyl]-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin (10). Following a reported procedure,[27] a stirred suspension of **10-Ts** (230 mg, 0.438 mmol) and LiOH (53.0 mg, 2.20 mmol) in anhydrous DMF (2 mL) was treated with $HSCH_2COOH$ (77.0 μL, 1.10 mmol) at room temperature. The reaction mixture was stirred for 5 h at 65 °C under argon. Ethyl acetate was added, and the resulting mixture was washed (water, brine), dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1:1)], affording a white solid (118 mg, 72%): mp 110−112 °C; ^{1}H NMR (300 MHz) δ 0.92 (s, 3H), 1.10−1.12 (m, 24H), 2.03 (s, 3H), 2.28 (AB, J = 16.8 Hz, 1H), 2.37 (AB, J = 16.8 Hz, 1H), 2.51 (ABX, ^2J = 14.9 Hz, ^3J = 11.8 Hz, 1H), 2.68 (ABX, ^2J = 14.9 Hz, ^3J = 2.8 Hz, 1H), 3.56−3.59 (m, 1H), 6.01−6.03 (m, 1H), 6.90−6.92 (m, 1H), 9.90−9.93 (br s, 1H); ^{13}C NMR δ 11.6, 18.9, 20.6, 23.0, 27.3, 27.7, 42.0, 54.4, 80.1, 87.2, 103.7, 104.0, 109.4, 121.9, 131.8, 175.6. Anal. Calcd for $C_{23}H_{38}N_2Si$: C, 74.53; H, 10.33; N, 7.56. Found: C, 74.25; H, 10.29; N, 7.49.

Chlorin Formation: Zn(II)-3-Bromo-17,18-dihydro-10-mesityl-18,18-dimethylporphyrin (ZnC−Br^{3}M^{10}). A solution of **4a** (75 mg, 0.20 mmol) and **9** (54 mg, 0.20 mmol) in distilled CH_2Cl_2 (6 mL) was treated with a solution of *p*-TsOH·H_2O (0.19 g, 1.0 mmol, 5 mol equiv relative to the western half **9**) in distilled methanol (2 mL) under argon. The red reaction mixture was stirred at room temperature for 30 min. The reaction mixture was washed (10% $NaHCO_3$, water, brine), dried (Na_2SO_4), and concentrated, yielding a brown solid. The solid was dissolved in CH_3CN (20 mL), and the resulting solution was treated with 2,2,6,6-tetramethylpiperidine (0.340 mL, 2.00 mmol), $Zn(OAc)_2$ (370 mg, 2.00 mmol), and AgOTf (154 mg, 0.600 mmol). The resulting suspension was refluxed for 14 h exposed to air. The crude mixture was concentrated and chromatographed [silica, CH_2Cl_2], affording a green solid (45 mg, 37%): ^{1}H NMR δ 1.85 (s, 6H), 2.01 (s, 6H), 2.60 (s, 3H), 4.50 (s, 2H), 7.23 (s, 2H), 8.37 (d, J = 4.1 Hz, 1H), 8.50 (s, 1H), 8.55 (d, J = 4.4 Hz, 1H), 8.60 (d, J = 4.4 Hz, 1H), 8.68 (s, 1H), 8.77 (s, 1H), 8.88 (d, J = 4.1 Hz, 1H), 9.73 (s, 1H); LD-MS obsd, 598.3; ESI-MS obsd, 598.0720; calcd, 598.0711 ($C_{31}H_{27}BrN_4Zn$); λ_{abs} 408, 614 nm.

Chlorin Vinylation: Zn(II)-17,18-Dihydro-10-mesityl-18,18-dimethyl-3-vinylporphyrin (ZnC-V^{3}M^{10}). Following a procedure for Stille coupling with porphyrins,[28] a mixture of **ZnC-Br^{3}M^{10}** (20 mg, 0.033 mmol), $Bu_3SnCH{=}CH_2$ (20 μL, 0.068 mmol), and $(PPh_3)_2PdCl_2$ (3.0 mg, 0.0042 mmol) was refluxed in THF (2 mL) for 14 h using a Schlenk line. The reaction mixture was concentrated and chromatographed [silica, CH_2Cl_2], affording a blue solid (12 mg, 66%): ^{1}H NMR δ 1.86 (s, 6H), 2.02 (s, 6H), 2.60 (s, 3H), 4.50 (s, 2H), 5.85 (d, J = 10.8 Hz, 1H), 6.47 (d, J = 17.5 Hz, 1H), 7.23 (s, 2H), 8.19 (dd, J = 17.5, 10.8 Hz, 1H), 8.33 (d, J = 4.1 Hz, 1H), 8.50 (d, J = 4.4 Hz, 1H), 8.52 (s, 1H), 8.55 (d, J = 4.4 Hz, 1H), 8.62 (s, 1H), 8.81 (d, J = 4.1 Hz, 1H), 8.83 (s, 1H), 9.68 (s, 1H); LD-MS obsd, 546.7; FAB-MS obsd, 546.1739; calcd, 546.1762 ($C_{33}H_{30}N_4Zn$); λ_{abs} 413 (log ϵ = 5.18), 621 (4.66) nm; λ_{em} = 625 nm.

Chlorin Ethynylation: Zn(II)-17,18-Dihydro-10-mesityl-18,18-dimethyl-3-[2-(triisopropylsilyl)ethynyl]porphyrin (ZnC-E^{3}M^{10}). Following a procedure for Sonogashira coupling with chlorins,[15] a mixture of **ZnC-Br^{3}M^{10}** (18 mg, 0.030 mmol), (triisopropylsilyl)acetylene (14 μL, 0.060 mmol), $Pd_2(dba)_3$ (4.2 mg, 0.0045 mmol), and P(*o*-tol)$_3$ (11 mg, 0.036 mmol) was heated at 60 °C in toluene/triethylamine (5:1, 12 mL) using a Schlenk line. After 7 h, (triisopropylsilyl)acetylene (14 μL, 0.060 mmol), $Pd_2(dba)_3$ (4.2 mg, 0.0045 mmol), and P(*o*-tol)$_3$ (11 mg, 0.036 mmol) were added to the reaction mixture. After 18 h, the reaction mixture was concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (2:1)], affording a green solid (11 mg, 52%): ^{1}H NMR δ 1.38 (m, 18H), 1.40 (m, 3H), 1.85 (s, 6H), 2.01 (s, 6H), 2.60 (s, 3H), 4.51 (s, 2H), 7.22 (s, 2H), 8.36 (d, J = 4.1 Hz, 1H), 8.50−8.54 (m, 2H), 8.60 (d, J = 4.1 Hz, 1H), 8.67 (s, 1H), 8.80−8.85 (m, 2H), 9.88 (s, 1H); LD-MS obsd, 700.5; FAB-MS obsd, 700.2930; calcd, 700.2940 ($C_{42}H_{48}N_4SiZn$); λ_{abs} 416 (log ϵ = 5.14), 627 (4.73) nm; λ_{em} = 630 nm.

Chlorin Acetylation: Zn(II)-13-Acetyl-17,18-dihydro-10-mesityl-18,18-dimethylporphyrin (ZnC-M^{10}A^{13}). The standard procedure entails (1) zinc demetalation, (2) Pd-mediated coupling with tributyl(1-ethoxyvinyl)tin, (3) acidic hydrolysis of the coupled product, and (4) zinc metalation, as described in detail as follows. A solution of **ZnC-M^{10}Br^{13}** (50 mg, 0.083 mmol) in CH_2Cl_2 (1.0 mL) was treated dropwise with TFA (0.13 mL, 1.6 mmol) over 2 min. The solution was stirred at room temperature for 2 h. CH_2Cl_2 was added, and the organic layer was washed (saturated aqueous $NaHCO_3$, water, brine) and then dried (Na_2SO_4). The crude mixture was concentrated and used in the next step. Following a procedure for the replacement of a bromo group with an acetyl group on an aromatic substrate,[29] a mixture of the crude product, tributyl(1-ethoxyvinyl)tin (49 μL, 0.14 mmol), and $(PPh_3)_2PdCl_2$ (10 mg, 0.014 mmol) was refluxed in THF (7 mL) for 20 h using a Schlenk line. The reaction mixture was treated with 10% aqueous HCl (4 mL) at room temperature for 2 h. CH_2Cl_2 was added, and the organic layer was separated. The organic layer was washed (saturated aqueous $NaHCO_3$, water, brine), dried (Na_2SO_4), and concentrated. The resulting residue was dissolved in $CHCl_3$ (5 mL). The solution was treated with $Zn(OAc)_2$·$2H_2O$ (320 mg, 1.45 mmol) in MeOH (2 mL), and the reaction mixture was stirred

overnight at room temperature. Concentration followed by chromatography of the crude mixture [silica, CH_2Cl_2/hexanes (1:1)] gave a green solid (25 mg, 53%): ^{1}H NMR δ 1.82 (s, 6H), 2.00 (s, 6H), 2.60 (s, 3H), 2.72 (s, 3H), 4.47 (s, 2H), 7.20 (s, 2H), 8.30 (d, J = 4.4 Hz, 1H), 8.48 (s, 1H), 8.68 (d, J = 4.4 Hz, 2H), 8.81 (s, 1H), 8.96 (d, J = 4.4 Hz, 1H), 9.38 (s, 1H), 9.55 (s, 1H); LD-MS obsd, 560.7; ESI-MS obsd, 562.1700; calcd, 562.1711 ($C_{33}H_{30}N_4OZn$); λ_{abs} 418 (log ϵ = 5.17), 632 (4.84) nm; λ_{em} = 636 nm.

Acknowledgment. This research work was supported by the NIH (GM36238). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at North Carolina State University. Partial funding for the facility was obtained from the North Carolina Biotechnology Center and the National Science Foundation.

Supporting Information Available: Experimental procedures; molar absorption coefficient determination method and spectral graph; fluorescence yield determination method; and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060208O