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Studies in Chlorin Chemistry. 3. A Practical Synthesis of C,D-Ring Symmetric Chlorins of Potential Utility in Photodynamic Therapy

William G. O'Neal, William P. Roberts, Indranath Ghosh, Hui Wang, and Peter A. Jacobi*

Burke Chemical Laboratory, Dartmouth College, Hanover, New Hampshire 03755

peter.a.jacobi@dartmouth.edu

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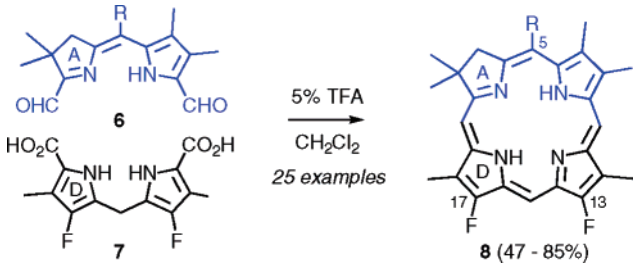

C,D-ring symmetric chlorins **8** were prepared in 47−85% yield, on scales up to several hundred milligrams, by condensation of appropriately substituted bis-formyldihydrodipyrrins **6** and dipyrromethane bis-carboxylic acids **7** in 5% TFA/CH_2Cl_2 (25 examples). Target chlorins were chosen to systematically probe the effect of lipophilic and hydrophilic substituents on tissue partitioning and cellular membrane penetration in photodynamic therapy (PDT).

Introduction

The chlorins are a class of 18π-electron aromatic tetrapyrroles formally derived from porphyrins by saturation of a peripheral double bond (cf. ring A, Figure 1). Chlorophyll a (**1**, R = phytyl) is the most ubiquitous example, serving as a light-harvesting chromophore in photosynthetic plants, algae, and cyanobacteria (certain bacteriochlorophylls perform a similar function in phototrophic bacteria).[1] However, a number of lesser known chlorins also play important biological roles. Cyclopheophorbide (**2**) and related species are thought to inhibit damaging oxidative processes in certain marine species, including *Darwinella oxeata* (a sponge), the short-necked clam *Ruditapes philippinarum*, and the scallop *Patinopecten yessoensis*.[2] Also, the structurally unique chlorin bonellin (**3**) is a hormone responsible for sexual differentiation in the marine worm *Bonella viridis*.[3] Finally, in addition to their natural functions, synthetically derived chlorins have attracted significant attention in both medical and materials sciences. Due to their favorable photophysical properties, chlorins show promise in tumor photodynamic therapy (PDT), a technique that employs photostimulated production of singlet oxygen to selectively eradicate malignant tissue.[4] In a relatively new area of exploration, materials engineers have studied this ring system as a chromophore in artificial photosynthesis.[5]

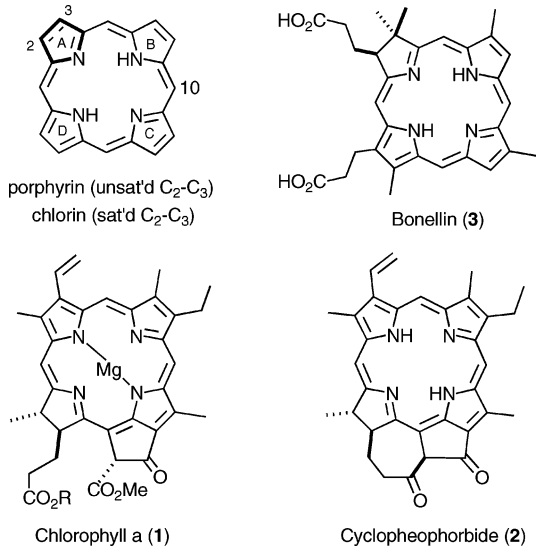

FIGURE 1. Some naturally occurring chlorins.

(1) Montforts, F.-P.; Glasenapp-Breiling, M. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Eds.; Springer: Wien, New York, 2002; Vol. 84, pp 1−51.

(2) (a) Karuso, P.; Berguquist, P. R.; Buckleton, J. S.; Cambie, R. C.; Clark, G. R.; Rickard, C. E. F. *Tetrahedron Lett.* **1986**, *27*, 2177−2178. (b) Watanabe, N.; Yamamoto, K.; Ihshikawa, H.; Yagi, A. *J. Nat. Prod.* **1993**, *56*, 305−317.

(3) Agius, L.; Ballantine, J. A.; Ferrito, V.; Jaccarini, V.; Murray-Rust, P.; Pelter, A.; Psaila, A. F.; Schembri, P. J. *Pure Appl. Chem.* **1979**, *51*, 1847.

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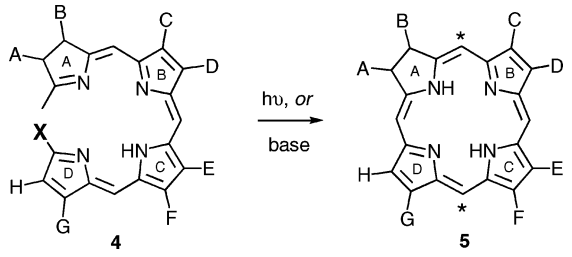
SCHEME 1. Battersby−Montforts Synthesis of Chlorins

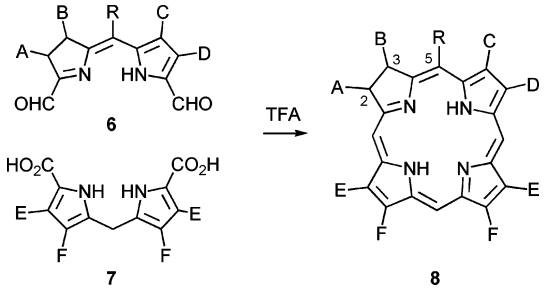


Most de novo syntheses of chlorins are modeled on the methodology of Battersby[6a] and Montforts,[6b] involving either photochemical or alkali-induced ring closure of properly substituted linear tetrapyrroles **4** (Scheme 1; X = OMe, Br, etc.).[7] Tetrapyrroles **4** are derived from simpler ring systems employing techniques such as sulfide contraction,[6b,8] thio-Wittig reaction,[9] and reductive cyclization of pyrrole-substituted nitroketones.[10] While elegant in concept, the cyclization of **4** to **5** can be problematic and is typically carried out on small scales, employing metal templates, and affording **5** in modest to good yields.[6,8]

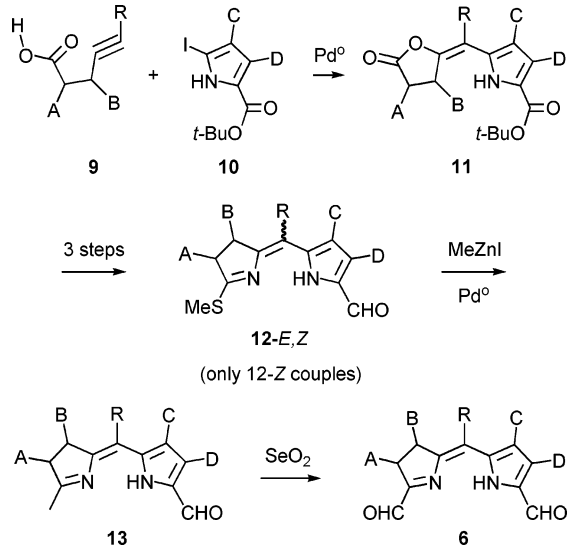
In 2001, we described in communication form a new synthesis of chlorins based upon a variant of the MacDonald porphyrin synthesis[11] and involving condensation of bis-formyldihydrodipyrrins **6** with symmetrical dipyrromethanes **7** (Scheme 2).[12] Simple dissolution of **6** and **7** in neat TFA was found to afford chlorins **8** in 35−45% yield with no special precautions against air or light and without metal complexation. A key feature of this approach is that the chlorin chromophore is obtained directly in the proper oxidation state and with no need for subsequent isomerization. We believe this characteristic accounts in large part for the simplicity of the experimental conditions.

Since dipyrromethanes of type **7** are readily available,[13] a practical synthesis of A,B-ring dialdehydes **6** is an essential component of this 2+2 approach. Our original route to bis-

SCHEME 2. Chlorin Synthesis by the 2+2 Method



SCHEME 3. First-Generation Synthesis of A,B-Ring Precursors 6



formyldihydrodipyrrins **6** built upon the ready availability of enelactones **11**, prepared in 70−96% yield from alkyne acids **9** and iodopyrroles **10** (Scheme 3).[12] Lactones **11** were then converted to *E,Z*-mixtures of thioimidates **12** by a three-step sequence consisting of (1) aminolysis, (2) thiolactam formation, and (3) concomitant decarboxylative formylation/S-methylation employing trimethylorthoformate (TMOF) in neat TFA.[9b] We intended to convert both isomers of **12** to the corresponding dihydrodipyrrins **13** by transition-metal-catalyzed methylation. In practice, this transformation worked well with *Z*-thioimidates **12**-*Z* employing the reagent system Pd(0)/MeZnI. The resulting *Z*-dihydrodipyrrins **13**-*Z* were then oxidized in good yield to the desired diformyl derivatives **6**. Surprisingly, however, the corresponding *E*-thioimidates **12**-*E* were unreactive toward methylation using Pd(0)/MeZnI and most other commonly employed cross-coupling techniques (trace quantities of **13** were produced with Ni(II) catalysts). Eventually, this difference was traced to a selective activating effect of Zn, which serves to polarize the thioimidate C−S bond in **12**-*Z* by chelation.[14] This reactivity pattern had far reaching consequences because the ratio of **12**-*Z*:**12**-*E* decreased dramatically with increasing size

(4) Bonnett, R. *Chemical Aspects of Photodynamic Therapy*; Gordon and Breach: Amsterdam, 2000.

(5) (a) Wasielewski, M. R.; Wiederrecht, G. P.; Svec, W. A.; Niemczyk, M. P. *Sol. Energy Mater. Sol. Cells* **1995**, *38*, 127−134. (b) Tamiaki, H.; Yagai, S. *J. Photosci.* **2002**, *9*, 66−69.

(6) (a) Battersby, A. R.; Dutton, C. J.; Fookes C. J. R.; Turner, S. P. D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1557−1567. (b) Montforts, F.-P. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 778−779. (c) Montforts, F.-P.; Gerlach, B.; Höper, F. *Chem. Rev.* **1994**, *94*, 327−347. (d) Montforts, F.-P.; Glasenapp-Breiling, M. *Prog. Heterocycl. Chem.* **1998**, *10*, 1−24.

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(8) Montforts, F.-P.; Schwartz, U. M. *Liebigs Ann. Chem.* **1991**, 609.

(9) (a) Battersby, A. R.; Turner, S. P. D.; Block, M. H.; Sheng, Z.-C.; Zimmerman, S. C. *J Chem. Soc. Perkin Trans. 1* **1988**, 1577. (b) Arnott, D. M.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 265.

(10) (a) Harrison, P. J.; Sheng, Z.-C. Fookes, C. J. R.; Battersby, A. R. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1667. (b) Battersby, A. R.; Dutton, C. J.; Fookes, C. J. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1569. (c) Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160. (d) Balasubramanian, T.; Strachan, J.-P.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7919. (e) Taniguchi, M.; Ra, D.; Mo, G.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2001**, *66*, 7342. (f) Ptaszek, M.; Bhaumik, J.; Kim, H.-J.; Taniguchi, M.; Lindsey, J. S. *Org. Process Res. Dev.* **2005**, *9*, 651−659.

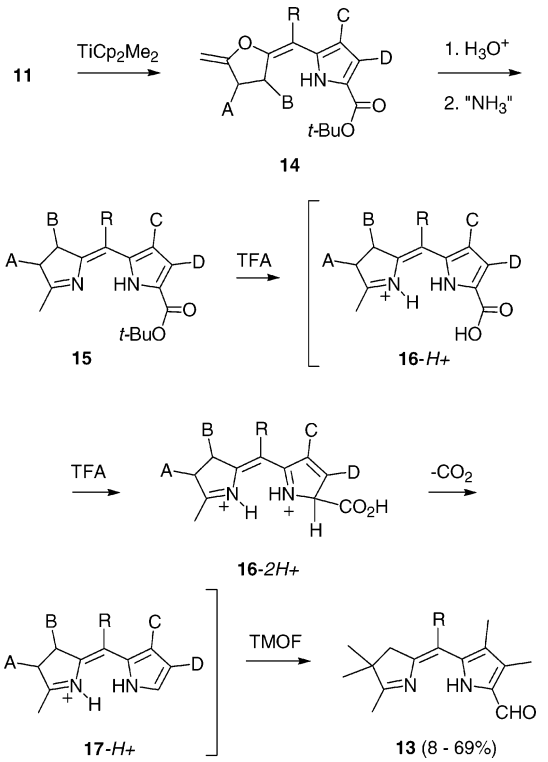
(11) Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384.

(12) Jacobi, P. A.; Lanz, S.; Ghosh, I.; Leung, S. H.; Lower, F.; Pippin, D. *Org. Lett.* **2001**, *3*, 831.

(13) (a) For an overview, see: Smith, K. M. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 1, p 4. (b) Jackson A. H.; Pandey R. K.; Smith K. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 299−305. (c) Fischer, H.; Orth, H. *Die Chemie des Pyrrols*; Akademische Verlagsgesellschaft: Leipzig, 1934; Vol. 1, p 333. (d) Mironov, A. F.; Ovsepyan, T. R.; Evstigneeva, R. P.; Preobrazenskii, N. A. *Zh. Obshch. Khim.* **1965**, *35*, 324. (e) Freeman B. A.; Smith, K. M. *Synth. Commun.* **1999**, *29*, 1843−1855.

(14) Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, *67*, 9304.

SCHEME 4. Synthesis of 13 by Method A (Conditions *i*)



of R (i.e., H > Me ≫ Ph), making it impractical to incorporate larger *meso*-substituents (C_5 in **8**). Because of this complication, we were able to prepare only a few chlorin precursors **6** by this method.

The properties of *meso*-substituents R can significantly influence tissue partitioning of chlorins in PDT,[15] but introduction of these groups by existing methodology has typically been challenging. We have devoted much effort since our original paper to developing improved synthetic routes to A,B-ring dialdehydes **6**, incorporating diverse substituents A−D and in particular *meso*-groups R. Because dihydrodipyrrins **13** had proven to be useful precursors to dialdehydes **6**, we focused primarily on the conversion of lactones **11** to intermediates **13**. In this paper, we describe two new syntheses of these materials, each of which is best suited for the incorporation of particular *meso*-substituents (Section I). In addition, we report greatly improved conditions for the oxidation of **13** to **6** (Section II) and the condensation of **6** and **7** to afford C,D-ring symmetric chlorins **8** (Section III).

Results and Discussion

I. Synthesis of Formyldihydrodipyrrins 13. Summary. We have developed two new syntheses of **13** from **11**: Method A involves conversion of lactones **11** to dihydrodipyrrins **15** (Scheme 4), which are transformed to **13** by decarboxylative formylation using one of two procedures (conditions *i* or *ii*). Method B is based on the decarboxylative formylation of lactones **11**. Subsequent conversion to **13** is accomplished by lactone ring opening, followed by aminolysis of the intermediate diketones **24** (Scheme 9). Method B is most useful for the synthesis of dihydrodipyrrins **13** in which R = small- to medium-sized alkyl group. Other derivatives of **13** are best prepared by method A, utilizing the appropriate decarboxylative formylation procedure (conditions *i* for R = H, conditions *ii* for R = Ph or alkyl).

Method A. After our initial communication,[12] we found that lactones **11** undergo clean reaction with the Petasis reagent ($TiCp_2Me_2$), affording high yields of enol ethers **14** incorporating a wide range of *meso*-substituents R (Scheme 4).[16] This discovery provided the basis for a very streamlined synthesis of dihydrodipyrrins **15**, which were formed in "one pot" by hydrolysis of **14** to the corresponding diketones, followed by condensation with an appropriate ammonia source. Importantly, the Petasis reagent was compatible with commonly occurring functional groups such as propionate esters (D = $CH_2CH_2CO_2$-Me), as well as regioisomeric substitution patterns in ring A (A,B = di-Me, di-H).

Conditions *i*. With esters **15** in hand, we first attempted decarboxylative formylation under standard conditions.[17] Unfortunately, pretreatment of **15** with TFA followed shortly thereafter with trimethylorthoformate (TMOF) proved to be highly capricious, affording **13** in yields ranging from 8% to 69%, depending partly upon the nature of *meso*-substituents R. Only with R = H were we able to obtain reproducible yields in the range of ∼70%. These difficulties were not entirely unexpected since Battersby et al. experienced similar problems with a closely related ring system during the course of a synthesis of bonellin (**3**).[10b]

It is well-known that pyrroles bearing electron-withdrawing groups exhibit decreased reactivity toward electrophilic substitution and decarboxylation.[18] As illustrated in Scheme 4, we suspect that rapid protonation of the pyrroline ring under the reaction conditions leads to intermediates such as **16**-*H*+, which are analogous to monopyrroles bearing electron-withdrawing groups. Furthermore, decarboxylation via a dication of type **16**-*2H*+ would be highly unlikely. Thus, the poor behavior of dihydrodipyrrins under conditions *i* may be due in part to the inhibition of decarboxylation and/or formylation (i.e., **16**-*H*+ → **17**-*H*+ → **13**) by competitive protonation at the basic pyrroline ring nitrogen in **16**.

We explored many approaches for improving the conversion of **15** to **13**, initially employing *meso*-phenyl substrate **15a** in combination with variants of conditions *i* (Scheme 5). As above, these experiments gave erratic yields of the desired formylated compound **13a**, accompanied by significant decomposition. In most cases, the only identifiable byproduct was the trifluoromethyl ketone **18a** (13−18%). Battersby et al. also observed trifluoromethyl ketone formation in their studies cited above,[10b] but the origin of this compound was not investigated.

Interestingly, we could find no trace of the presumed intermediates **16a** and **17a** in the crude reaction mixtures, and it remains an open question whether formylation precedes or follows decarboxylation. In the case of ketone **18a**, two observations provided insight into the question of origin: First, **15a** gave essentially identical yields of **18a** upon treatment with TFA alone, seemingly eliminating any mechanistic role for

(15) Pandey, R. K.; Zheng G. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 6, pp 157−230.

(16) O'Neal, W. G.; Roberts, W. P.; Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2005**, *70*, 7243−7251.

(17) Clezy, P. S.; Fookes, C. J. R.; Liepa, A. J. *Aust. J. Chem.* **1972**, *25*, 1979−1990.

(18) Jackson, A. H. In *Pyrroles*; Jones, R. A., Ed.; The Chemistry of Heterocyclic Compounds; John Wiley & Sons: New York, 1990; Vol. 48, Part 1, pp 301, 315.

SCHEME 5. Formation of Side Product 18a

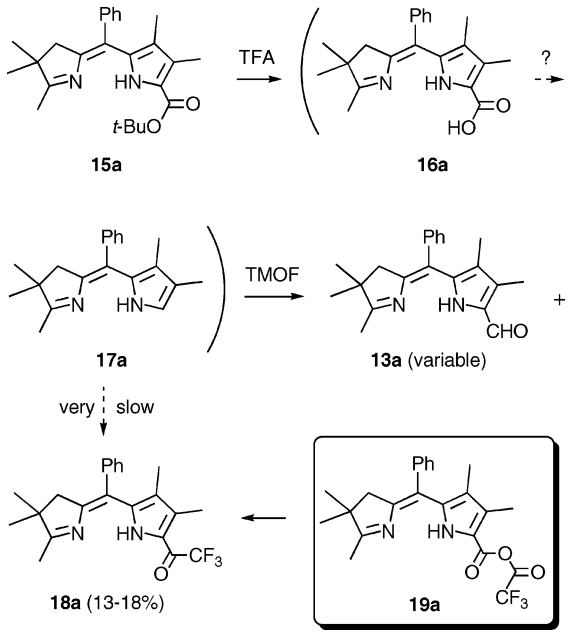
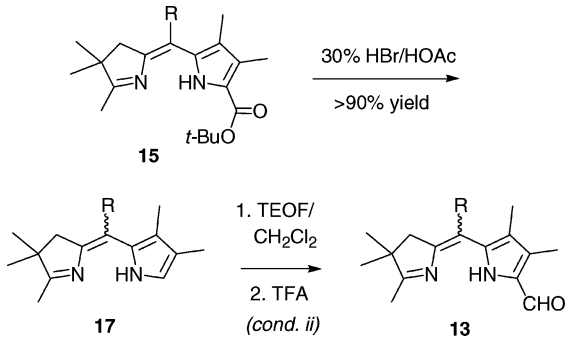


TABLE 1. Isolated Yields of 13 Prepared by Method A (Conditions *ii*)

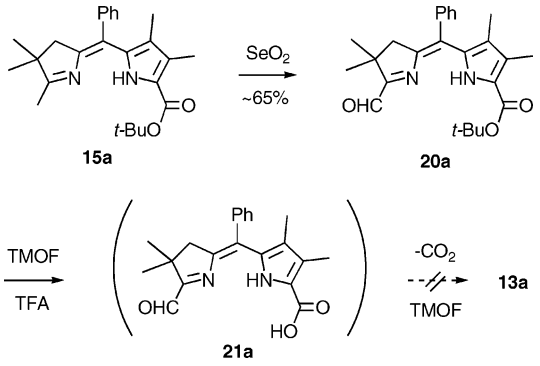


15	R	overall yield of 13-*Z*,*E*
a	Ph	*Z* (64%), *E* (9%)
b	Me	25% combined
c	H	<15% combined
d	C_5H_{11}	*Z* only (57%)
e	$C_{10}H_{21}$	*Z* only (61%)

TMOF in the formation of this compound. Second, **17a** prepared independently (Table 1) reacted only very slowly with TFA under conditions that led to rapid conversion of **15a** to **18a**. Together, these results suggest that a likely intermediate in the conversion of **15a** to **18a** is the mixed anhydride **19a**, which might be transformed to **18a** in either inter- or intramolecular fashion. In any event, it was clear that decarboxylation of **15a** with TFA would inevitably lead to substantial loss of starting material to this side reaction.

In an effort to circumvent this problem, we briefly explored the possibility of reversing the order of decarboxylative formylation and oxidation (Scheme 6). Our thought was that the electron-withdrawing formyl group in **20a** would decrease the basicity of the pyrroline ring, thereby facilitating protonation of the pyrrole ring. Although we obtained reasonable yields in the conversion of **15a** to **20a** (~65%), all attempts at decarboxylative formylation produced only the carboxylic acid **21a** along with decomposition products. Decarboxylation also failed with very strong acid combinations such as HBr/HOAc.[19]

SCHEME 6. Reversed Order of Oxidation and Decarboxylative Formylation



Conditions *ii*. In contrast to the reaction with TFA, methylpyrroline **15a** underwent clean decarboxylation with HBr/HOAc, affording a 96% yield of the α-free pyrrole **17a** as a mixture of *Z*- and *E*-isomers (Table 1). With decarboxylation no longer an issue, we examined a number of milder reagents for effecting the desired formylation of **17a** to **13a**. Of these, only the Vilsmeier reagent ($POCl_3$/DMF)[20] exhibited modest promise, affording a 43% yield of **13a** (*Z*-isomer only). Employing TMOF/TFA as a formylating agent, the yields of **13a** were actually lower than those obtained by direct decarboxylative formylation of **15a** to **13a** (Scheme 5). This was mainly because **17a** was unstable to prolonged exposure to TFA. In experiments designed to minimize this problem, we found that **13a**-*Z*,*E* was obtained in 73% yield when a solution of crude **17a** in CH_2Cl_2/triethylorthoformate (TEOF) was added to precooled TFA (*Conditions ii*). These conditions provided reproducible results and were also satisfactory for preparing formyl derivatives **15d** (R = C_5H_{11}, 57%) and **15e** (R = $C_{10}H_{21}$, 61%). However, for substrates bearing small *meso*-substituents even these conditions proved to be too harsh (**15b,c**).

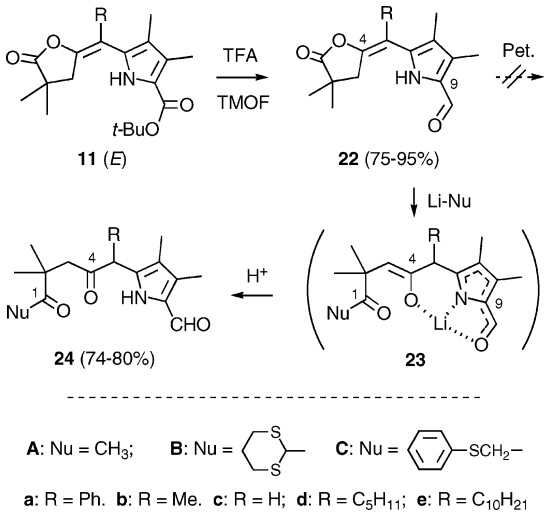
Method B. In parallel studies, we were exploring a second strategy for synthesizing **13** that provided additional flexibility. Based on the mechanistic considerations described above, we expected that enelactones **11** would be better substrates for decarboxylative formylation since these compounds do not contain a pyrroline nitrogen to compete for protonation (Scheme 7). Satisfyingly, **11** routinely afforded 75−95% yields of formyl derivatives **22** upon treatment with TEOF/TFA (*E*-isomers only). We further hoped that **22** might undergo a selective Petasis reaction at the lactone carbonyl group, as previously observed with ester lactones **11** (cf. Scheme 4). However, all attempts at effecting this conversion produced complex mixtures.

We had previously examined the ring opening of *ester*-lactones **11** with alkyllithium species Li−Nu, but we were unable to prevent multiple addition of sterically unhindered nucleophiles such MeLi.[16] Nevertheless, we attempted the same transformation with formyl lactones **22** and were pleased to find that these species underwent selective ring opening with a variety of nucleophiles Li-Nu (**22** → **23** → **24**). Even Li-Me (Li-**A**), possessing little if any steric hindrance, showed excellent chemoselectivity, affording 74−80% yields of **24aA**−**eA** upon slow addition at −78 °C. At present, we have no rigorous explanation for this selectivity, although it is likely that the acidic

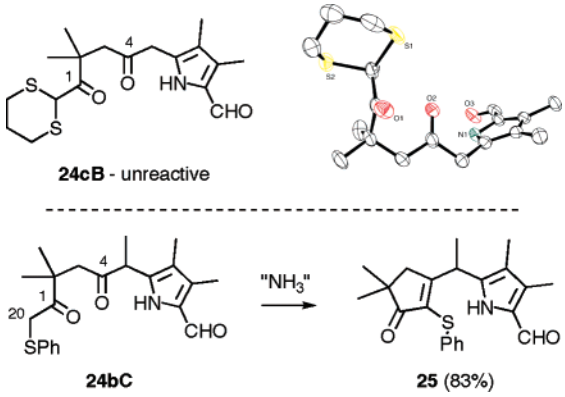
(19) Neya, S.; Ohyama, K.; Funasaki, N. *Tetrahedron Lett.* **1997**, *38*, 4113−4116.

(20) Silverstein, R. M.; Ryskiewicz, E. E.; Willard, C. *Organic Syntheses*; Wiley & Sons: New York, 1963; Collect. Vol. 4, p 831.

SCHEME 7. Method B: Ring Opening of Lactones 22 by Various Nucleophiles



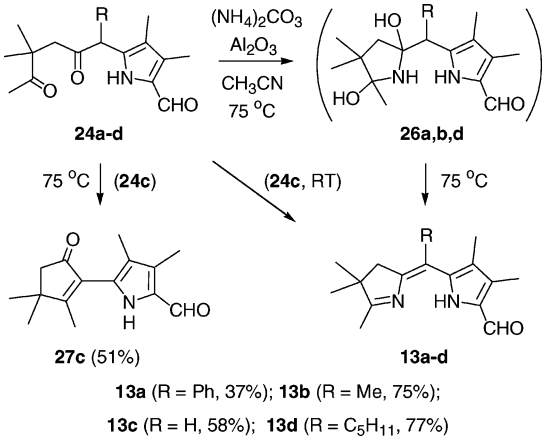
SCHEME 8. Method B: Failed Pyrroline Ring Closures of "Oxidized Diketones" 24



pyrrole N−H group plays a role both in protecting the formyl group and in preventing multiple addition (two equivalents of Li−Nu are required for complete reaction). As a working hypothesis, we suggest that the C-4 ketone deriving from **22** is stabilized in a chelated structure of type **23**, maintaining the enolate tautomer until acid workup.

Of particular interest, reaction of **22c** with lithiodithiane (Li-**B**) cleanly produced the protected glyoxaldehyde derivative **24cB** (74%), while (phenylthio)methyllithium (Li-**C**) gave a 78% yield of ring-opened species **24bC**. Both **24cB** and **24bC** held out the possibility of directly attaining the desired oxidation state of **6** after pyrroline formation.[21] Unfortunately, we were unable to effect the desired ring closure of diketones **24cB** or **24bC** despite intensive efforts over a period of many months (Scheme 8). Dithiane **24cB** was typically recovered intact following aminolysis, most likely due to steric hindrance at the C-1 carbonyl group (X-ray analysis subsequently confirmed this suspicion; cf. Scheme 8 and Supporting Information). In contrast, thioanisole derivative **24bC** underwent rapid aldol condensation to cyclopentenone **25** under mildly basic conditions (83%), reflecting the increased acidity of the C-20 methylene protons (chlorin numbering).

SCHEME 9. Method B: Pyrroline Ring Closure of Diketones 24



Even simple diketone derivatives **24a**−**e** presented a number of hurdles to cyclization, partly because of the presence of the very sensitive formyl group (Scheme 9). Formylpyrroles as a class are generally unstable to acids,[22] a property that was especially pronounced with **24a**−**e**. These substrates underwent rapid decomposition with even weakly acidic ammonium salts. In contrast, basic or neutral sources of ammonia cleanly afforded mixtures of hemiaminal intermediates **26**, but these species were resistant to dehydration and easily reverted to diketones **24**. Working with substrate **24b** (R = Me), we eventually found that the combination of $(NH_4)_2CO_3$/basic Al_2O_3 in CH_3CN at 75 °C gave ~75% yields of the corresponding dihydrodipyrrin **13b**, a significant improvement over method A (cf. Table 1). In analogous fashion, diketone **24d** (R = *n*-pentyl) afforded **13d** in much improved yield (77%). However, the relatively unhindered substrate **24c** (R = H) required special care. This material was susceptible to competing aldol condensation and upon aminolysis at 75 °C gave predominantly the aldol product **27c** (51%) along with only 18% of dihydrodipyrrin **13c**. After further experimentation, we found that the aldol pathway was greatly reduced by effecting aminolysis at rt for 24 h before briefly heating to 75 °C, affording **13c** in 58% yield along with 17% of **27c**. Finally, we were surprised to find that the *meso*-Ph diketone **24a** underwent significant decomposition upon attempted aminolysis, since in related examples the Ph-substituent appeared to have a stabilizing influence.[16]

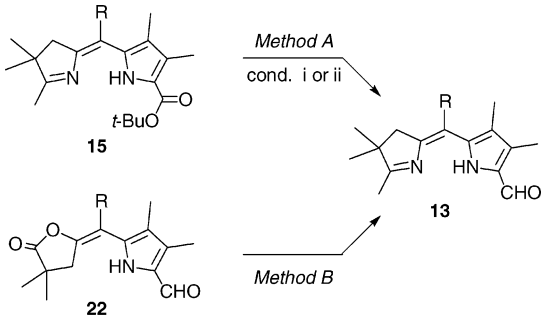
Summary. Because of the unpredictable effect of *meso*-substituents R on substrate reactivity/stability, a truly general synthesis of formyl derivatives **13** remains elusive. However, this investigation culminated in two complementary routes to these key intermediates that together are far more efficient than our original approach.[12] The utility of each route is summarized in Scheme 10. Three general conclusions can be drawn: (1) Synthesis of meso-H derivative **13c** was accomplished in best overall yield using method A, conditions *i*. (2) Derivatives of **13** bearing larger *meso*-substituents (R = Ph or $C_{10}H_{21}$) were best prepared using method A, conditions *ii*. (3) Derivatives of **13** bearing small- to medium-sized *meso*-alkyl groups (R = Me or C_5H_{11}) were best prepared using method B.

II. Oxidation of Pyrrolines 13 to Bis-formyldihydrodipyrrins 6. In our original studies, we carried out the conversion of

(21) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 333−340. (b) Bakuzis P.; Bakuzis M. L. F.; Fortes C. C.; Santos R. *J. Org. Chem.* **1976**, *41*, 2769−2770.

(22) Jackson, A. H. In *Pyrroles*; Jones R. A., Ed.; The Chemistry of Heterocyclic Compounds; John Wiley & Sons: New York, 1990; Vol. 48, Part 1. p 316

SCHEME 10. Summary of Two New Syntheses of 13[a]



13a (R = Ph, 73%).[b] **13b** (R = Me, 75%).[c] **13c** (R = H, 60%).[a]
13d (R = C_5H_{11}, 57%).[c] **13e** (R = $C_{10}H_{21}$, 61%).[b]

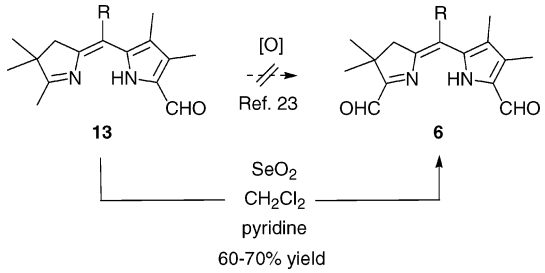
[a] Key: (a) conditions *i*: (1) neat TFA, (2) TMOF, 25 °C; (b) conditions *ii*: (1) HBr/HOAc, (2) TEOF/CH_2Cl_2, (3) TFA, 0 °C; (c) method B: (1) 2 equiv of MeLi, (2) $(NH_4)_2CO_3/CH_3CN$, 75 °C.

formyldihydrodipyrrins **13a**−**c** to dialdehydes **6a**−**c** by oxidation with selenium dioxide (cf. Scheme 3).[12] While this procedure generally gave satisfactory yields of **6a**−**c**, the final products were invariably contaminated with selenium metal that was very difficult to separate. Among other consequences, this made obtaining accurate analytical data difficult and no doubt also impacted subsequent steps. We therefore spent considerable time exploring other means of accomplishing the desired oxidation, eventually resorting to a simple modification of the original procedure. A brief account of our findings is presented here.

The literature contains many examples of related oxidations employing a wide variety of reagents. Of these, we screened 15−20 procedures that appeared to offer the most promise (see ref 23 for a complete listing).[23−25] Generally speaking, these fell into three categories: (1) direct oxidation using powerful reagents of the Cr(VI), Co(II), Cu(II), and Pb(IV) families;[24] (2) oxidation initiated by bis-halogenation (NCS, NBS, $SOCl_2$, etc.) followed by hydrolysis;[25] and (3) methyl anion generation followed by in situ capture with oxidants including diselenides, disulfides, NBS, etc.[25b] In several cases, we examined both stoichiometric and catalytic variants of the literature procedures. The results were uniformly discouraging, with some reagents exhibiting little reactivity and others causing rapid decomposition (Scheme 11).

Ultimately, we returned to the SeO_2 procedure, exploring the effect of reagent purity, additives, and co-oxidants. Freshly sublimed SeO_2 provided no apparent advantage,[26] nor did so-

SCHEME 11. Oxidation of Dihydrodipyrrin 13



a: R = Ph. **b**: R = Me. **c**: R = H; **d**: R = C_5H_{11}; **e**: R = $C_{10}H_{21}$

called "wet" solvents described in the literature as having beneficial effects (in our case even trace amounts of water accelerated decomposition).[27] We did, however, observe very clean reactions using dry CH_2Cl_2 as solvent with 1−2 equiv of pyridine as additive (the rate-accelerating effect of pyridine is well documented).[27] Employing **13b** (R = Me) as a substrate, we consistently obtained yields of **6b** in the range of 65−70% following this protocol. While these results were promising, ICP-MS analysis indicated that the product was still contaminated with up to 0.61 wt % (2 mol %) of selenium. While these experiments were underway, we became aware of a report describing the removal of colloidal selenium by brief heating in DMF. This produces a black metallic allotrope that can be easily removed by filtration.[28] When this step was applied to the crude oxidation product prepared as above, the resultant precipitate was easily removed, the overall yield remained essentially the same, and **6b** was obtained in a high state of purity. In analogous fashion, diformyl derivatives **6a**−**e** were prepared in 60−70% yield without further optimization.

III. Chlorin Formation. The experiments described above provided a convenient and versatile synthesis of A,B-ring dialdehydes **6**. To further enhance the practicality of the 2+2 methodology, we next endeavored to optimize the final condensation of precursors **6** and **7** to afford C,D-ring symmetric chlorins. Our original conditions for this reaction called for dissolution of **6** and **7** in neat TFA, which was deemed necessary to initiate decarboxylation of **7** to the presumably more reactive α-unsubstituted derivatives (Scheme 12).[12] This protocol afforded 35−45% yields of a limited number of chlorins **8**. With greater quantities of **6** available, we began more detailed studies, which revealed that our assumption pertaining to decarboxylation was not valid.

We first examined the stability of representative substrates **6b** and **7b** in neat TFA, now aware of the potential side reactions that this solvent might induce (Scheme 12). Under these conditions, dihydrodipyrrin **6b** decomposed within minutes at ambient temperature. Dipyrromethane **7b** afforded moderate yields of the bis-decarboxylated product **29b** along with significant quantities of trifluoroacylated derivative **28b**,[29] mirroring our experience with dihydrodipyrrins **15** outlined in Scheme 5. When reacted with **6b** under otherwise identical conditions, isolated and purified dipyrromethane **29b** (for which we expected trifluoroacylation to be minimized; cf. Scheme 5) gave *lower* yields of chlorin **8bb** than did dicarboxylic acid **7b** (33% vs 42%). To explore this result further, we screened

(23) (a) Reagents that were screened include: PCC, PDC, CAN, DDQ, MnO_2, CrO_3, $Pb(OAc)_4$, $Co(OAc)_2$, CuI/TBHP, $CuCl_2$/TBHP, Pd/TBHP, $Pd(OAc)_2$/ PhI$(OAc)_2$, $(SePh)_2$/PhIO_2, *t*-BuI/$FeCl_2$/DMSO, $CuCl_2$/LiCl, NCS/NBS, SO_2Cl_2. Leading references are included for certain reagents.

(24) (a) Co(II): Salvador, J. A. R.; Clark J. H. *Chem. Commun.* **2001**, 33−34. (b) Cu(I): Salvador, J. A. R.; Melo, M. L. Sá e; Neves, A. S. C. *Tetrahedron Lett.* **1997**, *38*, 119−122. (c) Cu(I): Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 407−414. (d) Cu(II): Rothenburg, G.; Feldberg, L.; Wiener, H.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2429−2434. (e) Pd/TBHP: Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727−2730. (f) Pd$(OAc)_2$/PhI$(OAc)_2$: Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301. (g) $(SePh)_2$/PhIO_2: Barton, D. H. R.; Crich, D. *Tetrahedron* **1985**, *41*, 4359. (h) *t*-BuI/$FeCl_2$/DMSO: Vismara, E.; Fontana F.; Minisci, F. *Gazz. Chim. Ital.* **1987**, *117*, 135−136.

(25) (a) $CuCl_2$/LiCl: Nobrega, J. A.; Gonçalves, S. M. C.; Peppe, C. *Synth. Commun.* **2002**, *32*, 3711−3717. (b) NCS/NBS/SO_2Cl_2: Tehrani, K. A.; Borremans, D.; De Kimpe, N. *Tetrahedron* **1999**, *55*, 4133−4152.

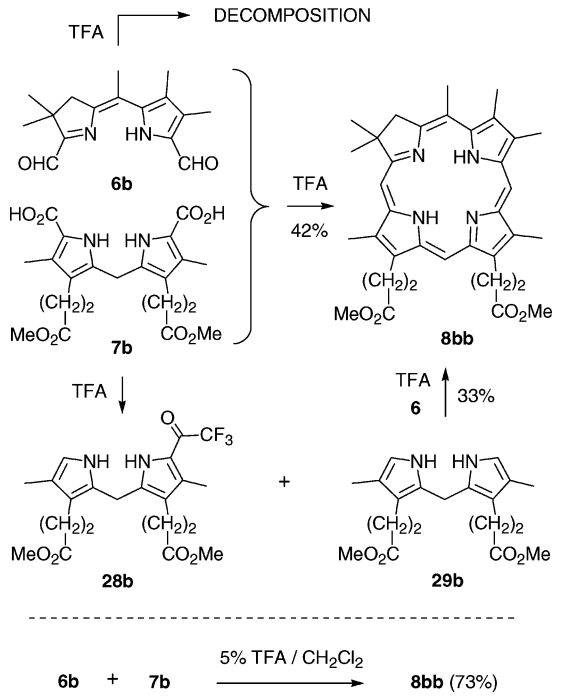
(26) Kaplan, H. *J. Am. Chem. Soc.* **1941**, *63*, 2654−2655.

(27) Trachtenberg, E. N. In *Oxidation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1969; pp 19−187.

(28) Milstein, S. R.; Coats, E. A. *Aldrichim. Acta* **1978**, *11*, 10.

(29) Xie, H.; Lee, D. A.; Wallace, D. M.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1996**, *61*, 8508−8517.

SCHEME 12. Optimization of Chlorin Formation by the 2+2 Method



numerous solvent and acid combinations with **29b**, including such Lewis acids as $TiCl_4$, BF_3, and $Sc(OTf)_3$ that have been successfully employed in similar condensations.[30] In the present case, these catalysts caused significant decomposition, and little or no chlorin **8bb** could be detected by TLC and/or UV analysis. More promising results were obtained with Bronsted acids, especially TsOH in $MeOH/CH_2Cl_2$.[31] Unfortunately, these conditions proved unreliable for larger scale syntheses of **8bb**. On the basis of these experiments, it appeared that decarboxylation was at the least not a prerequisite to chlorin formation, raising the possibility that dicarboxylic acid **7b** might be a superior condensation partner under more refined conditions.

Working from this premise, we eventually identified the combination of 5% TFA in CH_2Cl_2 as a particularly effective medium for condensation,[32] affording chlorin **8bb** in a remarkably high state of purity after washing with either 3M NH_4OH or saturated $KHCO_3$. Final purification by chromatography consistently afforded 65−75% yields of **8bb** on scales up to several hundred milligrams (typically, however, reactions were run on 25−50 mg scale for convenience). In analogous fashion, we prepared chlorin derivatives **8aa**−**ee** bearing lipophilic substituents ranging up to *n*-decyl at C_5, along with aliphatic esters of chain length 2−10 at C_{13} and C_{17} (Table 2; the potential usefulness of a carboxylate functionality is described below). Yields employing the optimized conditions ranged from 47 to 85% and are shown in bold. Where applicable, yields employing other conditions are also included.

(30) Geier, G. R., III; Callinan, J. B.; Rao, P. D.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2001**, *5*, 810−823.

(31) (a) Burns, D. H.; Li Y. H.; Shi, D. C.; Caldwell, T. M. *J. Org. Chem.* **2002**, *67*, 4536−4546. (b) Nguyen, L. T.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1996**, *61*, 998−1003.

(32) For use of TFA/CH_2Cl_2 in a related context, see: (a) Lash, T. D. *J. Porphyrins Phthalocyanines* **1997**, *1*, 29−44. (b) Lash, T. D. *Chem. Eur. J.* **1996**, *2*, 1197−1200.

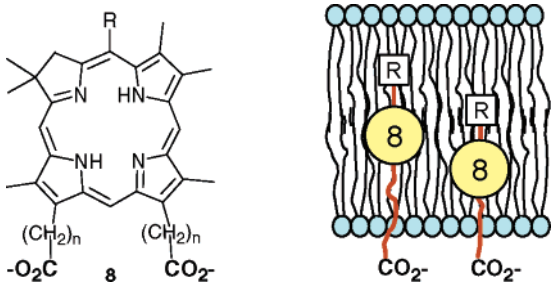


FIGURE 2. Schematic representation of the effect of tether length $-(CH_2)_n-$ on cellular membrane penetration. The hydrophilic carboxylate groups "anchor" at the aqueous interface.

Conclusion

An important component of these studies was preparation of C,D-ring symmetric chlorins **8** bearing a substitution pattern that could be useful in probing structure−activity relationships in photodynamic therapy (PDT, vide supra). It has been known for many years that lipophilic substituents can exert a strong influence on such critical parameters as drug uptake, intracellular location, and photosensitizing efficacy.[15] Moreover, as recently shown by Ehrenberg et al.,[33] carboxylate "anchors" of the type incorporated in rings C and D in **8** might be tailored in length to either minimize or maximize cellular membrane penetration and, thus, overall exposure to photogenerated $^1O_2$ (Figure 2). Chlorins **8aa**−**ee** in Table 2, incorporating both a lipophilic "head" and a hydrophilic "tail", provide an attractive starting point for testing this hypothesis.

Finally, the described methodology should also be suitable for preparing chlorins of potential interest in materials science. It is worth noting, though, that with C,D-ring symmetric chlorins **8** our synthetic objectives were simplified by the fact that it was not necessary to differentiate either the formyl groups in **6** or the α-pyrrole positions in dipyrromethanes **7**. The application of this 2 + 2 strategy to the synthesis of unsymmetrical chlorins presents additional challenges that will be the subject of a forthcoming paper.

Experimental Section

Representative procedures for the synthesis of chlorins **8**:

5-[1-(4,4-Dimethyl-5-oxodihydrofuran-2-ylidene)ethyl]-3,4-dimethyl-1*H*-pyrrole-2-carbaldehyde (22b). TFA (8.80 mL, 118 mmol) was added to **11b** (1.0 g, 3.0 mmol) under a nitrogen atmosphere, and the solution was stirred vigorously for 5 min. The reaction was cooled to 0 °C for 10 min and then treated with triethyl orthoformate (2.7 mL, 16.4 mmol). After 20 min, the reaction was poured into 10% aq KH_2PO_4 (40 mL) at 0 °C and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed sequentially with water and saturated aq $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 3:7) to give **22b** (695 mg, 89%) as a colorless crystalline solid: mp 172.5−174 °C; R_f (4:6 EtOAc/hexanes) 0.41; IR (thin film) 3253, 1799, 1700, 1628, 1079 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 6H), 1.91 (s, 3H), 2.01 (t, J = 1.71, 3H), 2.27 (s, 3H), 2.58 (q, J = 1.71, 2H), 9.54 (s, 1H), 9.74 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.2, 9.7, 16.1, 25.0, 40.5, 40.5, 104.9, 119.2, 129.2, 132.5,

(33) (a) Lavi, A.; Weitman, H.; Holmes, R. T.; Smith, K. M.; Ehrenberg, B. *Biophys. J.* **2002**, *82*, 2101−2110. (b) Bronshtein, I.; Afri, M.; Weitman, H.; Frimer, A. A.; Smith, K. M.; Ehrenberg, B. *Biophys. J.* **2004**, *87*, 1155−1164.

TABLE 2. Isolated Yields of Chlorins Prepared by the 2+2 Method[a]

C-D rings \ A-B rings	6a	6b	6c	6d	6e
7a	**8aa** (40%,[a] **74%**[c])	**8ba** (44%,[a] **72%**[c])	**8ca** (38%,[a] **58%**[c])	**8da** (39%[b])	**8ea** (38%[b])
7b	**8ab** (39%,[a] **60%**[c])	**8bb** (42%,[a] **73%**[c])	**8cb** (39%,[a] **63%**[c])	**8db** (51%[b])	**8eb** (42%[b])
7c	**8ac (75%[c])**	**8bc (74%[c])**	**8cc (57%[c])**	**8dc (49%[c])**	**8ec (72%[c])**
7d	**8ad (68%[c])**	**8bd (64%[c])**	**8cd (51%[c])**	**8dd (49%[c])**	**8ed (85%[c])**
7e	**8ae (54%[c])**	**8be (68%[c])**	**8ce (55%[c])**	**8de (47%[c])**	**8ee (77%%[c])**

[a] Conditions: (a) neat TFA; (b) TsOH/MeOH/CH_2Cl_2; (c) 5% TFA in CH_2Cl_2.

136.3, 146.7, 177.0, 180.0. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; O, 18.37. Found: C, 68.54; H, 7.28; N, 5.33.

3,4-Dimethyl-5-(1,4,4-trimethyl-2,5-dioxohexyl)-1*H*-pyrrole-2-carbaldehyde (24b). A solution of **22b** (1.77 g, 6.77 mmol) in THF (130 mL) was cooled to −78 °C and treated dropwise with 1.6 M MeLi in Et_2O (8.40 mL, 13.5 mmol) over 20 min. The reaction was then quenched by addition to 200 mL of saturated aq NH_4Cl. After the mixture was allowed to warm to room temperature, Et_2O (50 mL) was added, and the layers were separated. The organic layer was washed sequentially with water and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting yellow oil was purified by flash chromatography (silica gel, EtOAc/hexanes = 3:7) to give **24b** (1.50 g, 80%) as a colorless crystalline solid: mp 103−104 °C; R_f (2:3 EtOAc/hexanes) 0.25; IR (thin film) 3253, 1706, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.12 (s, 3H), 1.13 (s, 3H), 1.36 (d, J = 7.3, 3H), 1.93 (s, 3H), 2.16 (s, 3H), 2.25 (s, 3H), 2.59 (d, J = 17.9, 1H), 2.87 (d, J = 17.9, 1H), 3.89 (q, J = 7.1, 1H), 9.53 (s, 1H), 9.74 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.6, 9.0, 15.7, 25.1, 25.5, 25.7, 44.5, 45.9, 51.2, 118.5, 128.9, 132.4, 136.1, 176.8, 207.5, 213.3; HRMS (EI) calcd for $C_{16}H_{23}NO_3$ 277.1678, found 277.1678. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05; O, 17.31. Found: C, 69.44; H, 8.35; N, 4.96.

3,4-Dimethyl-5-[1-(4,4,5-trimethyl-3,4-dihydropyrrol-2-ylidene)ethyl]-1*H*-pyrrole-2-carbaldehyde (13b). A solution of **24b** (1.35 g, 4.9 mmol) in CH_3CN (53 mL) was treated with $(NH_4)_2CO_3$ (4.6 g, 49 mmol) and basic alumina (6.7 g, grade I), flushed with nitrogen, and heated to 75 °C in a sealed flask for 8 h. At the

end of this period, the mixture was cooled to room temperature, filtered, and concentrated. The residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:2) to give **13b** (940 mg, 75%) as a crystalline solid: mp 156−157 °C; R_f (1:2 EtOAc/hexanes) 0.27; IR (thin film) 3252, 1635, 1589 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.20 (s, 6H), 2.11 (s, 3H), 2.16 (s, 3H), 2.17 (s, 3H), 2.26 (s, 3H), 2.58 (s, 2H), 9.58 (s, 1H), 11.77 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.8, 11.2, 15.7, 17.9, 26.0, 43.8, 47.8, 113.3, 118.9, 128.3, 131.4, 136.9, 151.6, 176.0, 187.2; HRMS (EI) calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1726. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84; O, 6.19. Found: C, 74.41; H, 8.72; N, 10.78.[12]

5-[1-(5-Formyl-4,4-dimethyl-3,4-dihydropyrrol-2-ylidene)-ethyl]-3,4-dimethyl-1*H*-pyrrole-2-carbaldehyde (6b). A solution of **13b** (0.80 g, 3.1 mmol) in CH_2Cl_2 (62 mL) and pyridine (0.37 mL, 3.7 mmol) was treated with SeO_2 (0.41 g, 3.7 mmol) and stirred at rt for 2 h. The solvent was then removed by rotary evaporation, and the residue was redissolved in DMF (30 mL) and heated to 80 °C for 15 min. The reaction mixture was cooled to room temperature, filtered, and poured into water (100 mL). The solution was extracted with CH_2Cl_2 (4 × 30 mL), and the combined organic extracts washed sequentially with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, EtOAc/hexanes = 2:3) to give **6b** (599 mg, 71%) as a yellow crystalline solid: mp 135−137 °C; R_f (1:2 EtOAc/hexanes) 0.34; IR (thin film) 3302, 1687, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.37 (s, 6H), 2.20 (s, 3H), 2.22 (s, 3H), 2.28 (s, 3H), 2.73 (s, 2H), 9.66 (s, 1H), 9.94 (s, 1H), 11.32 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.9, 11.8, 19.3, 26.1, 46.0, 46.3, 122.0, 125.3, 130.0, 131.2, 135.3, 152.0, 177.4, 177.5, 190.5; HRMS (EI) calcd for $C_{16}H_{19}N_2O_2$ 271.1447, found 271.1450. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29; O, 11.75. Found: C, 70.45; H, 7.42; N, 10.12.[12]

3-[18-(2-Methoxycarbonyl-ethyl)-3,7,8,10,13,13,17-heptamethyl-12,13,22,24-tetrahydroporphin-2-yl]propionic Acid Methyl Ester (8bb). Nitrogen was bubbled through a suspension of **6b** (201 mg, 0.74 mmol) and **7b** (321 mg, 0.74 mmol) in CH_2Cl_2 (67 mL) for 10 min. The mixture was treated with TFA (3.36 mL) and stirred at room temperature in the dark for 24 h. The reaction was then poured into 3 M aqueous NH_4OH (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed sequentially with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:5) to give **8bb** (313 mg, 70%) as a green crystalline solid that was identical to the literature compound.[12]

Acknowledgment. Financial support of this work by the National Institutes of Health (NIGMS Grant No. GM38913) is gratefully acknowledged. We are grateful to Victor G. Young, Jr. and the X-ray Crystallographic Laboratory, Department of Chemistry, University of Minnesota, for X-ray analysis of **24cB**. William G. O'Neal is the recipient of an NSF predoctoral fellowship.

Supporting Information Available: Experimental details, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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