A New Synthesis of Chlorins
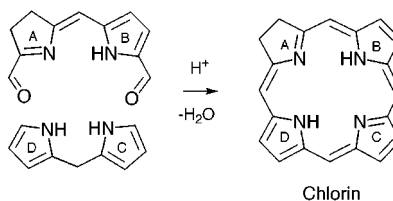
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ABSTRACT

Chlorin

A new synthesis of chlorins has been developed, based upon the acid-catalyzed condensation of dialdehydes AB with dipyrromethanes CD.

In Nature, aromatic tetrapyrroles can be divided formally into two classes: (1) those that are fully oxidized, the most common of which are the 22 π-electron porphyrins, and (2) those that are partially reduced (hydroporphyrins) but still contain the required 18 π-electrons for aromaticity (Figure 1).[1] The porphyrin ring is ubiquitous, in part due to its
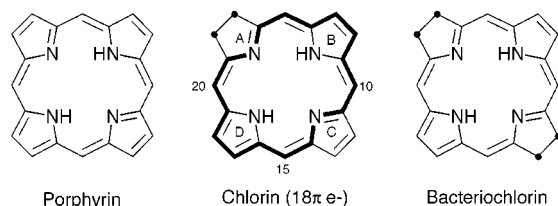

Figure 1. Aromatic macrocyclic tetrapyrroles.

exceptional stability. Compounds of this class are found in geological shale (geoporphyrins) and have even been detected spectroscopically in interstellar space.[1e] Representative hy-

droporphyrins include members of the chlorin and bacteriochlorin families, corresponding to the H_2- and H_4-oxidation level, respectively. In general, these ring systems are less stable than the porphyrins.

Both porphyrins and hydroporphyrins serve diverse biological functions. The porphyrin Heme is the most important biological carrier of oxygen and chlorophyll (a chlorin) is the principal light gathering chromophore of photosynthesis (bacteriochlorophyll, a bacteriochlorin, plays a similar role in bacteria).[1] Various hydroporphyrins have also been identified as cofactors for redox enzymes.[1e] In addition to their biological importance, many naturally occurring and synthetic hydroporphyrins are of interest in both materials science and medicine. For example, the tolylporphin class of bacteriochlorins has been found to reverse tumor multidrug resistance (MDR).[2] Agents of this type might provide new tools for cancer chemotherapy. Also, semisynthetic chlorins are being evaluated in tumor photodynamic therapy (PDT).[3] This technique uses an absorbed pigment to eradicate malignant tissue by photostimulated production of singlet oxygen.

(1) (a) Flitsch, W. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1988; Vol. 43. (b) Montforts, F.-P.; Gerlach, B.; Höper, F. *Chem. Rev.* **1994**, *94*, 327. (c) Montforts, F.-P.; Glasenapp-Breiling, M. *Prog. Heterocycl. Chem.* **1998**, *10*, 1. (d) 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. (e) Montforts, F.-P.; Glasenapp-Breiling, M.; Kusch, D. *Houben-Weyl* **2000**, 577.

(2) (a) Prinsep, M. R.; Caplan, F. R., Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 385. (b) Minchan, T. G.; Cook-Blumerg, L.; Kishi, Y.; Prinsep, M. R.; Moore, R. E. *Angew. Chem.* **1999**, *111*, 975, and references therein.

(3) (a) Kozyrev, A. N.; Suresh, V.; Das, S.; Senge, M. O.; Shibata, M.; Dougherty, T. J.; Pandey, R. K. *Tetrahedron* **2000**, *56*, 3353, and references therein. (b) Montforts, F.-P.; Meier, A.; Haake, G.; Höoper, F. *Tetrahedron Lett.* **1991**, *32*, 3481.

Not surprisingly, porphyrins are the easiest of the macrocyclic tetrapyrroles to prepare, since the ring itself is very stable and has no stereogenic centers. Successful synthetic efforts in this area date back over 65 years.[4a] In contrast, few general methods are available for synthesizing members of the hydroporphyrin class of tetrapyrroles. Most efforts in this area have focused on "semisynthesis", involving transformations of more readily accessible precursors. These include reactions occurring at the periphery of porphyrins,[4] such as oxidation,[4b] reduction,[4c] and various cycloadditions;[4d] tautomerization of porphyrinogens and related materials;[4e] and modifications of naturally occurring chlorins and bacteriochlorins.[1e,3]

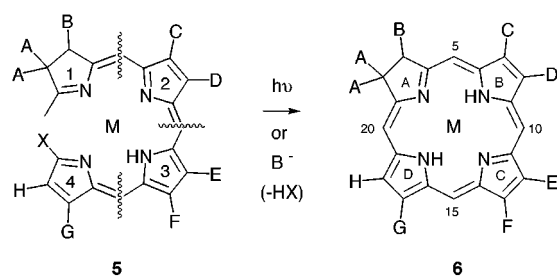The vast majority of de novo chlorin syntheses are modeled after the Battersby methodology (Figure 2), which

Figure 2. Battersby−Montforts synthesis of chlorins.

was elegantly employed in the first rational synthesis of bonellin.[5] In its most general form, this strategy is based upon either a photochemical or thermally induced ring closure of a properly substituted bilatriene **5** (X = OMe, Br). Bilatrienes **5**, in turn, are constructed from monocyclic building blocks of type **1**−**4**, which are typically joined by means of either a sulfide contraction[6] or a thio-Wittig reaction[7] or a related technique. The thermal cyclization conditions require copper chelation for activation (X = Br) and afford chlorins **6** in 5−10% yield after decomplexation. The photochemical ring closure is higher yielding (∼20%; X = OMe) but requires up to 1 week of irradiation of very dilute solutions. Both procedures are carried out on milligram quantities.

A significant improvement to this methodology was developed by Montforts et al., who employed Zn(II) as a template and carried out the cyclization of **5** by employing base catalysis (Figure 2, X = Br, I).[8] With DBU as base,

and sulfolane as solvent (110 °C), these authors obtained yields of bonellin derivatives in the range 55−75%, on scales of 10−20 mg. Finally, Lindsey et al. have recently extended this methodology to include the synthesis of *meso*-substituted chlorins. Zn(II)-complexed chlorins were obtained in up to a 10% yield, on an ∼20 mg scale.[9]

A number of challenges remain in chlorin synthesis. For example, the preparation of monocyclic precursors of type **1**−**4** is not trivial and often requires separation of mixtures after lengthy reaction sequences. Second, it would be useful to have more flexibility in the introduction of *meso*-substituents, of potential importance in the design of PDT agents (vide supra). Third, new methodology should be adaptable to the synthesis of enantiomerically pure chlorins. And finally, experimental procedures should be simplified and be capable of implementation on larger scales.[9b]

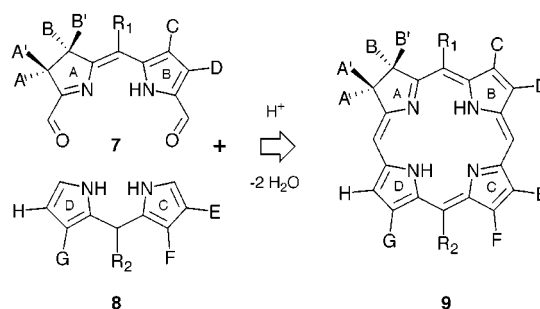One means of addressing these issues would employ a variant of the MacDonald porphyrin synthesis (Figure 3).

Figure 3. "MacDonald-Like" Approach to Chlorins.

The precursors **7** and **8** are in the proper oxidation state for direct condensation to afford chlorins **9** (−2 H$_2$O), and macrocycle formation should be facile.[10] Surprisingly, however, this approach to chlorins has not been described, most likely due to difficulties in preparing A,B-ring dialdehydes of type **7**. In this paper we describe a general synthesis of **7** and the successful incorporation into chlorins of type **9**.

Our synthetic plan for **7** took advantage of the ready availability of alkyne acids **10** and iodopyrroles **11** (Scheme 1).[11] Recently we employed these materials to prepare enantiomerically pure dihydropyrromethenones **13**, the first step of which involved Pd^0-initiated coupling−cyclization to afford enelactones **12**.[11a] Aminolysis of **12** at −33 °C, followed by keto-amide cyclization, then gave **13** in excellent overall yield. We hoped to extend this work to the synthesis

(4) (a) Rothemund, P. *J. Am. Chem. Soc.* **1935**, *57*, 2010. (b) Inhoffen, H. H.; Nolte, W. *Liebigs Ann. Chem.* **1969**, 167. (c) Bonnett, R.; White, R. D.; Winfield, U.-J.; Berenbaum, M. C. *Biochem. J.* **1989**, *261*, 277. (d) Tomé, A. C.; Lacerda, P. S. S.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *Chem. Commun.* **1997**, 1199. (e) Burns, D. H.; Shi, D. C.; Lash, T. D. *Chem. Commun.* **2000**, 299. See also refs 1 and 9a.

(5) (a) Battersby, A. R.; Dutton, C. J.; Fookes, C. J. R.; Turner, S. P. D.; *J. Chem. Soc., Chem. Commun.* **1983**, 1235. (b) Battersby, A. R.; Dutton, C. J.; Fookes, C. J. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1569.

(6) Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 5, and references therein.

(7) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079.

(8) (a) Montforts, F.-P.; Schwartz, U. M.; *Liebigs Ann. Chem.* **1991**, 709. (b) Abels, Y.; Montforts, F.-P. *Tetrahedron Lett.* **1997**, *38*, 1745, and references therein.

(9) (a) Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160. (b) According to one practitioner, "rational routes to chlorins ... have typically required such synthetic mastery that implementation has been confined to Elite specialists".[9a]

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

(11) (a) Jacobi, P. A.; Liu, H. *J. Org. Chem.* **1999**, *64*, 1778, and references therein. See also: (b) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

Scheme 1

Scheme 1

12 (Y = O)
13 (Y = NH) - - ▶

7
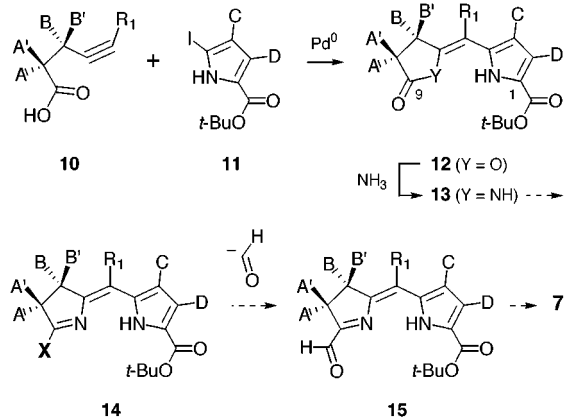
of **7** by adding CHO groups to C_1 and C_9. In principle, the C_9 formyl group could be introduced by initial conversion to activated imidoyl derivatives of type **14** (X = leaving group), followed by displacement with a "formyl anion" equivalent (**14 → 15**). Decarboxylative formylation at C_1 in **15** was expected to be straightforward.[12]

Our initial studies were carried out with the alkyne acid **10a** (Scheme 2), which gave a 96% yield of the enelactone

Scheme 2

Scheme 2

12a (Y = O; 96%)
13a (Y = NH; 68%)
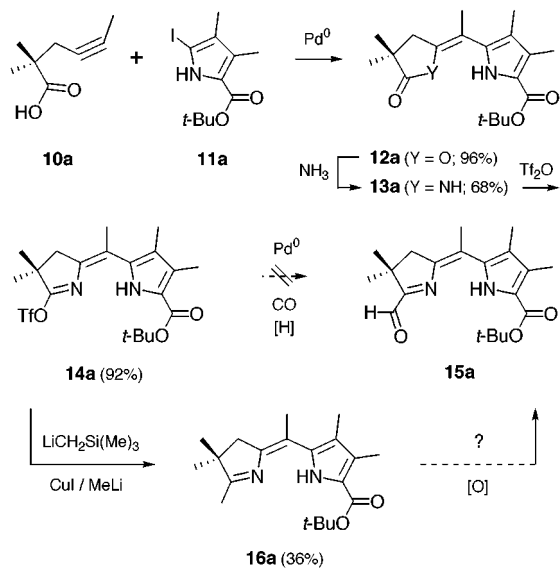
12a upon Pd^0-initiated coupling−cyclization with the io-dopyrrole **11a** (>20 g scales). Aminolysis of **12a**, followed by cyclodehydration with Montmorillonite clay, then afforded the desired enamide **13a** (68%). At this point we explored a number of methods for enamide activation.[11a] The most direct of these involved imidoyl triflate formation, which was accomplished in 92% yield using Tf_2O and 2,6-di-*tert*-butyl-

4-methylpyridine. Surprisingly, however, triflate **14a** was relatively unreactive toward nucleophilic displacement, returning mainly starting material with various "formyl anion" equivalents.[13] We also investigated several Pd^0-catalyzed formylations, all without success.[14] Ultimately, only one organocopper species afforded even modest yields of displacement products. This was the Bertz reagent,[15] which gave 36% of the methyl substitution product **16a**. We were hopeful that **16a** might be converted to the desired **15a** by oxidation. However, we could not isolate sufficient quantities of **16a** by this route to test this idea.

Much better results were obtained with the thioimidate derivative **18a** (Scheme 3), which was derived from lactam

Scheme 3

Scheme 3

17a (99%)
18a (72%)
19a (68%)
16a (88%)
20a (62%)
15a (32%)
7a (99%)
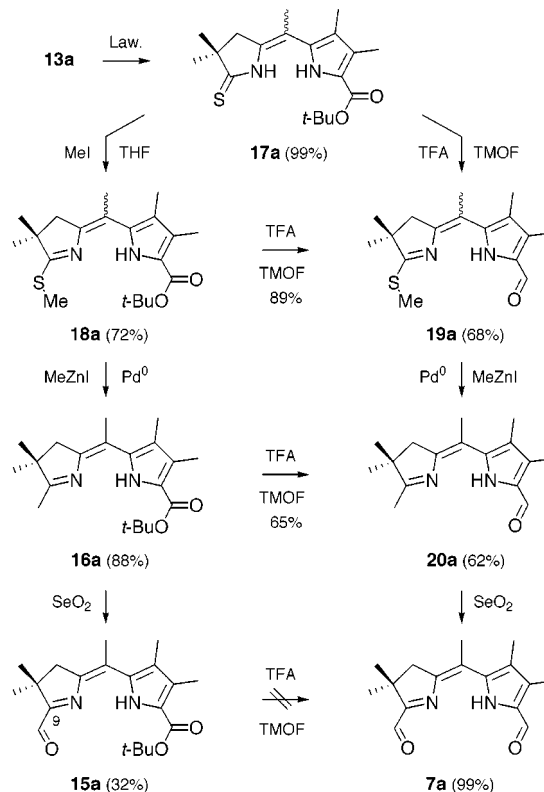
13a by sulfonation with Lawesson's reagent (99%), followed by S-methylation (MeI, 72%) (*Z,E*-mixtures are indicated by a wavy bond). This approach built upon the studies of Fukuyama[16a] and Liebeskind,[16b,c] who have investigated the

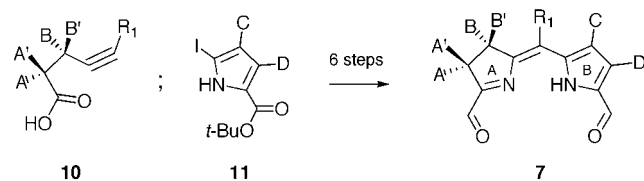(12) Gossauer, A.; Hinze, R.-P. *J. Org. Chem.* **1978**, *43*, 283.

(13) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.

(14) See, for example: Bernabé, P.; Rutjes, F. P. J. T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 3561.

(15) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. *J. Am. Chem. Soc.* **1996**, *118*, 10906. The methyl transfer reagent was prepared by following the procedure given for the corresponding *n*-butyl species.

(16) (a) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189. (b) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9949. (c) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229. We gratefully acknowledge stimulating discussions with Professor Liebeskind on this subject. (d) For best results, the MeZnI reagent must be prepared by following the procedure of Fukuyama et al. (ref 16a). The reagent derived by treatment of MeMgCl with ZnI was considerably less reactive.

Table 1. Summary of Yields[a]

compd	12	13	17	19	20[19]	7
a	96%	68%	99%	68%	62%	99%
b	98%	89%	91%	68%	71%	68%
c	85%	75%	86%	71%	73%	62%
d	74%	76%	49%	41%	57%	99%

[a] Compound numbers correspond to Schemes 1−3.

Pd[0]-catalyzed cross-coupling reaction of thioester derivatives with various organometallic compounds. In particular, reagents RZnI cleanly afford the product of formal nucleophilic displacement (no reaction is observed in the absence of Pd[0]). These results were readily extended to the case of thioimidate **18a**, which gave an 88% yield of methyl derivative **16a** upon reaction with MeZnI/Pd[0].[16d] With ample quantities of **16a** in hand, we could obtain reasonable quantities of formyl derivative **15a** by oxidation with SeO$_2$.[17] Unexpectedly, however, we were unable to accomplish the decarboxylative formylation of **15a** leading to **7a**, presumably due to the inductive influence of the C$_9$-formyl group. This was remedied by reversing the order of decarboxylation and oxidation. Thus, methyl derivative **16a** was cleanly converted to the formyl compound **20a** (TFA/TMOF), which gave an essentially quantitative yield of the desired dialdehyde **7a** upon oxidation with SeO$_2$.

Finally, we were able to streamline the synthesis of **7a** by effecting the methylation and decarboxylative formylation of **17a** concomitantly (TFA/TMOF). This transformation was modeled after a similar reaction reported by Battersby et al.[18] and gave a 68% yield of **19a** directly. The structure of **19a** was confirmed by decarboxylative formylation of the *S*-methyl derivative **18a**, which gave identical material but in a less efficient fashion. It remained now to carry out the cross-coupling reaction of **19a** with MeZnI, a potentially complex step. However, this reaction proved to be remarkably selective and gave a 62% yield of **20a** with no evidence of nucleophilic attack at the aldehyde group.[19] Previously we had converted **20a** to **7a** in 99% yield using SeO$_2$, thereby completing the synthesis. This route to A,B-ring precursors of type **7** appears to be quite general (Table 1) and is compatible with a wide range of functionality.

Numerous C,D-ring precursors of general structure **8** are readily available.[9a,20] We chose dipyrromethanes **8e,f** as

(17) Werner, A.; Sánchez-Migallón, A.; Fruchier, A.; Elguero, J.; Fernández-Castano, C.; Foces-Foces, C.; *Tetrahedron* **1995**, *51*, 4779.

(18) 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.

Scheme 4

e: E,F,G,H = Me; R$_2$ = H
f: E,H = Me; F,G = P^{Me}; R$_2$ = H
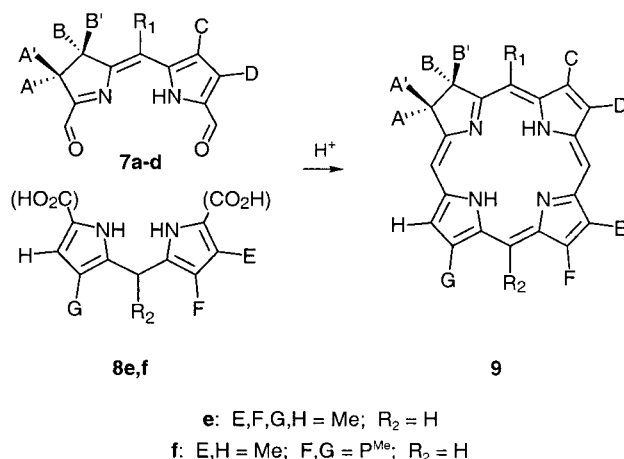
yield chlorin 9 (format: 7x + 8y → 9xy)		
9ae: 44%	**9af**: 42%	**9be**: 38%
9bf: 39%	**9ce**: 40%	**9cf**: 39%

representative examples to attempt the synthesis of chlorins **9** (Scheme 4). The condensation of **7** and **8** turned out to be straightforward, requiring no particular precautions against air or light and no metal complexation. For example, simple dissolution of **7a** and **8e** in neat TFA afforded 44% of chlorin **9ae** after 1.5 h at ambient temperature. In analogous fashion, we prepared chlorins **9af−cf** in the yields summarized in Scheme 4. Thus far we have made no efforts to optimize these conditions.

We believe this approach is useful because of its flexibility and the simplicity of the experimental conditions. Currently we are extending this work to the synthesis of unsymmetrical C,D-ring chlorins, as well as to bacteriochlorins and other biologically important hydroporphyrins.

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

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(19) Yields refer to those obtained with the major *Z*-isomers of **19**. The corresponding *E*-isomers underwent cross-coupling either very slowly or not at all.

(20) See, for example: (a) Okada, K.; Saburi, K.; Nomura, K.; Tanino, H. *Tetrahedron Lett.* **1998**, *39*, 2365. (b) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391.