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Synthesis of the chlorin macrocycle by the '3 + 1' approach

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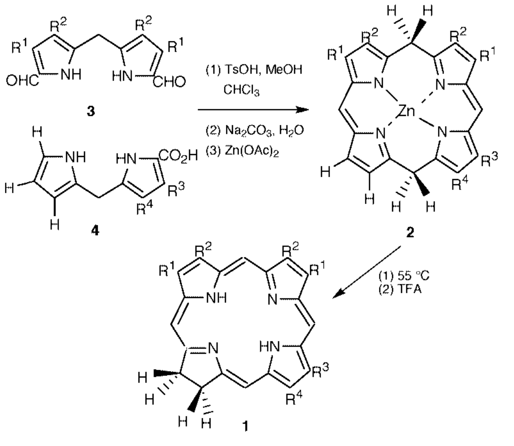
The one-step regioselective synthesis of a chlorin macrocycle from a tripyrrane and bisformylpyrrole is described for the first time; the chlorin is furnished in 46% yield and is constructed from readily prepared pyrroles.

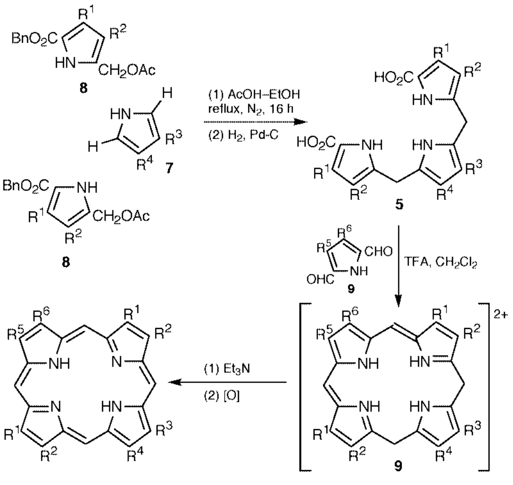
The magnesium chlorins (dihydroporphyrins) found in the photosynthetic proteins of green plants[1] are utilized in light harvesting arrays and electron transfer reaction centers. With similar photophysical characteristics to their chlorophyll counterparts, synthetic chlorins are potentially useful chromophores for use in molecular wires and antenna arrays, all of which make them interesting synthetic targets.[2] The preparation of chlorins regioselectively functionalized for supramolecular assembly is no small task, for in the preparation of an asymmetrically substituted macrocycle it is possible to produce a maximum of eight isomers: four pyrroline-ring regioisomers, each of which could exhibit *cis* or *trans* stereochemistry. We have recently reported the preparation of chlorins **1** from the rearrangement of metallated 5,15-porphodimethenes **2** (Scheme 1).[3] Advantages to this method are (i) the synthesis is highly regioselective, with only one out of four possible pyrroline ring isomers formed as shown, and (ii) the synthesis is short, as the porphodimethene is furnished directly from readily prepared open-chained pyrrolic intermediates *via* the '2 + 2' MacDonald condensation[4] of 1,9-diformyldipyrromethanes **3** and dipyrromethanes **4**. However, a general limitation to our approach is that one of the dipyrromethanes must be symmetrical or the '2 + 2' condensation will furnish two isomeric chlorin macrocycles.

The last few years have seen the active development of the '3 + 1' approach to the synthesis of porphyrins[5] and porphyrin analogs.[6] In this method the macrocyclic ring is furnished by the condensation of tripyrrane **5** with 2,5-diformylpyrrole **6** (Scheme 2). The tripyrrane is prepared in one step by the electrophilic substitution of pyrrole **7** with 2 equiv. of acetoxymethylpyrrole **8**. In theory, the method could allow the preparation of a porphyrin with four different pyrroles and the only symmetry constraint would be that the 2,5-diformylpyrrole must have identical β-substituents in order to form one isomeric porphyrin upon condensation with an asymmetrically substituted tripyrrane. The varied ring substituent pattern that this method allows makes the '3 + 1' approach to the construction of a chlorin macrocycle an attractive alternative to the more symmetry constrained '2 + 2' method. However, the intermediates of the condensation are not known. The 5,10-porphodimethene **9**, other dihydroporphyrins as well as porphyrinogens (5,10,15,20,22,24-hexahydroporphyrin) have all been postulated as intermediates.[5] The latter is not the correct oxidation state to rearrange to a chlorin, and it was not clear if all or just a portion of the dihydroporphyrin intermediates produced in the condensation could be easily metallated or then rearranged into a chlorin like the tautomer **2**. We now have determined the identity of the condensation intermediate and report the first synthesis of a chlorin that utilizes a '3 + 1' approach to prepare the macrocyclic ring.

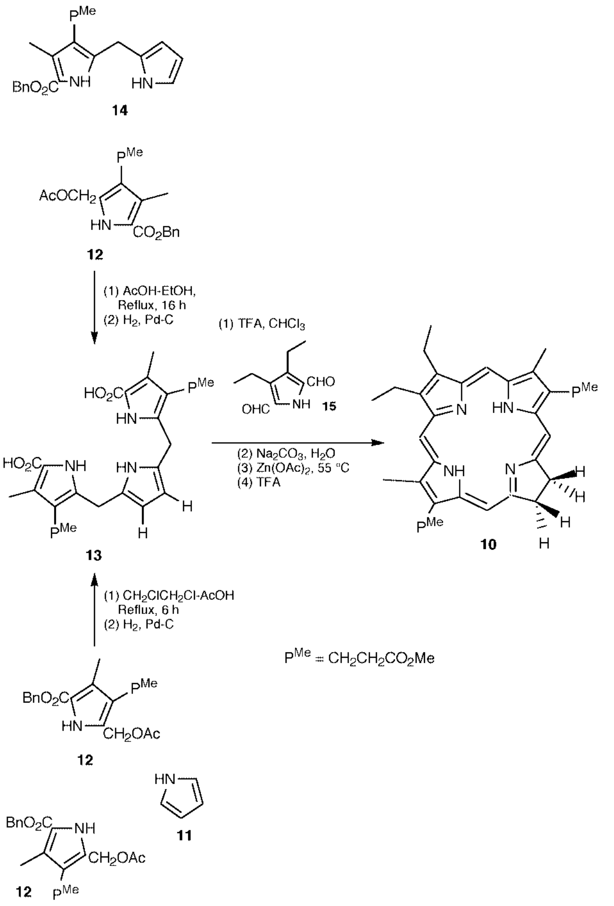
The '3 + 1' synthesis of chlorin **10** is shown in Scheme 3. To demonstrate the utility of the '3 + 1' approach, chlorin **10** was chosen as a target because its substituent pattern was not efficiently accessible *via* the '2 + 2' approach. Pyrrole (**11**) was used because the absence of β-substituents on this ring was expected to control the regiochemistry by analogy to the earlier '2 + 2' chlorin syntheses and furnish only the one ring-reduced isomer as shown.[3] Its use also precluded the formation of pyrroline ring stereoisomers. The propanoate ester pyrroles were used because it was felt that the ensuing substituent pattern on the chlorin macrocycle could lend itself to the fabrication of supramolecular chlorin assemblies of interest. Our initial attempts to make the precursor tripyrrane **13** in the usual manner[5,6] by refluxing pyrrole with 2 equiv. of acetoxymethylpyrrole **12** in an EtOH–AcOH solution overnight did not furnish **13** as expected. This literature procedure works well when the 2,5-unsubstituted pyrrole is substituted in its 3,4-position with electron-donating alkyl substituents. However, the electrophilic substitution reaction of pyrrole with **12** was slow, allowing the solvolysis of **12** and the resultant production of the unreactive ether by-product. We therefore prepared the known dipyrromethane **14**[3] first and refluxed it in an EtOH–AcOH



Scheme 1



Scheme 2



Scheme 3

solution overnight with the acetoxymethylpyrrole **12** to furnish tripyrrane **13** in 60% yield. This demonstrates for the first time that the mild reaction conditions which allow the formation of the acid-sensitive tripyrrane in one step from three pyrrole precursors also work well when using a dipyrromethane and acetoxymethylpyrrole. On the other hand, when pyrrole and 2 equiv. of acetoxymethylpyrrole **12** were refluxed in a 1,2-dichloroethane–AcOH solution for 6 h the tripyrrane **13** was furnished in 45% yield. Pyrrole **12** did not decompose to form an unreactive by-product in the modified reaction mixture.

The benzyl esters of tripyrrane **13** were hydrogenolysed over 10% palladium-on-charcoal and the resulting diacid tripyrrane condensed with 2,5-bisformylpyrrole **15**[5c] in the presence of 5% TFA in $CHCl_3$ under an inert atmosphere.[7] After 2 h the solution was neutralized with $NaHCO_3$, washed with water and dried over Na_2SO_4. The reaction mixture was filtered through an alumina plug, metallated with a saturated solution of $Zn(OAc)_2$ in MeOH, and heated to 55 °C for 2 h. The crude product was demetallated in TFA and chromatographed on alumina (Grade III, eluted with CH_2Cl_2–benzene 65 : 35) to furnish chlorin **10** in 46% yield along with 8% of the corresponding porphyrin.[8] UV–VIS spectroscopy of the reaction mixture after neutralization with $NaHCO_3$ and before metallation revealed that the main macrocyclic intermediate formed in the '3 + 1' condensation was a phlorin (432 nm, broad adsorption at 720 nm). This was a gratifying result, for we have previously shown that the reaction of $Zn(OAc)_2$ with a phlorin produced a metallated 5,15-porphodimethene that would rearrange to chlorin upon heating.[3a] If the 5,10-porphodimethene **9** was ever formed during the '3 + 1' condensation, it must have equilibrated rapidly to the thermodynamically more stable phlorin upon neutralization.

In conclusion, the '3 + 1' approach furnished chlorin in yields as high, if not higher, than with chlorins prepared *via* the '2 + 2' approach. The preparation of a tripyrrane from dipyrromethane and pyrrole precursors demonstrates the feasibility of synthesizing an asymmetrically substituted tripyrrane (*i.e.* one made from three different pyrroles), and corresponding asymmetrically substituted chlorin via the '3 + 1' approach. The relative brevity and simplicity of the synthetic route, utilizing readily prepared precursor pyrroles, makes this an attractive method for the regioselective synthesis of chlorins.

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Notes and references

1 H. Scheer, in *Chlorophylls*, ed. H. Scheer, CRC Press, Boca Raton, 1991, pp. 3–30; *Photosynthesis, A Comprehensive Treatise*, ed. A. S. Raghavendra, Cambridge University Press, Cambridge, 1998.

2 For reviews on chlorin assemblies, see M. R. Wasielewski, in *Chlorophylls*, ed. H. Scheer, CRC Press, Boca Raton, 1991, pp. 269–286; M. R. Wasielewski, *Chem. Rev.*, 1992, **92**, 435.

3 (*a*) D. H. Burns, T. L. Caldwell and M. W. Burden, *Tetrahedron Lett.*, 1993, **34**, 2883; (*b*) D. H. Burns, Y. H. Li, D. C. Shi and M. O. Delaney, *Chem. Commun.*, 1998, 1677.

4 G. Arsenault, E. Bullock and S. F. MacDonald, *J. Am. Chem. Soc.*, 1960, **82**, 4384.

5 For an overview, see (*a*) T. D. Lash, *Chem. Eur. J.*, 1996, **2**, 1197; (*b*) A. Boudif and M. Momenteau *J. Chem. Soc., Perkin Trans. 1*, 1996, 1235; (*c*) T. D. Lash, *J. Porphyrins Phthalocyanines*, 1997, **1**, 29.

6 (*a*) T. D. Lash, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2533; (*b*) T. D. Lash and S. T. Chaney, *Chem. Eur. J.*, 1996, **2**, 944.

7 The preparation and purification of the chlorin were performed in a Vacuum Atmosphere glove box under a nitrogen atmosphere.

8 All new compounds exhibited satisfactory spectral and elemental analysis.

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