Porphyrin Synthesis by the "3+1" Approach: New Applications for an Old Methodology

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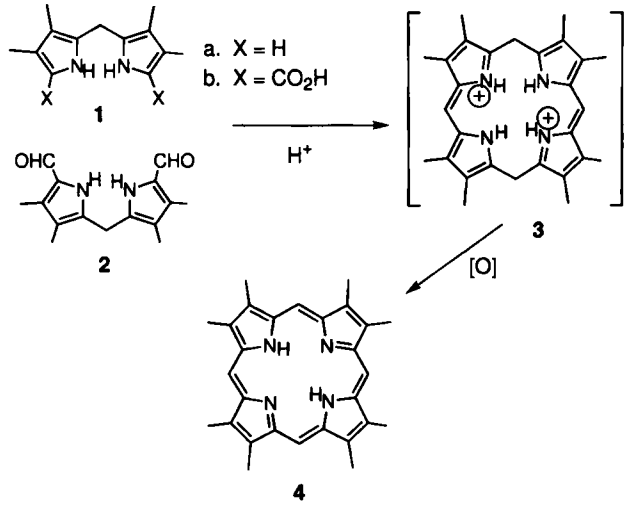
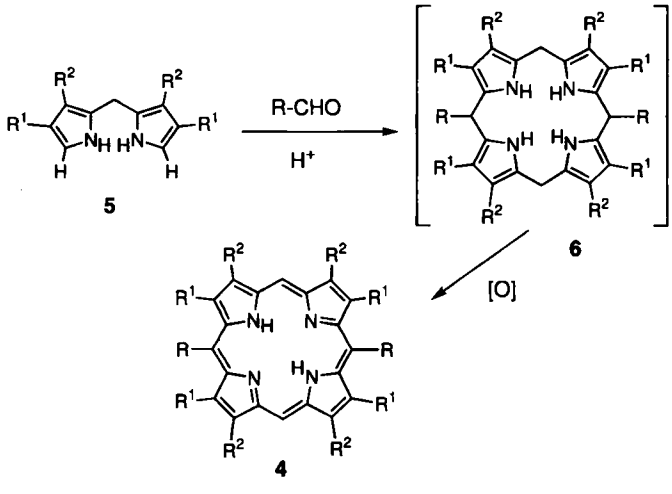
Abstract: Acid-catalyzed condensation of tripyrranes with pyrrole-2,5-dicarboxaldehydes, followed by oxidation with an electron-deficient quinone, affords porphyrin products in excellent yields. This previously little used methodology has now been exploited in the synthesis of novel porphyrin structures, including tetrapyrrolic compounds with fused aromatic rings. By utilizing other aromatic or unsaturated dialdehydes, the "3+1" approach also allows the synthesis of new aromatic porphyrinoid systems, including benzene- and pyridine-containing macrocycles and carbaporphyrins.

Keywords: aromaticity · MacDonald condensation · porphyrinoids · pyrroledialdehydes · tripyrranes



Scheme 1. S. F. MacDonald's "2+2" porphyrin synthesis.

Although it has been more than seventy years since the first porphyrin syntheses were published,[1] new methodologies for the preparation of porphyrinoid systems continue to be developed. This is due to the unparalleled significance of porphyrins in diverse areas, including biology, biochemistry, medicine, catalysis, and material science, and in burgeoning new arenas such as molecular recognition and nanotechnology. Fischer's early synthetic studies utilized pyrromethene intermediates,[1, 2] and it was only in the late 1950's that alternative strategies for the synthesis of asymmetrically substituted porphyrins were introduced. In particular, MacDonald[3] and Woodward[4] independently demonstrated that 5,5'-diunsubstituted dipyrrylmethanes **1a**, or the related dicarboxylic acids **1b**, condensed with diformyldipyrrylmethanes **2** in the presence of an acid catalyst to generate porphodimethenes **3** and subsequent oxidation afforded the corresponding porphyrins **4** in good yields (Scheme 1).[3] This "2+2" methodology[5] continues to be widely used in the synthesis of both porphyrins[6] and related conjugated macrocycles.[7] The principal limitation to this method is that one of the two condensing dipyrrolic units must be symmetrical or mixtures of isomeric porphyrin products will result. Other "2+2" syntheses have been introduced using intermediates at different oxidation levels. In particular, dipyrrylmethanes **5** have been shown to condense with aldehydes in the presence of an acid catalyst to give the related porphyrinogens **6**, and oxidation, generally with an electron deficient quinone, affords the porphyrins **4** (Scheme 2).[8] A number of methods have been introduced that involve the intermediacy of open-chain tetrapyrrolic structures,[9, 10] and these allow the synthesis of totally asymmetrical porphyrin systems. However, these methods tend to involve a significantly larger number of steps, and this leads to lower overall yields.



Scheme 2. Porphyrin formation from dipyrrylmethanes and aldehydes.

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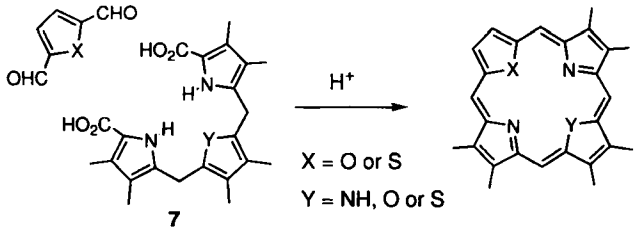
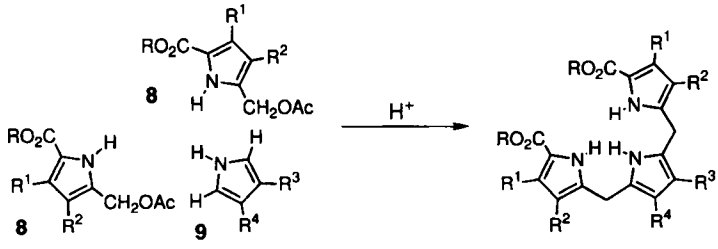
In their pioneering studies on the synthesis of porphyrinoid systems (including expanded porphyrins), Woodward[11] and Johnson[12] made use of tripyrrolic intermediates known as tripyrranes (**7**; Scheme 3). Johnson also introduced the concept of carrying out the synthesis of porphyrinoids by a "3+1" variation on the MacDonald condensation (Scheme 3).[13] This



Scheme 3. A. W. Johnson's "3+1" synthesis of oxa- and thiaporphyrins.

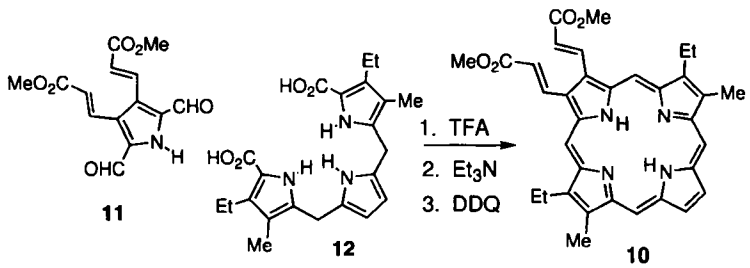
methodology was very successfully employed in the synthesis of porphyrin analogues with one or two furan or thiophene subunits. During the 1960's and 1970's, many alternative routes for porphyrin synthesis were reported, and the "3+1" approach was not further pursued. However, in the last two years this situation has radically altered, so much so that some authors have claimed this approach to be a new type of porphyrin synthesis.[14-21]

The original disinterest in the "3+1" methodology was no doubt due in part to the difficulties involved in obtaining the required tripyrrane intermediates. However, a direct route to tripyrranes has now been developed where two equivalents of an acetoxymethylpyrrole **8** are condensed with a 2,5-diunsubstituted pyrrole **9** in the presence of refluxing hydrochloric acid and ethanol (Scheme 4).[22] A variety of alternative acid catalysts

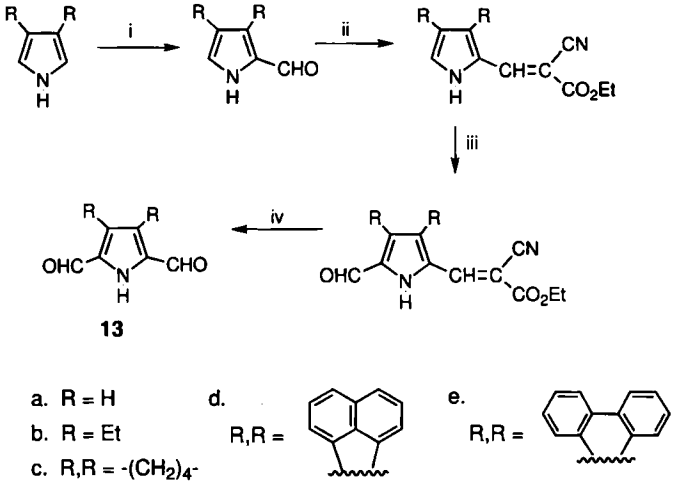


Scheme 4. J. L. Sessler's tripyrrane synthesis.

have been employed in this chemistry, including Montmorillonite clay,[14] *p*-toluenesulfonic acid,[23] and acetic acid.[15-17] In the latter case, the conditions are sufficiently mild for *tert*-butyl ester moieties to be employed as protective groupings.[15-17,24] Although tripyrranes have been widely used in the synthesis of expanded porphyrins such as sapphyrins,[11,12] pentaphyrins,[25] and hexaphyrins,[26,27] the first synthesis of a tetrapyrrolic porphyrin structure by the "3+1" approach was only reported in 1994.[14] In this case, Boudif and Momenteau obtained a bisacrylate-substituted porphyrin **10** by condensing pyrroledialdehyde **11** with tripyrrane dicarboxylic acid **12**, obtained by hydrogenolysis of the corresponding dibenzyl ester, in the presence of trifluoroacetic acid in dichloromethane (Scheme 5). Following neutralization of the reaction mixture and oxidation with DDQ, the new porphyrinoid chromophore **10** was isolated in 33% yield. The primary impediment in this synthesis was the unacceptably low yields obtained in the preparation of pyrroledialdehyde **11**. However, much more efficient routes are available for the synthesis of pyrroledialdehydes **13a** and **13b**,[28] and this approach has been extended to the synthesis of the related polycyclic pyrroles **13c-e** (Scheme 6).[15-17]

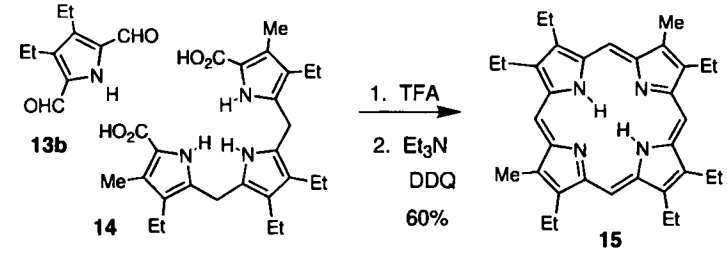


Scheme 5. Boudif and Momenteau's "3+1" synthesis of a bisacrylate-substituted porphyrin.



Scheme 6. Synthesis of 2,5-pyrroledialdehydes. i) $POCl_3$-DMF, 0 °C, then NaOAc, H_2O, reflux; ii) $NCCH_2CO_2Et$, EtOH, cat. piperidine, reflux 2 h; iii) $POCl_3$-DMF, 0 °C; iv) NaOH, H_2O, reflux.

The easily prepared dialdehyde **13b** was found to condense with tripyrrane **14** in the presence of TFA-CH_2Cl_2; oxidation with DDQ then gave the hexaethylporphyrin **15** in 60% yield (Scheme 7).[15] This chemistry has also been applied to the synthesis of porphyrins with fused ring systems. The readily available *c*-annelated pyrroles **16**[15,17,29] were shown to condense with two equivalents of the acetoxymethylpyrroles **17** to give the tripyrrane di-*tert*-butyl esters **18** in excellent yields (Scheme 8). In a one-pot sequence, the *tert*-butyl esters were cleaved with



Scheme 7. "3+1" Synthesis of an etioporphyrin.

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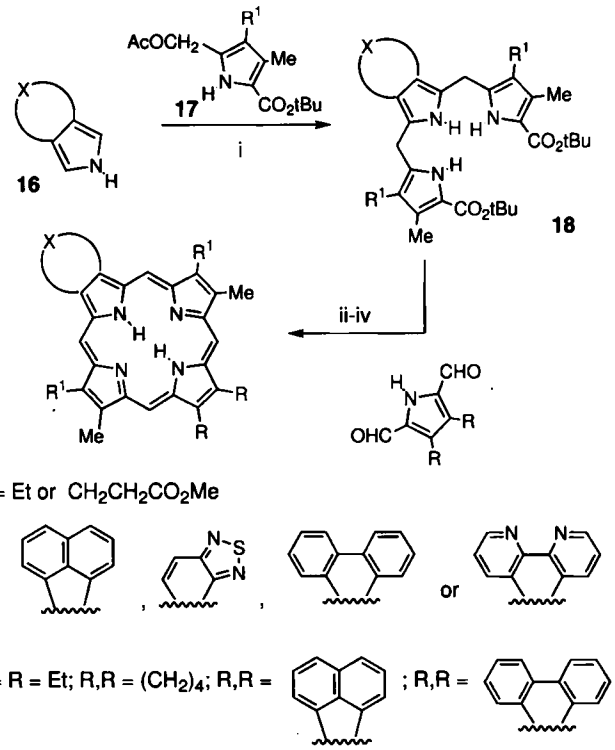
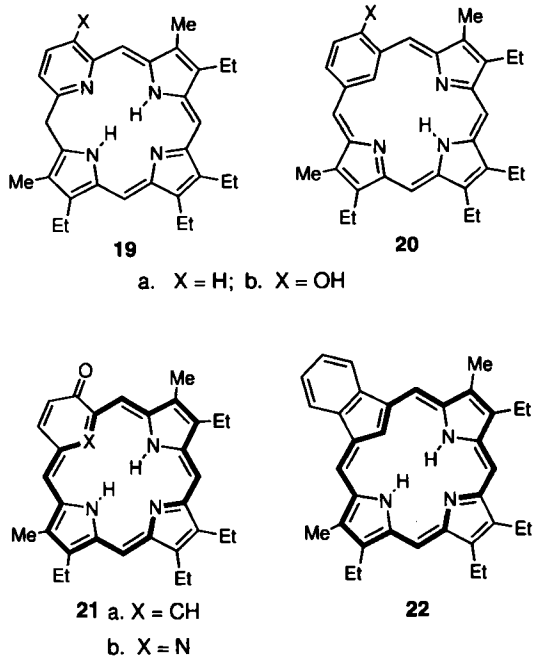
TFA, the mixture was diluted with dichloromethane, a pyrroledialdehyde was added, and after two hours the solution was neutralized with triethylamine and oxidized with DDQ. By this approach, the synthesis of acenaphtho-, thiadiazolobenzo-, phenanthro-, and phenanthrolinoporphyrins was accomplished (Scheme 8).[15–17] The latter system, which could not be obtained by the "2+2" MacDonald synthesis, was prepared in exceptionally high yields (72–83%) by the "3+1" protocol. Phenanthrolinoporphyrins have great potential in the area of molecular recognition, and have been mooted as suitable "alligator clips" in the development of molecular wires.[30]



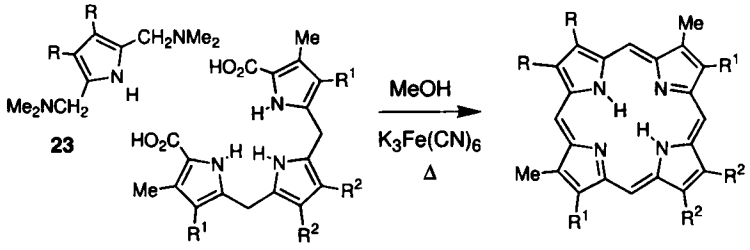
Scheme 8. "3+1" Synthesis of porphyrins with fused aromatic ring systems. i) 7% AcOH–EtOH, N_2, 16 h, reflux; ii) TFA, 10 min, N_2; iii) CH_2Cl_2, 2 h, 25 °C, N_2; iv) Et_3N, 1 equiv DDQ, 1 h.

Concurrent with these developments, the "3+1" strategy has been applied to the synthesis of porphyrin analogues with pyridine or benzene subunits. Berlin and Breitmaier demonstrated that 2,6-pyridinedicarboxaldehyde condensed with tripyrrane **14** in the presence of HBr to give the dihydropyriporphyrin **19a**, and that isophthalaldehyde similarly afforded benziporphyrin **20a**.[19] Subsequently, we reported the synthesis of the related fully aromatic systems oxybenziporphyrin **21a**[20] and oxypyriporphyrin **21b**,[21] again by the "3+1" approach. In these cases, a hydroxyl substituent was introduced (as in structures **19b** and **20b**), and this underwent a facile keto–enol tautomerization to afford the novel aromatic macrocycles **21a** and **21b**, both of which have pathways for 18 π electron delocalization. The first syntheses of carbaporphyrins (e.g., **22**), albeit in low yields, have also recently been accomplished by this methodology.[31] These exciting developments suggest that many fundamentally new porphyrinoid ring systems can be obtained using the "3+1" strategy.

As was the case for "2+2" porphyrin syntheses, the "3+1" approach can also be carried out at a lower oxidation level. This methodology has been used in the synthesis of heterocyclic ana-



logues of *meso*-tetraarylporphyrins,[32] although it appears to be of little value in the stepwise synthesis of asymmetrically substituted *meso*-tetraarylporphyrins.[33] More significantly, in a recent disclosure Smith et al. have reported "3+1" syntheses of porphyrins using 2,5-bis(dimethylaminomethyl)pyrroles **23** in place of pyrroledialdehydes (Scheme 9).[23] These functionalized pyrroles were prepared in good yields by treating 2,5-diunsubstituted pyrroles with an excess of Eschenmoser's salt. Condensation of pyrroles **23** with tripyrranes in refluxing methanol containing potassium ferricyanide as an oxidant gave porphyrin products in moderate to good yields.[23] The use of nonacidic conditions was critical if the fragmentation–recombination reactions were to be avoided.[34] In addition, rapid oxidation of the putative porphyrinogen intermediate was necessary so that degradation or isomerization processes could be minimized. Although some minor porphyrin by-products were generated using this protocol (separated by column chromatography), and there were some indications that the chemistry was not entirely general, this report provides a valuable complementary methodology to the previously discussed pyrroledialdehyde "3+1" porphyrin synthesis.



Scheme 9. K. M. Smith's "3+1" synthesis of porphyrins from tripyrranes and 2,5-bis(dimethylaminomethyl)pyrroles.

After more than two decades of lying fallow, the "3+1" approach has been revived and shown to be a valuable and versatile route for porphyrin synthesis. Although one of the two condensing units (tripyrrane or pyrroledialdehyde) must be symmetrical to avoid the formation of isomeric products, the

symmetry constraints differ from those associated with the MacDonald "2+2" approach, and this allows the synthesis of structures that would be difficult to obtain by other synthetic procedures. The rapid acceptance of the "3+1" methodology over the last two years suggests that this chemistry will be widely utilized in the future, and the approach is likely to allow access to novel porphyrinoid structures of both theoretical and practical significance.

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[1] H. Fischer, B. Walach, *Justus Liebigs Ann. Chem.* **1926**, *450*, 164.

[2] a) H. Fischer, H. Orth, *Die Chemie des Pyrrols*, Vol. I, Akademische Verlag, Leipzig, **1934**; b) *ibid.* Vol. II (i), **1937**; c) H. Fischer, H. Stern, *ibid.* Vol. II (ii), **1940**.

[3] G. P. Arsenault, E. Bullock, S. F. MacDonald, *J. Am. Chem. Soc.* **1960**, *82*, 4384.

[4] R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Dutler, J. Hannah, F. P. Hauck, S. Ito, A. Langemann, E. LeGoff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, H. Volz, *J. Am. Chem. Soc.* **1960**, *82*, 3800; *Tetrahedron* **1990**, *46*, 7599.

[5] A. W. Johnson, *Pure Appl. Chem.* **1971**, *28*, 195.

[6] For example, J. A. S. Cavaleiro, A. M. d'A. Rocha Gonsalves, G. W. Kenner, K. M. Smith, *J. Chem. Soc. Perkin Trans. I* **1974**, 1771; T. D. Lash, J. J. Catarello, *Tetrahedron* **1993**, *49*, 4159.

[7] E. Vogel, W. Haas, B. Knipp, J. Lex, H. Schmickler, *Angew. Chem.* **1988**, *100*, 445; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 406; T. D. Lash, *J. Org. Chem.* **1992**, *57*, 4312.

[8] H. Ogoshi, H. Sugimoto, T. Nishiguchi, T. Watanabe, Y. Matsuda, Z. Yoshida, *Chem. Lett.* **1978**, 29; M. J. Gunter, L. N. Mander, *J. Org. Chem.* **1981**, *46*, 4792; R. Young, C. K. Chang, *J. Am. Chem. Soc.* **1985**, *107*, 898.

[9] A. H. Jackson, G. W. Kenner, *Nature*, **1967**, *215*, 1126; A. H. Jackson, G. W. Kenner, K. M. Smith, *J. Chem. Soc. (C)* **1971**, 502; J. A. P. Baptista de Almeida, G. W. Kenner, R. Rimmer, K. M. Smith, *Tetrahedron* **1976**, *32*, 1793; R. P. Evstigneeva, *Pure Appl. Chem.* **1981**, *53*, 1129; K. M. Smith, G. W. Craig, *J. Org. Chem.* **1983**, *48*, 4302; P. S. Clezy, *Aust. J. Chem.* **1991**, *44*, 1163.

[10] Improved syntheses of symmetrically substituted porphyrins have also been the subject of numerous recent investigations: e.g., J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney, A. M. Marguerettaz, *J. Org. Chem.* **1987**, *52*, 827; b) J. S. Lindsey, R. W. Wagner, *J. Org. Chem.* **1989**, *54*, 828.

[11] V. J. Bauer, D. R. Clive, D. Dolphin, J. B. Paine III, F. L. Harris, M. M. King, J. Loder, S.-W. C. Wang, R. B. Woodward, *J. Am. Chem. Soc.* **1983**, *105*, 6429.

[12] M. J. Broadhurst, R. Grigg, A. W. Johnson, *J. Chem. Soc. Perkin Trans. I* **1972**, 2111. See also: J. L. Sessler, M. J. Cyr, A. K. Burrell, *Synlett* **1991**, 127.

[13] M. J. Broadhurst, R. Grigg, A. W. Johnson, *J. Chem. Soc. (C)* **1971**, 3681. A. W. Johnson in *Porphyrins and Metalloporphyrins* (Ed.: K. M. Smith), Elsevier, Amsterdam, **1975**, pp. 729–754.

[14] A. Boudif, M. Momenteau, *J. Chem. Soc. Chem. Commun.* **1994**, 2069; *J. Chem. Soc. Perkin Trans. 1* **1996**, 1235.

[15] Y. Lin, T. D. Lash, *Tetrahedron Lett.* **1995**, *36*, 9441.

[16] Details of our studies on the "3+1" methodology were reported at the following meetings: 209th National Meeting of the American Chemical Society, Anaheim, California (USA), April 1995 (T. D. Lash, B. H. Novak, Y. Lin, M. J. Melquist, J. R. Patel, *Book of Abstracts*, ORGN 177); 210th National Meeting of the American Chemical Society, Chicago, Illinois, (USA), August 1995 (T. D. Lash, Y. Lin, *Book of Abstracts*, ORGN 179). This work was supported by the National Science Foundation under Grant No. CHE-9500630 and the Donors of the Petroleum Research Fund, administered by the American Chemical Society.

[17] P. Chandrasekar, T. D. Lash, *Tetrahedron Lett.* **1996**, *37*, 4873.

[18] A report on the synthesis of a "mono-hook" porphyrin by the "3+1" approach was published recently: J. L. Sessler, J. W. Genge, A. Urbach, P. Sanson, *Synlett* **1996**, 187. These authors noted that the acid-catalyzed condensation of diformyltripyrranes with 3,4-diethylpyrrole failed to give any porphyrin products. As the initial condensation is likely to afford an electron-deficient pyrromethene unit that would be unable to react with a second pyrrole aldehyde moiety, this factor presumably prevents porphyrin formation.

[19] K. Berlin, E. Breitmaier, *Angew. Chem.* **1994**, *106*, 229; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 219; K. Berlin, E. Breitmaier, *ibid.* **1994**, *106*, 1356 and **1994**, *33*, 1246.

[20] T. D. Lash, *Angew. Chem.* **1995**, *107*, 2703; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2533.

[21] T. D. Lash, S. T. Chaney, *Chem. Eur. J.* **1996**, *2*, 944–948.

[22] J. L. Sessler, M. R. Johnson, V. Lynch, *J. Org. Chem.* **1987**, *52*, 4394.

[23] L. T. Nguyen, M. O. Senge, K. M. Smith, *J. Org. Chem.* **1996**, *61*, 998.

[24] Improved syntheses of pyrrolic intermediates have also facilitated these studies. See: J. B. Paine III, D. Dolphin, *J. Org. Chem.* **1985**, *50*, 5598; D. H. R. Barton, J. Kervagoret, S. Z. Zard, *Tetrahedron* **1990**, *46*, 7587; N. Ono, H. Kawamura, M. Bougauchi, K. Maruyama, *ibid.* **1990**, *46*, 7483; T. D. Lash, M. C. Hoehner, *J. Heterocyclic Chem.* **1991**, *28*, 1671; T. D. Lash, J. R. Bellettini, J. A. Bastian, K. B. Couch, *Synthesis* **1994**, 170.

[25] H. Rexhausen, A. Gossauer, *J. Chem. Soc. Chem. Commun.* **1983**, 275. A. K. Burrell, G. Hemmi, V. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **1991**, *113*, 4690.

[26] R. Charriere, T. A. Jenny, H. Rexhausen, A. Gossauer, *Heterocycles* **1993**, *36*, 1561.

[27] J. L. Sessler, A. K. Burrell, *Top. Curr. Chem.* **1991**, *161*, 177–273.

[28] R. Miller, K. Olsson, *Acta Chem Scand. B* **1981**, *35*, 303. J. B. Paine III, R. B. Woodward, D. Dolphin, *J. Org. Chem.* **1976**, *41*, 2826. E. Vogel, N. Jux, E. Rodriguez-Val, J. Lex, H. Schmickler, *Angew. Chem.* **1990**, *102*, 1431; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1387.

[29] T. D. Lash, B. H. Novak, Y. Lin, *Tetrahedron Lett.* **1994**, *35*, 2493. N. Ono, H. Hironaga, K. Simizu, K. Ono, K. Kuwano, T. Ogawa, *J. Chem. Soc. Chem. Commun.* **1994**, 1019. T. D. Lash, B. H. Novak, *Tetrahedron Lett.* **1995**, *36*, 4381. T. D. Lash, B. H. Novak, *Angew. Chem.* **1995**, *107*, 723; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 683.

[30] M. J. Crossley, P. L. Burn, S. J. Langford, J. K. Prashar, *J. Chem. Soc. Chem. Commun.* **1995**, 1921.

[31] K. Berlin, C. Steinbeck, E. Breitmaier, *Synthesis* **1996**, 336.

[32] P.-Y. Heo, K. Shin, C.-H. Lee, *Tetrahedron Lett.* **1996**, *37*, 197. See also: A. Ulman, J. Manassen, *J. Am. Chem. Soc.* **1975**, *97*, 6540; *J. Chem. Soc. Perkin Trans. I* **1979**, 1066.

[33] C.-H. Lee, F. Li, K. Iwamoto, J. Dadok, A. A. Bothner-By, J. S. Lindsey, *Tetrahedron* **1995**, *51*, 11645.

[34] For example, A. H. Jackson, W. Lertwanawatana, R. K. Pandey, K. R. N. Rao, *J. Chem. Soc. Perkin Trans. I* **1989**, 374.