5,10-Diphenyltripyrrane, a useful building block for the synthesis of *meso*-phenyl substituted expanded macrocycles

Christian Brückner, Ethan D. Sternberg, Ross W. Boyle and David Dolphin*

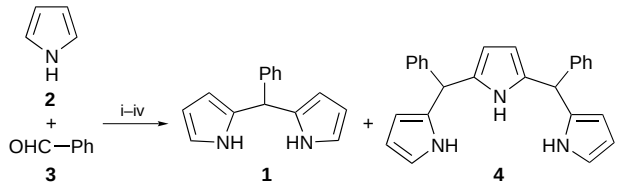
Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, V6T 1Z1, Canada

Pyrrole and benzaldehyde were condensed under acidic conditions to produce a mixture of 5-phenyldipyrromethane and 5,10-diphenyltripyrrane; the tripyrrane was utilized in syntheses of *meso*-phenylsapphyrins, *meso*-diphenylpentaphyrin and *meso*-hexaphenylhexaphyrin.

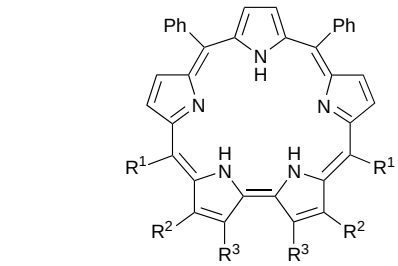
Expanded porphyrins[1] are a diverse class of pyrrolic compounds containing a larger macrocycle than that found in porphyrins. They are being utilized in fields such as photodynamic therapy (PDT),[2] neutral substrate binding, anion recognition[3] and annulene research.[4] Although β-unsubstituted *meso*-aryl substituted porphyrins are very prominent in the synthetic porphyrin field,[5] they are rarely found in expanded porphyrins.[6–8] This, perhaps, reflects the lack of a suitable building block as well as the reduced stability of some of these systems, as will be outlined below.

We report here the improved preparation of 5-phenyldipyrromethane, itself an important building block for *meso*-phenylporphyrinoids,[8] the one-step synthesis of the novel building block 5,10-diphenyltripyrrane and its use in 3 + 2- and 3 + 3-type syntheses to yield three *meso*-phenyl substituted sapphyrins varying in their β-substituents, a partially β-substituted pentaphyrin and a fully β-unsubstituted *meso*-hexaphenylhexaphyrin.

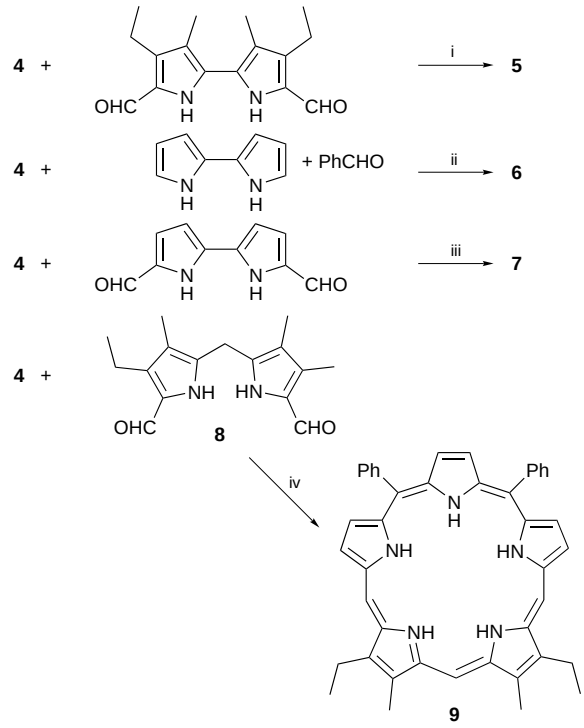
5-Phenyldipyrromethane **1** was synthesized by condensing excess pyrrole **2** and benzaldehyde **3** in the presence of an acid according to the procedures of Lee and Lindsey[9] or Carrel,[10] with the exception that generally 50% lower benzaldehyde to pyrrole ratios were used and, most importantly, work-up procedures were altered. The crude oils resulting from the condensation were, after pre-purification by column chromatography, transferred into a sublimation apparatus and heated under high vacuum (Scheme 1). Under these conditions, **1** sublimed as a white crystalline material of analytical purity. The reaction could be scaled up to provide up to 15 g (*ca.* 50% yield) of **1** per run. The residue left in the bottom of the sublimation apparatus hardened, upon cooling, into a red–orange glass. Analysis of this glass proved that it contained *ca.* 95% 5,10-diphenyltripyrrane **4**.† Lee and Lindsey[9] and Vigmond *et al.*[11] have previously reported the occurrence of a small amount of an unstable tailing component which, based on ^{1}H NMR spectroscopy, was provisionally assigned structure **4**. In subsequent work, Lee and co-workers synthesized this tripyrrane in a multi-step procedure and utilized it in the formation of heteroporphyrins.[11] Tripyrrane **4** was obtained by us in yields ranging typically from 10–20%, and, even when ground into a powder, is stable in the solid form but could not, in our hands,



Scheme 1 *Reagents and conditions*: i, pyrrole, PhCHO (1 : 10) (neat), TFA (5%), 1 h, under N_2, or pyrrole, PhCHO (1 : 8), PhMe, reflux, TsOH (cat.), under N_2; ii, evaporation of solvents *in vacuo*; iii, flash chromatography (silica gel, CH_2Cl_2); iv, sublimation at 130 °C at 1 torr, initial heating: 1 °C min^{-1}



5 R^1 = H, R^2 = Et, R^3 = Me
6 R^1 = Ph, R^2 = R^3 = H
7 R^1 = R^2 = R^3 = H



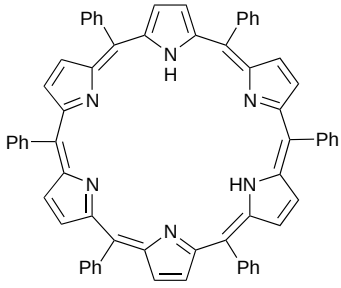
Scheme 2 *Reagents and conditions*: i, abs. EtOH (1 mM), O_2 bubble, TsOH (4 equiv.); evaporation of solvents *in vacuo*; column chromatography (neutral alumina, activity I, 2.5% MeOH–CH_2Cl_2); ii, CH_2Cl_2, under N_2, $BF_3{\cdot}Et_2O$ (cat.), 1 h; chloranil, reflux, 30 min; evaporation of solvents *in vacuo*; column chromatography (neutral alumina, activity I, 2.5% MeOH–CH_2Cl_2); preparative TLC (alumina, 1 : 1 CH_2Cl_2–CCl_4); iii, abs. EtOH (1 mM), O_2 bubble, TsOH (4 equiv.); evaporation of solvents *in vacuo*; trituration with $CHCl_3$; preparative TLC (silica gel, 0.5% MeOH–CH_2Cl_2); iv, CH_2Cl_2, TFA (cat.), 48 h, room temp., neutralisation with Et_3N, then an additional 36 h; column chromatography (neutral alumina, 1–3% MeOH–Ch_2Cl_2); then preparative TLC (silica gel, CH_2Cl_2–20% EtOAc–1% Et_3N)

be further purified without retrieving it as an unstable oil. We attribute this, in part, to the presence of three stereoisomers in **4**. This route to tripyrrane **4** is comparatively simple given that the syntheses of β-alkyltripyrranes generally involve many reaction steps from starting materials which are not commercially available, unlike pyrrole and benzaldehyde. It is anticipated that the ease of preparation of **4** will encourage its use as a synthetic building block.

With the novel 5,10-diphenyltripyrrane **4** in hand, we had the opportunity to prepare *meso*-diphenyl substituted sapphyrins **5** and **7**‡ and, in a four-component Rothemund-type condensation, *meso*-tetraphenylsapphyrin **6** (Scheme 2). Recently, Sessler *et al.* published the synthesis of **5** *via* a multi-component condensation under Lindsey-type conditions[6] and Chmielewski *et al.* published the isolation of sapphyrin **6** as a side-product from a Rothemund synthesis of tetraphenylporphyrin.[7] Both procedures, however, produce the particular sapphyrins in low yields (*ca.* 10 and 1.1%, respectively) and both require extensive chromatographic work-up. The syntheses presented here using the preformed tripyrrolic precursor are short, produce up to 39% yield in the final sapphyrin condensation (for **5**) and, due to the absence of any other porphyrinic by-products, require only minimal chromatographic work-up. The inversion of one pyrrolic unit in **7** upon protonation–deprotonation as observable by NMR spectroscopy is analogous to that described before for **6**.[7] The *meso*-positions flanking the 'flipping' pyrrolic unit do not participate in this inversion.

A TFA catalysed 3 + 2-type condensation of tripyrrane **4** and dipyrromethane **8** in the presence of nitrogen, followed by treatment with base and then by chromatography, produced the orange *meso*-diphenyltetra-β-alkyl pentaphyrin **9** in 13% yield (Scheme 2). The pentaphyrin was characterized by 1H NMR spectroscopy, mass spectrometry and UV-VIS spectroscopy.§ Its optical properties are similar to those of previously reported β-alkyl pentaphyrins.[13] The strongly solvent-dependent ^{1}H NMR spectrum can be rationalized in terms of inversions of pyrrolic units similar to those observed in sapphyrins. However, unlike the stable β-alkyl pentaphyrins, this macrocycle exhibited poor stability even in the solid state and decomposed when exposed to air, with a half-live of several days. It remains to be seen whether the macrocycle can be stabilized by metal complexation.[14]

On the other hand, a 3 + 3-type condensation reaction employing **4** and benzaldehyde **3** furnished, after oxidation with chloranil and chromatography, a blue product which could be identified by its mass and UV-VIS spectra as the *meso*-hexaphenylhexaphyrin **10**.¶ Its ^{1}H NMR was complex and



10

largely depended on pH and the nature of the solvent. This may reflect its non-static conformation. Such flexibility of the macrocycle has also been observed for β-alkyl hexaphyrins. Further studies of this macrocycle were hampered by its instability.

The above examples prove the synthetic utility of **4**. It also emerges that the *meso*-phenyl substituted versions of the larger expanded macrocycles pentaphyrin and hexaphyrin exhibit a significantly decreased stability when compared with their β-alkyl analogues. This stability trend has been observed before,[8] and, if this is a general trend, may limit the extent to which *meso*-phenyl substituted analogues of other known expanded macrocycles can be made.

This work was supported by the Natural Sciences and Engineering Council of Canada.

Footnotes and References

* E-mail: david@dolphin.chem.ubc.ca

† *Selected data* for **4**: ^{1}H NMR (200 MHz, CD_2Cl_2): δ 5.35 (s, 2 H), 5.78 (d, J = 4, 2 H), 5.89 (s, 2 H), 6.14 (m, 2 H), 6.66 (m, 2 H), 7.15–7.38 (m, 10 H), 7.75 (br s, 1 H), 7.88 (br s, 2 H); HRMS (EI, 200 °C) $C_{26}H_{23}N_3$ requires 377.1892. Found: 377.1881.

‡ *Selected data* for **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ −1.52 (s, 2 H), −0.1 (br s, 1 H), 7.15–7.20 (m, 1 H), 7.25–7.30 (m, 1 H), 7.60 (t, ^3J 7, 2 H), 7.85 (t, ^3J 8, 4 H), 8.49 (br s, 4 H), 9.24 (d, ^3J 4.5, 2 H), 9.43 (d, ^3J 4.5, 2 H), 9.60 (d, ^3J 4.5, 2 H), 10.20 (d, ^3J 5.0, 2 H), 10.27 (s, 2 H); λ_{max}/nm (CH_2Cl_2–trace Et_3N) (log ε) 478 (4.86), 506 (4.71), 626 (3.67), 686 (3.97), 708 (sh), 786 (3.62); HRMS (EI, 180 °C) $C_{36}H_{25}N_5$ requires 527.21100. Found: 527.21015. For **7**·2HCl: λ_{max}/nm (CH_2Cl_2–trace HCl) (log ε) 482 (5.47), 656 (4.13), 682 (4.13), 724 (sh), 758 (4.70) nm.

§ *Selected data* for **9**: ^{1}H NMR (400 MHz, $CDCl_3$–TFA): δ −3.6 (br s, 1 H), 2.9 (br s, 2 H), 2.12 (t, ^3J 8.2, 6 H), 4.08 (s, 6 H), 4.56 (br q, ^3J 8, 4 H), 7.5 (br m, 10 H), 8.1 (m, 4 H), 8.6 (br s, 2 H), 11.4 (s, obscured by TFA signal), 11.5 (s, obscured by TFA signal); λ_{max}/nm (CH_2Cl_2–TFA) (log ε) 492 (1.21), 682 (0.072), 742 (0.046); HRMS (LSIMS, thioglycerol) $C_{43}H_{40}N_5$ requires 626.32837. Found: 626.32756.

¶ *Selected data* for **10**: λ_{max}/nm (CH_2Cl_2) (rel. intensity) 385 (0.95), 466 (0.46), 520 (0.5) 636 (1.0); HRMS (EI, 350 °C) $C_{66}H_{44}N_6$ requires 920.36273. Found: 920.36550.

1 J. L. Sessler and S. J. Weghorn, *Expanded, Contracted, and Isomeric Porphyrins*, Pergamon, N.Y., 1997; A. Jasat and D. Dolphin, *Chem. Rev.*, 1997, in the press.
2 D. Dolphin, *Can. J. Chem.*, 1994, **72**, 1005; R. Bonnett, *Chem. Soc. Rev., 1995, 19.*
3 J. L. Sessler, M. Cyr, H. Furuta, V. Král, T. Mody, T. Morishima, M. Shionoya and S. Weghorn, *Pure Appl. Chem., 1993*, 65, 393; B. L. Iverson, K. Shreder, V. Kral, D. A. Smith, J. Smith, J. L. Sessler, *Pure Appl. Chem.*, 1994, **66**, 845.
4 D. O. Mártire, N. Jux, P. F. Aramedía, R. M. Negri, J. Lex, S. E. Braslavsky, K. Schaffner, and E. Vogel, *J. Am. Chem. Soc.*, 1992, **114**, 9969; E. Vogel, *Pure Appl. Chem.*, 1993, **65**, 143.
5 J. B. Kim, A. D. Adler and F. R. Longo, in *The Porphyrins*, ed. D. Dolphin, Academic Press, New York, 1978, vol. 1, pp. 85–100; J. S. Lindsey, S. Prathapan, T. E. Johnson and R. W. Wagner, *Tetrahedron*, 1994, **50**, 8941.
6 J. L. Sessler, L. Lisowski, K. A. Boudreaux, V. Lynch, J. Barry and T. J. Kodadek, *J. Org. Chem.*, 1995, **60**, 5975.
7 P. J. Chmielewski, L. Latos-Grazynski and K. Rachlewicz, *Eur. J. Chem.*, 1995, **1**, 68.
8 R. W. Boyle, L. Y. Xie and D. Dolphin, *Tetrahedron Lett.*, 1994, **35**, 5377; L. Y. Xie, R. W. Boyle and D. Dolphin, *J. Am. Chem. Soc*., 1996, **118**, 4853.
9 C.-H. Lee and J. S. Lindsey, *Tetrahedron*, 1994, **50**, 11427.
10 T. Carell, Ph.D. Thesis, Ruprechts-Karl-Universität, Germany, 1993. See footnotes of: G. Shipps, Jr. and J. Rebek, Jr., *Tetrahedron Lett.*, 1994, **35**, 6823.
11 S. J. Vigmond, M. C. Chang, K. M. R. Kallury and M. Thompson, *Tetrahedron Lett.*, 1994, **35**, 2455.
12 P.-Y. Heo, K. Shin and C.-H. Lee, *Tetrahedron Lett.*, 1996, **37**, 197; P. Y. Heo and C.-H. Lee, *Bull. Korean Chem. Soc.*, 1996, **17**, 515.
13 H. Rexhausen, and A. Gossauer, *J. Chem. Soc., Chem. Comm.*, 1983, 275; R. E. Dansodanquah, L. Y. Xie and D. Dolphin, *Heterocycles*, 1995, **41**, 2553.
14 A. K. Burrell, G. Hemmi, V. Lynch, and J. L. Sessler, *J. Am. Chem. Soc.*, 1991, **113**, 4690.

Received in Corvallis, OR, USA, 26th February 1997; revised manuscript received, 26th June 1997; 7/04510G