Syntheses of symmetrically substituted 5-alkyl- and 5-aryl-dihydrodipyrrins and of porphyrins and bisporphyrins therefrom

David A. Lee and Kevin M. Smith *

Department of Chemistry, University of California, Davis, CA 95616, USA

Acid-catalysed treatment of 2-unsubstituted pyrroles with alkyl or aryl acetals affords good yields of the corresponding symmetrical 5-substituted dihydrodipyrrins (*e.g.* 7, 19, 38, 51, 52). Using MacDonald '2 + 2' methodology, such dihydrodipyrrins are transformed in several steps into 5,15-disubstituted porphyrins (*e.g.* 5, 23, 24, 26, 36), wherein the 5- and 15-substituents can be identical or different. Further functionalization of 5 affords nickel(II) 5-vinyl-15-substituted porphyrin 4 which, after Vilsmeier formylation ($POCl_3$–DMF) of the nickel(II) complex, yields the corresponding nickel(II) 5-(formylvinyl)porphyrin 3; cyclization under acidic conditions then gives the nickel 15-phenylbenzochlorin 1. Nickel(0)-catalysed reductive dimerization of the nickel(II) 15-(*p*-chloromethylphenyl)porphyrin 48 yields the dihydrostilbene dimer 53, which can also be obtained in lower yield by reductive dimerization of 5-(*p*-chloromethylphenyl)dihydrodipyrrin 57, followed by MacDonald-type cyclization and metallation of the free-base dimer 54.

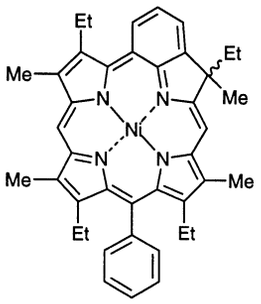
Benzochlorins have recently attracted attention as potential second generation photosensitizers in photodynamic therapy (PDT) of tumours.[1] PDT utilizes a protocol involving administration of a sensitizer (which is hopefully localized or retained preferentially in tumour tissue), followed by irradiation with light of a particular wavelength to initiate tumour necrosis. Optimum penetration of tissue by light is observed[2] to be in the range 650–860 nm; thus sensitizers, such as benzochlorins and certain other tetrapyrroles which absorb strongly in that region, offer significant advantages for PDT compared with Photofrin®, the mixture of hematoporphyrin oligomers (optimum λ 630 nm), which is currently approved in the USA and elsewhere. The standard methodology for benzochlorin synthesis[3] involves acid-catalysed cyclization of a *meso*-acrolein substituted porphyrin. *meso*-Acrolein porphyrins can be obtained by a fairly lengthy route involving Vilsmeier formylation of a copper(II) or nickel(II) porphyrin, Wittig reaction, reduction and reoxidation to formylvinyl, with a demetallation step included at some point.[3] Alternatively, the vinylogous Vilsmeier reagent from *N*,*N*-dimethylaminoacrolein can be used to directly attach a *meso*-acrolein unit to the metalloporphyrin.[4] Unfortunately, except in rare cases,[4,5] Vilsmeier formylation of porphyrins is not regioselective (unless, for example one uses a symmetrical or 5,15-disubstituted porphyrin)[6,7] and so we chose to focus attention on the design and regioselective synthesis of a model benzochlorin **1**, to be approached *via* the 15-vinylporphyrin **2**. It is now well-known that the Vilsmeier reagent (generated by reaction of $POCl_3$ and DMF) reacts regiospecifically at the terminus of vinyl substituents in preference to unsubstituted *meso*-positions of metalloporphyrins.[8] Thus, we expected that it should be possible to prepare the 15-formylvinylporphyrin **3** uniquely from the 15-vinylporphyrin **4**, by reaction with Vilsmeier reagent. In order to utilize this type of pathway it would be necessary to design and develop a regioselective route to prepare *meso*-vinylporphyrins.

Although *meso*-vinylporphyrins have previously been prepared,[9] there have been no reported regioselective examples for their preparation. We envisioned preparation of the 15-vinylporphyrin **2** directly by E2 elimination from a 15-(2-halogenoethyl) functionality, as found for example in the 15-(2-chloroethyl)porphyrin **5**. Finally, we decided upon the MacDonald ('2 + 2') approach to fabricate the porphyrin nucleus,[10,11] by condensation of the 5-(2-chloroethyl)dihydrodipyrrin-1,9-dicarboxylic acid **6** with an appropriate symmetrical dihydrodipyrrin, for example 1,9-diformyldihydrodipyrrin **9**; compound **9** can, in turn, be prepared from the corresponding diethyl 1,9-dicarboxylate **10** *via* **11**. Alternatively, we could prepare a direct precursor to **7** such as 5-(2-hydroxyethyl)dihydrodipyrrin **12**. The hydroxyethyl functionality of dihydrodipyrrin **12** could be converted into the required 2-chloroethyl group by treatment with thionyl chloride, following preparation of the corresponding 15-(2-hydroxyethyl)porphyrin. An element of regiocontrol would be established early in our synthesis, based on the use of appropriately functionalized dihydrodipyrrin precursors.

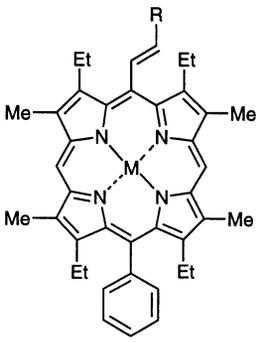
Though syntheses of a variety of *meso*-5-alkyl and *meso*-5-aryl substituted and/or functionalized dihydrodipyrrins have been reported in the literature,[12–16] prior to our communication[15] in this area, no general methodology had been reported for the preparation of a *meso*-5-functionalized dihydrodipyrrin in which the functional group is on an aliphatic chain. However, in 1954, Kleinspehn and Corwin[12] made initial progress in the preparation of *meso* acetic ethyl ester functionalized dihydrodipyrrins and in 1990 Burns and Smith[13] used a modified acid catalyst system (TFA and acetic acid) and a modified Michael acceptor to facilitate Kleinspehn's approach.[12] In 1994 Liddell *et al.* reported[14] the preparation of a 5-butyric methyl ester dihydrodipyrrin. As with the previous methods, this route requires the preparation of two different pyrrolic precursors, where the ideal synthesis of symmetrical dihydrodipyrrins would require only one. Therefore, we developed an alternative route,[15] namely the condensation of 2-unsubstituted pyrroles with functionalized aliphatic acetals.

5-Aryl-dihydrodipyrrins, for example dihydrodipyrrin **14**, can now be obtained in good to excellent yields by condensation of 2-unsubstituted pyrroles with commercially available or readily prepared aromatic acetals or aldehydes in the presence of an acid catalyst.[15–17] We rationalized that functionalized aliphatic acetals would be the synthetic equivalent of the methyl chloromethoxyacetate reagents used by Neef and Heaney to prepare analogous dimers of furans, thiophenes and indoles,[18,19] and numerous functionalized acetals are commercially available.

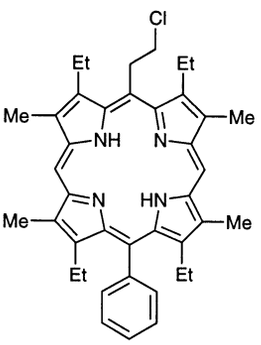
Initial attempts to condense 2 equiv. of 2-unsubstituted pyr-



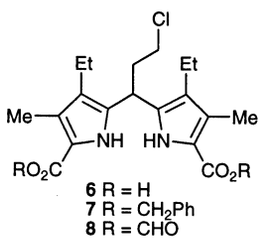
1



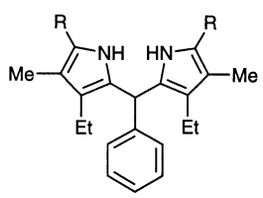
2 R = H; M = 2H
3 R = CHO; M = Ni
4 R = H; M = Ni



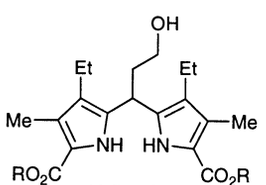
5



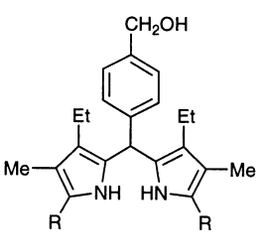
6 R = H
7 R = CH_2Ph
8 R = CHO



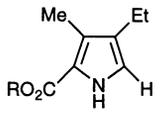
9 R = CHO
10 R = CO_2Et
11 R = H



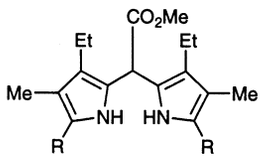
12 R = CH_2Ph
13 R = H



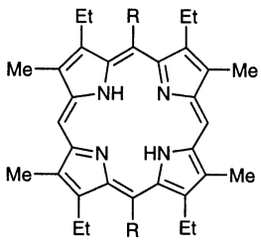
14 R = CO_2Et
15 R = H
16 R = CO_2CH_2Ph



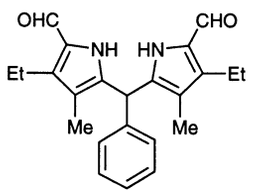
17 R = CH_2Ph
18 R = Et



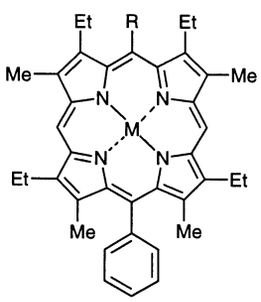
19 R = CO_2CH_2Ph
20 R = CO_2H
21 R = CHO
22 R = H



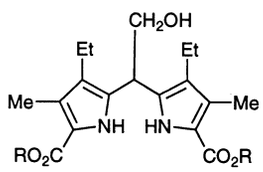
23 R = CO_2Me
24 R = CH_2CH_2Cl



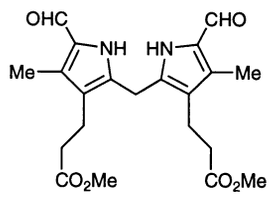
25



26 M = 2H; R = CO_2Me
27 M = Ni; R = $CH{=}CH_2$
28 M = Ni; R = CO_2Me
29 M = Ni; R = CH_2OH
30 M = Ni; R = CHO
31 M = Ni; R = H



32 R = CH_2Ph
33 R = H



34

role **17** with 1 equiv. of methyl dimethoxyacetate (MDMA) and catalytic HCl in refluxing ethanol gave only starting material. After several trial experiments, we settled upon toluene as reaction solvent and pyridinium toluene-*p*-sulfonate (PTs) as an anhydrous acid catalyst. The 2-unsubstituted pyrrole **17** (1 equiv.), MDMA (2 equiv.) and a catalytic amount of PTs in toluene were heated for 8 days to give the dihydrodipyrrin **19** (56%).

Catalytic hydrogenation of **19** gave the dihydrodipyrrin-1,9-dicarboxylic acid **20** which was formylated under Vilsmeier conditions to afford the 1,9-diformyldihydrodipyrrin **21** (73%). Using a modification[11] of the MacDonald condensation,[10] 1,9-diformyldihydrodipyrrin **21** and the 1,9-di-unsubstituted dihydrodipyrrin **22** gave the C_2 symmetric porphyrin **23** (*meso* protons: 10.28 ppm, s, 2 H) in 19% yield after oxidation with DDQ.

Condensation of the 5-phenyl-1,9-diformyldihydrodipyrrin **25** with the 5-substituted dihydrodipyrrin-1,9-dicarboxylic acid **20** gave the semi-symmetric porphyrin **26** (*meso* protons: 10.25 ppm, s, 2 H) in 30% yield after oxidation with DDQ. The structure of the product was confirmed by single crystal X-ray crystallography.‡

We envisioned a four-step reaction sequence for the conversion of **26** into Ni^{II}-*meso* vinylporphyrin **27**, involving metallation (to give **28**), reduction (to **29**), oxidation (to **30**) and a Wittig reaction to afford the desired *meso*-vinylporphyrin **27**. Metallation proceeded uneventfully, but reduction of the aldehyde to the alcohol could not be accomplished, though a number of reducing agents were employed ($NaBH_4$, BH_3·THF, LAH); the last of these caused only deformylation to give **31**. Though we eventually discovered that reduction of **26** with an excess of DIBAL afforded the desired product in good yield, at this point we turned our attention to reduction for the corresponding formyldihydrodipyrrins.

Treatment of dihydrodipyrrin **19** with an excess of diborane afforded the 5-(hydroxymethyl)dihydrodipyrrin **32**. Catalytic hydrogenolysis of **32** gave **33** in quantitative yield and condensation of **33** with 1,9-diformyldihydrodipyrrin **23** afforded porphyrin **35** as the major product in 14% yield. Once again, the *meso*-substituent had been eliminated. Our emphasis therefore changed toward the preparation of the 15-(2-hydroxyethyl)porphyrin **36** and from it, the 15-(2-chloroethyl)porphyrin **5**.

In theory, 5-(methoxycarbonylmethyl)dihydrodipyrrins can be reduced to afford the corresponding 5-(2-hydroxyethyl) ana-

‡ A full paper dealing with the crystal and molecular structure of a comprehensive series of 5,15-disubstituted porphyrins (*e.g.* **26**, **36**, **46** and **47**) has been submitted for publication.[20]

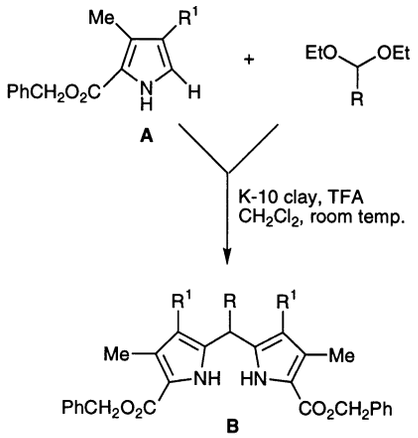


Table 1 Yields for transformation of pyrrole **A** into symmetrical dihydrodipyrrin **B**

Product (**B**)	R	Yield (%)
— *a,c*	CH_2Cl	91
— *b,d*	CH_2CN	41
7 *b*	CH_2CH_2Cl	87
12 *b*	CH_2CH_2OH	65
38 *b,e*	CH_2CO_2Me	62
40 *b*	(*p*-Ar)CH_2OCOCF_3	59

[a] R^1 = Me. [b] R^2 = Et. [c] H. Xie, D. A. Lee, D. M. Wallace, M. O. Senge and K. M. Smith, *J. Org. Chem.*, in the press. [d] See Experimental section. [e] Prepared using the dimethoxyacetal.

logues.[21] Attempts to synthesize **38** from pyrrole **17** and methyl 3,3-dimethoxypropionate (MDMP) using the PTs catalyst were complicated by formation of a by-product, often in yields as high as 88%, which was identified as **42**. But condensation of the 2-unsubstituted pyrrole **17** with MDMP, using Montmorillonite K-10 clay or TsOH gave the required product **38** in 62 or 77% yield, respectively. Reduction of **38** using an excess of diborane (6 equiv.) gave 5-(2-hydroxyethyl)dihydrodipyrrin **12** in 65% yield. This was subjected to catalytic hydrogenation and gave the expected dihydrodipyrrin-1,9-dicarboxylic acid **13** in quantitative yield. In order to prevent undesirable acid-catalysed side reactions during the MacDonald condensation, compound **12** was treated with acetic anhydride in pyridine to give the 5-(2-acetoxyethyl)dihydrodipyrrin **39** (81%). Subsequent catalytic hydrogenation gave quantitatively the dihydrodipyrrin-1,9-dicarboxylic acid **43**. Condensation of **43** with 1,9-diformyldihydrodipyrrin **9** under the modified MacDonald conditions provided the 15-(2-hydroxyethyl)porphyrin **36** (20%), along with a chromatographically more mobile porphyrin (5%) as a minor product which was identified as the 5-(2-acetoxyethyl)porphyrin **37**. The 5-(2-hydroxyethyl)porphyrin **36** was additionally characterized by a single X-ray crystal structure.‡,[20]

Having developed a direct route to prepare 15-(2-hydroxyethyl)porphyrins such as **36**, the use of 5-(2-chloroethyl)-dihydrodipyrrin **7** as a porphyrin precursor was also investigated. 5-(2-Hydroxyethyl)dihydrodipyrrin **12** was treated with a slight excess of thionyl chloride in pyridine, to give the 5-(2-chloroethyl)dihydrodipyrrin **7** (86%). Treatment of pyrrole **17** with commercially available chloropropionaldehyde diethyl acetal (CPDA) using the TsOH–toluene conditions gave extremely low yields of the 5-chloroethyldihydrodipyrrin **7**. Use of Montmorillonite K-10 clay and trifluoroacetic acid (TFA), however, allowed preparation of the 5-(2-chloroethyl)dihydrodipyrrins directly. The catalyst was prepared by treatment of K-10 clay suspended with TFA and was used for the preparation of a variety of 5-functionalized dihydrodipyrrins, in good to excellent yields (59–91%) and with minimal or no chromatographic purification. For example, the 5-(2-chloroethyl)-dihydrodipyrrin **7** was prepared in 87% yield from the 2-unsubstituted pyrrole **17** and CPDA. Table 1 summarizes a few examples using this modified catalyst system.

Some unusual results were also obtained; for example, an attempt to prepare 5-(4-hydroxymethylphenyl)dihydrodipyrrin **14** from 4-hydroxymethylbenzaldehyde diethyl acetal and the 2-unsubstituted pyrrole **17** afforded 5-(4-trifluoroacetoxymethylphenyl)dihydrodipyrrin **40** (59%). Additionally, when an attempt was made to synthesize the dihydrodipyrrin **19** from the 2-unsubstituted pyrrole **17** and methyl dimethoxyacetate, the dihydrodipyrrin **19** and a side product **41**, in which the methoxycarbonyl group had been cleaved, were obtained in an overall yield of 67%.

Catalytic hydrogenolysis of **7** gave the dihydrodipyrrin-1,9-dicarboxylic acid **6** in quantitative yield and condensation with the 1,9-diformyldihydrodipyrrin **9** afforded the 15-(2-chloroethyl)porphyrin **5** (28%) as the major product.

meso-Vinyl and *meso*-acrolein porphyrins

The most commonly used route to vinylporphyrins is by E2 elimination of the appropriate (2-chloroethyl)porphyrin precursors, using *tert*-butoxide or aqueous base.[22] 5-(2-Chloroethyl)porphyrin **5** was treated with aqueous base and gave the 15-vinylporphyrin **2** in quantitative yield. The nickel complex **4** was prepared by treatment of **2** with nickel(II) acetoacetonate and the product, upon treatment with $POCl_3$–DMF, yielded the corresponding *meso*-acrolein porphyrin **3** (57%), along with two minor by-products which were assumed to be *meso*-formylated materials (*e.g.* **44** and **45**). Such porphyrins are of some interest as synthetic precursors to other porphyrins and their reduced analogues. Since there exist only a limited number of synthetic routes of tri- and tetra-*meso*-substituted porphyrins in which all of the *meso* substituents are different,[17,23] we attempted to optimize the formation of the two minor products (**44** and **45**) by using longer reaction times. 15-Vinylporphyrin **4** was treated with an excess of Vilsmeier reagent ($POCl_3$–DMF) for several times the normal reaction time (used above) and provided an 89% total yield of 20-(formylvinyl)porphyrin **3** (41%), 20-vinyl-5-formylporphyrin **44** (15%) and 20-(formylvinyl)-5-formylporphyrin **45** (33%).

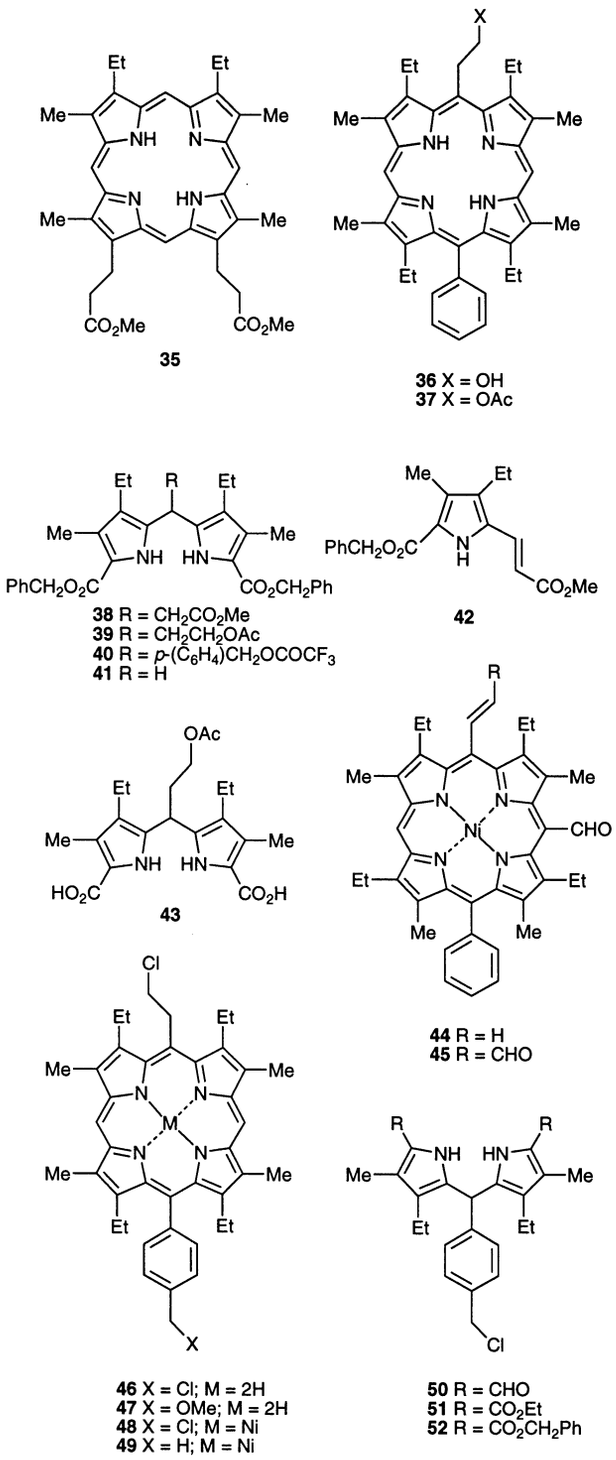
Benzochlorin

Several routes are available for benzochlorin synthesis from *meso*-acrolein porphyrins.[3–5] Treatment of Ni^{II}-*meso*-15-(formylvinyl)porphyrin **3** with conc. sulfuric acid gave the benzochlorin **1** (83%). Its optical spectrum showed a long wavelength absorption in the visible region at 672 nm (ε = 21 600), characteristic of such reduced porphyrin derivatives. Fig. 1 shows the optical spectra for nickel(II) 15-(2-formylvinyl)-porphyrin **3** and the corresponding benzochlorin **1**.

Diphenylethane linked bisporphyrins and bisdihydrodipyrrins

A number of bis-porphyrin systems have been synthesized in which the two porphyrin components are linked by ethane or ethene groups, as well as by stilbene moieties.[4,24–32] It was decided to test our proposed methodology by syntheses of dihydrostilbene-linked bisporphyrins. Part of the planned approach involved utilization[15] of low-valent oxidation states (particularly of nickel) for the reductive homo-coupling of appropriate benzylic halides.[33–40] Though such reductive coupling reactions have been employed extensively to dimerize a number of smaller systems, this methodology has not previously been applied to larger heterocyclic frameworks such as porphyrin and/or dihydrodipyrrin systems.

In 1982 Rieke and co-workers showed that nickel(0) could be used to mediate reductive coupling of benzylic halides to afford good yields of the corresponding dihydrostilbene linked dimers,[25,26] The nickel(0) reagent was prepared *in situ* by reduction of nickel(II) iodide with lithium metal in dimethoxyethane (DME), utilizing naphthalene as an electron carrier. The 1,9-



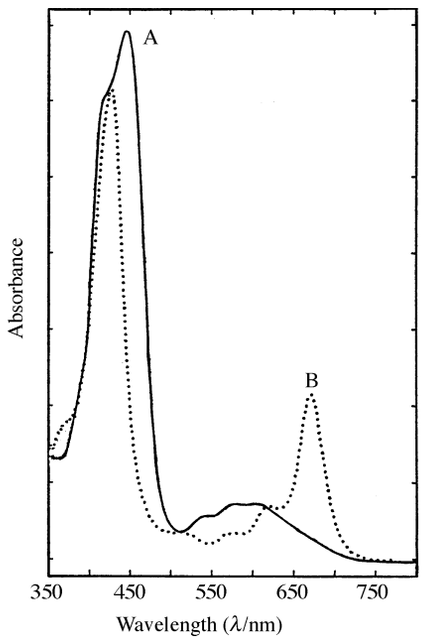
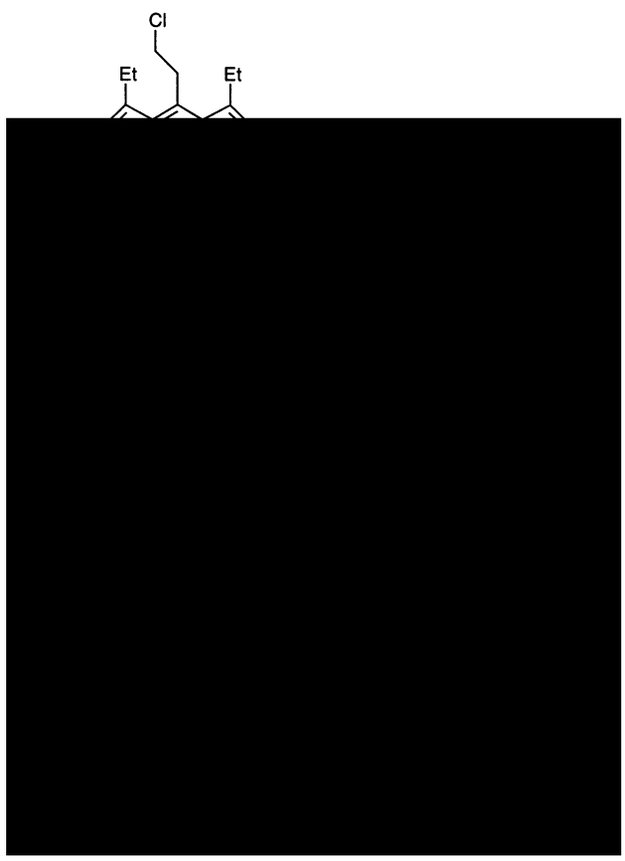


Fig. 1 Optical spectra, in dichloromethane, of A, nickel(II) 15-(2-formylvinyl)porphyrin **3** and, B, nickel(II) benzochlorin **1**



diformyldihydrodipyrrin **50** necessary for the preparation of 5-(4-chloromethylphenyl)-15-(2-chloroethyl)porphyrin **46**, was prepared in three steps (*via* **15**) in 72% yield from **51**. Condensation of *meso*-5-(2-chloroethyl)dihydrodipyrrin **6** with 1,9-diformyl-(*p*-chloromethylphenyl)dihydrodipyrrin **50** afforded the 5-(4-chloromethylphenyl)-15-(2-chloroethyl)porphyrin **46** (27%). A predictable side-product of the condensation was shown to be 5-(methoxymethylphenyl)-15-(2-chloroethyl)porphyrin **47**. The structures of both **46** and **47** were further confirmed by X-ray crystallography.‡[20]

Low-valent nickel reduction of the metal free porphyrin **46** was problematic, in common with observations[4,31,33,34,41,42] of similar reductive dimerizations. However, when the nickel(II) complex **48** was treated with freshly generated nickel(0) in DME, two products were obtained and identified as the desired bisporphyrin **53** (51%) and the *meso*-tolylporphyrin **49** (38%).

Reductive coupling of appropriately substituted dihydrodipyrrins was next investigated. The 5-[(4-hydroxymethyl)-phenyl]dihydrodipyrrins **14** and **16** were prepared in quantitative yields by condensation of 2 equiv. of the 2-unsubstituted pyrroles **18** or **17** with 4-(diethoxymethyl)benzyl alcohol in the presence of concentrated HCl. 5-(4-Chloromethylphenyl)-dihydrodipyrrins **51** and **52** were prepared from these substances using conditions similar to those utilized for the conversion of 5-(2-hydroxyethyl)dihydrodipyrrin **12** into 5-(2-chloroethyl)dihydrodipyrrin **7**. 5-(Hydroxymethylphenyl)-dihydrodipyrrin **14** was treated with thionyl chloride and pyridine