5,15-Diphenyl-7-oxobenzochlorins. Novel Long-wavelength Absorbing Photosensitizers for Photodynamic Therapy

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Copper(II)–5,15-diphenylporphyrin **1** is converted to 5,15-diphenyl-7-oxobenzochlorin **3** (M = 2H) by a modified Vilsmeier formylation, $\mathrm{BF_3}$-catalysed cyclization, oxidation and demetallation.

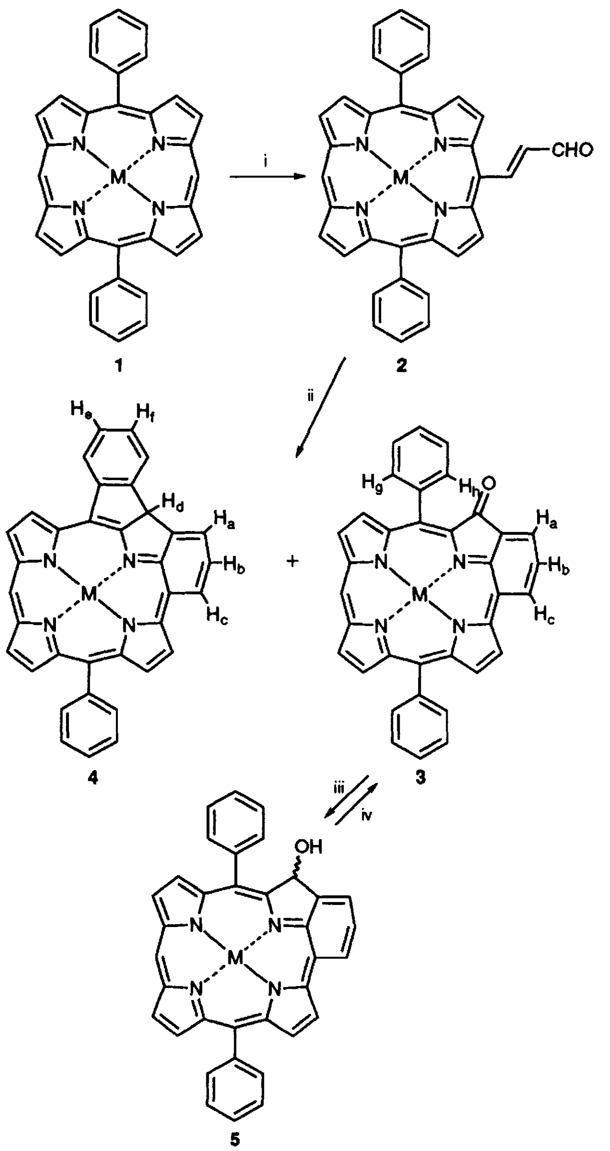
The area of photodynamic technologies, a rapidly expanding, multidisciplinary field, is concerned with harnessing the photosensitizing power of dyes and pigments to allow site-specific treatment of a number of medical conditions including cancer, psoriasis and artheriosclerotic plaques.[1,2] The drug currently approved for clinical photodynamic therapy of certain solid tumours, Photofrin®, is a mixture of haematoporphyrin oligomers with a long-wavelength absorption band at 630 nm. We have recently focused our research efforts on synthesizing photosensitizers that are isomerically pure with absorption maxima in the 700–800 nm region of the spectrum, where light scattering and absorption by normal tissue are minimized.[3]

Benzochlorins have received considerable attention as models for photosynthetic processes,[4] and as possible photodynamic sensitizers;[5,6] however, in these reports absorption maxima for the unmetallated derivatives are in the 670–680 nm range and/or the compound exists as a mixture of isomers. To date benzochlorins have been synthesized only from β-substituted porphyrins and, in all but one case, this resulted in the generation of a chiral centre at the β-pyrrolic position adjacent to that used for closure to the benzenoid ring. We envisaged that, using fully β-unsubstituted 5,15-diphenylporphyrins, the ring-closure step would yield a benzochlorin in which this adjacent β-position would be susceptible to oxidation to a ketone owing to its doubly allylic nature, thus allowing concomitant collapse of the chiral centre and extension of conjugation.

Copper(II)–5,15-diphenylporphyrin **1** (M = Cu) was synthesized from *meso*-phenyldipyrromethane, in two steps, using literature methods.[7] Treatment of **1** (M = Cu) with *N,N*-dimethylaminoacrolein–phosphorus oxychloride gave copper(II)–5,15-diphenyl-10-(2-formylvinyl)porphyrin **2** (M = Cu). Cyclization of **2** (M = Cu) was achieved using boron trifluoride–diethyl ether as catalyst and gave, unexpectedly, two products detected by TLC (R_f 0.84 and 0.37). Separation and analysis indicated that the more polar material was copper(II)–5,15-diphenyl-7-oxobenzochlorin **3** (M = Cu) while the less polar product **4** (M = Cu) gave a molecular ion *m/z* 15 lower than that of **3** (M = Cu) in the fast atom bombardment mass spectrum. As the presence of the paramagnetic copper(II) prevented acquisition of NMR spectra for these compounds the reaction sequence was repeated with nickel(II)–5,15-diphenylporphyrin **1** (M = Ni).

The analogous nickel complexes were formed and examined. The 400 MHz NMR spectrum for the more polar nickel complex confirmed it to be the 7-oxo compound **3** (M = Ni) while the less polar material **4** (M = Ni) showed unexpected signals in the δ 5–7 range and extensive splitting of the phenyl signals. Callot *et al.*[8] reported similar results for compounds where one of the phenyl rings of tetraphenylporphyrin was locked into a conformation coplanar with the porphyrin by fusing an *ortho*-phenyl position to an adjacent β-pyrrolic position *via* a one-carbon bridge. COSY and decoupling experiments allowed us to assign all the signals in the spectrum of the less polar nickel(II) complex **4** (M = Ni). The three protons of the newly formed benzenoid ring resonate at δ 5.78 (d, $\mathrm{H_a}$), 6.03 (t, $\mathrm{H_b}$) and 7.82 (d, $\mathrm{H_c}$); a 1H singlet ($\mathrm{H_d}$) appears at δ 6.09, while a 2H triplet at δ 7.56 ($\mathrm{H_e}$, $\mathrm{H_f}$) is coupled with the downfield 7H multiplet of the phenyl signals at δ 7.66–7.74. These results may be rationalized on the basis of distortion from planarity of the porphyrin conjugated system due to fusion of one of the *ortho*-phenyl positions to the adjacent 7-β-pyrrolic position. Thus efficient overlap of the porphyrin π-orbitals with those of the newly formed benzenoid ring is prevented and protons $\mathrm{H_a}$ and $\mathrm{H_b}$ show diene character. Proton $\mathrm{H_c}$ is deshielded by the anisotropic ring current of the porphyrin and comes to resonance further downfield. This distortion of the molecule was confirmed by molecular modelling using InsightII (Biosym, San Diego).

The NMR spectrum of **3** (M = Ni) showed signals for $\mathrm{H_a}$, $\mathrm{H_b}$, $\mathrm{H_c}$ at δ 9.07, 7.57, 8.14, respectively; the phenyl signals were a tight multiplet at δ 7.64–7.68, except for a doublet of doublets downfield at δ 7.83 resulting from the two *ortho*-



Scheme 1 *Reagents and conditions*: i, $\mathrm{Me_2NCHCHCHO}$, $\mathrm{POCl_3}$, $\mathrm{ClCH_2CH_2Cl}$, sonicate, 4 h; ii, $\mathrm{BF_3 \cdot OEt_2}$, $\mathrm{CH_2Cl_2}$; iii, $\mathrm{NaBH_4}$, $\mathrm{CH_2Cl_2}$–MeOH; iv, air or DDQ, $\mathrm{CH_2Cl_2}$

phenyl protons (H_g, H_h). These data seem to suggest a relief of the conformational strain imposed on **4** (M = Ni) which was again confirmed by molecular modelling. Treatment of **3** (M = Cu) with $NaBH_4$ in CH_2Cl_2–MeOH resulted in collapse of the long-wavelength absorption band at 730 nm which was replaced by a strong absorption centred at 666 nm; this change was accompanied by a shift in the Soret band from 372 to 408 nm. This more 'normal' chlorin spectrum was due to reduction of the ketone group in the 7 position to an unstable secondary alcohol **5** (M = Cu) which, on stirring the compound in solvent open to the air, spontaneously oxidized over several hours regenerating the ketone **3** (M = Cu). The latter transformation was effected immediately upon addition of DDQ to the solution.

Finally **3** (M = Cu) was cleanly demetallated by stirring in 15% (*v*/*v*) H_2SO_4 in CF_3CO_2H to give 5,15-diphenyl-7-oxobenzochlorin **3** (M = H_2) which has a broad absorption band centred at 746 nm. Work has begun in our laboratory to prepare and screen these compounds and a number of analogues for photodynamic activity.

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