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A one-step synthesis of a free base secochlorin from a 2,3-dimethoxy porphyrin†

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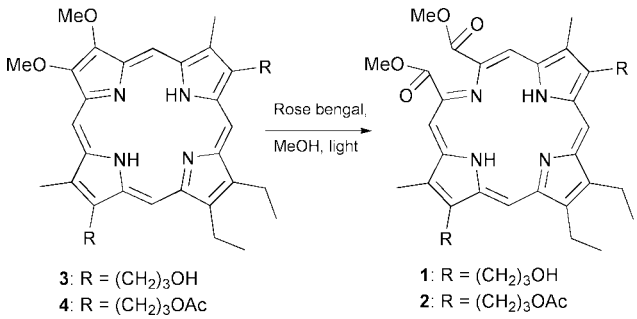
The synthesis and X-ray structure of a C_2 symmetric secochlorin 2, obtained by a photosensitized oxidative ring opening of a 2,3-dimethoxy porphyrin, is described.

Photodynamic therapy (PDT), a promising treatment for a number of medical disorders, relies on selectively retained photosensitizers that are able to produce an efficient cytotoxic response upon activation with light. Currently, several porphyrin- or expanded porphyrin-type macrocycles are in advanced clinical testing or recently approved as PDT photosensitizers.[1] A range of other pyrrolic macrocycles are also being considered as photosensitizers, among them secochlorins.[1a] The first secochlorin to be characterized structurally was obtained as the result of an unexpected oxidative ring-opening of a corrinato nickel(II) salt.[2] Secochlorin diketones and dialdehydes have also been obtained from an analogous oxidative cleavage involving the corresponding nickel(II) chlorin diols.[3–5] As yet, however, these compounds have not been prepared in their non-metalated forms. On the other hand, several synthetic, structural, and spectroscopic studies of free base secoporphyrazines have been reported in recent years. For instance, a secoporphyrazine was formed as a minor side product during the synthesis of magnesium(II) porphyrazine as the result of the Linstead macrocyclization of 2,3-bis(dimethylamino)-2(*Z*)-butenedinitrile.[6] The same compound was also obtained in high yield by subjecting simple free base porphyrazine to manganese dioxide-mediated oxidation.[7] This latter method was further extended to core-metalated (*e.g.* Zn^{II}) and unsymmetrical free base porphyrazines. We now report the synthesis of the C_2 symmetric free base secochlorins **1** and **2** obtained in the form of their bis(methyl esters) as a result of an oxidative ring opening of dimethoxy-substituted porphyrins. To the best of our knowledge, compounds **1** and **2** represent the first example of a non-porphyrazine derived secochlorin to be characterized structurally in its free base form.

The porphyrin **3** containing a 3,4-dimethoxypyrrole unit was chosen as the starting material for the present secochlorin synthesis. This choice reflects the fact that attempts to prepare **3** from the readily available tripyrrane precursor 2,5-bis[(5-formyl-3-(3-hydroxypropyl)-4-methylpyrrol-2-yl)methyl]-3,4-diethylpyrrole[8] and 3,4-dimethoxypyrrole[9] using the standard '3 + 1' approach[10] gave rise not only to the expected porphyrin but also to secochlorin **1** as a minor side product. The chemical composition of **1** was inferred from CI mass-spectrometric analysis. Unfortunately, it proved impossible to separate the secochlorin from the major reaction product, porphyrin **3**, by column chromatography unless the side chain 3-hydroxypropyl groups were acetylated. This done, however, the desired separation was easily effected to give **2** in low (~5%) yield.

The interesting nature of **1** and its acetylated derivative **2**, led us to seek a more efficient synthesis. Here, we were inspired by the realization that **1** could have arisen from an air-based oxidation of the dominant 2,3-dimethoxyporphyrin product **3**. Based on such thinking, we considered that treating porphyrins, such as **3**, with singlet oxygen would effect conversion into the corresponding secochlorin. On a more practical level, we also thought it might prove useful to start with the bis-acetoxy porphyrin **4**, rather than **3**, so as to simplify purification of the corresponding secochlorin **2**, assuming it were to be produced. Accordingly, as shown in Scheme 1, porphyrin **4** (*ca.* 0.1 mol dm^{-3}) was dissolved in O_2-saturated methanol containing Rose Bengal (*ca.* 150 mg l^{-1}) and subject to irradiation using a 250 W projection lamp as a light source for *ca.* 10 h. Under these conditions, wherein singlet oxygen is the dominant oxidant,[11] the C_2 symmetric secochlorin was obtained in *ca.* 70% yield.



Scheme 1

UV-vis spectral analysis revealed that the Soret band of secochlorin **2** is red-shifted by approximately 11 nm as compared to porphyrin **4** (Fig. 1). More significant spectral changes were observed in the so-called Q-band region of the visible-spectrum. In particular, compound **2** was found to display a broad Q-type absorption band at 678 nm that is *ca.* 50 nm red-shifted compared to what is observed for the corresponding porphyrin **4**. This red-shifting of the lowest energy transition makes secochlorin **2** potentially interesting as a PDT photosensitizer.

Proton NMR spectroscopic studies of **2** and **4** revealed,‡ in accord with expectations, that the OCH_3 signal is shifted upfield

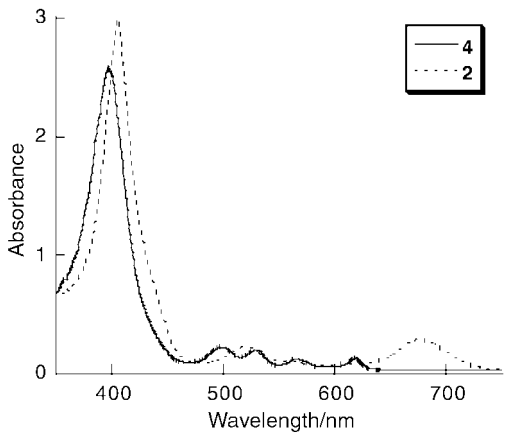


Fig. 1 Absorption spectra of porphyrin **4** and secochlorin **2**. CH_2Cl_2 solutions, room temperature.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b1/b102139g/

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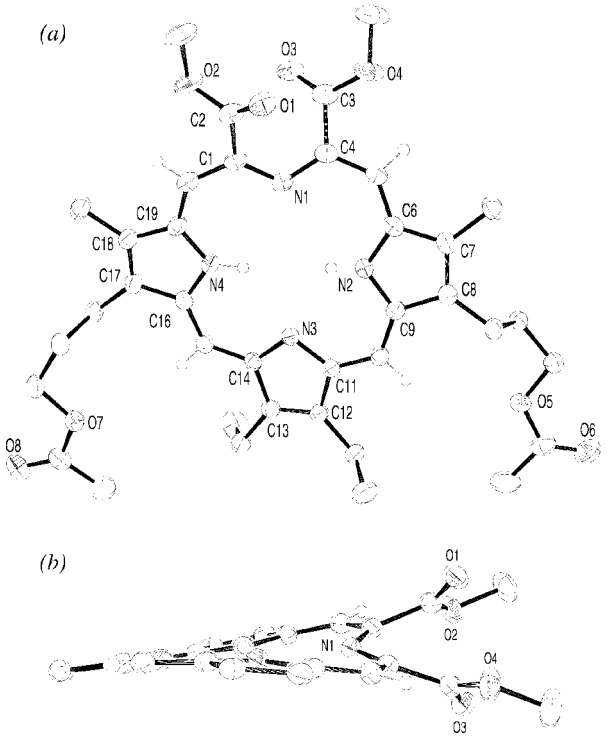

Fig. 2 Crystal structure of **2** showing a partial atom labelling scheme: *(a)* top and *(b)* side view. In the latter view, the pyrrole alkyl substituents are not shown on *(b)*. Thermal ellipsoids are scaled to the 50% probability level.

by *ca*. 0.6 ppm in secochlorin **2** (δ = 4.20 ppm) as compared to where it is seen in the case of porphyrin **4** (signal observed at 4.78 ppm). Presumably, it is the result of significant structural differences between **4** and **2**. Whereas the methoxy groups of **4** are bound directly to one of the porphyrin pyrroles, and hence in electronic contact with the main aromatic periphery, the methoxy groups of **2** are further removed from the principal secochlorin conjugation pathway. Further, they are tied up as ester groups. Separate from this, the four *meso*-carbon protons of porphyrin **4** were found to resonate as one singlet at 10.06 ppm, whereas in the case of **2** the corresponding protons resonate at slightly higher field and appear as two singlets (*i.e.* at 9.65 and 9.70 ppm, respectively).

A single-crystal X-ray diffraction analysis of **2** was also performed.§ This analysis confirmed the proposed secochlorin structure. In particular, it revealed that, on going from **4** to **2**, the dimethoxypyrrolic unit of porphyrin **4** gets transformed into a bis(methyl ester) moiety, without the connectivity of the macrocycle being otherwise modified (Fig. 2). The carbon–carbon bond lengths of the bis(methyl ester) unit [C1–C2 1.513(2), C3–C4 1.513(3) Å] are somewhat longer than the bond lengths in the pyrrole subunits [C6–C7 1.429(2), C8–C9 1.435(2), C11–C12 1.461(2), C13–C14 1.459(2), C16–C17 1.431(2), C18-C19 1.437(2) Å]. The C–N–C bond angle of the bis(methyl ester) [∠C1–N1–C4 120.24(14)°] was found to be significantly different from the bond angles seen for the pyrrolic units [∠C6–N2–C9 110.3(2)°, ∠C11–N3–C14 104.62(13)°, ∠C19–N4–C16 110.0°] and somewhat bigger than found for *meso*-tetraphenylsecochlorinato nickel(II)[6] [∠C1–N1–C4 114.3(3)°].

In summary, the synthesis of a novel secochlorin system by oxidative ring opening of a porphyrin is described. This convenient method, based on the singlet oxygen mediated ring opening of a 2,3-dimethoxyporphyrin, offers the prospect of allowing a range of new secochlorins to be prepared and isolated in their free base forms. Current work is focused on exploring the metallation chemistry of these new systems.

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Notes and references

‡ *Spectroscopic data* for **2**: ^{1}H NMR ($CDCl_3$), δ, ppm: −2.18 (s, 2H, NH), 1.79 (t, 6H, C*H*$_3$CH$_2$), 2.17 (s, 6H, pyrrole-C*H*$_3$), 2.51 (p, 4H, CH$_2$C*H*$_2$CH$_2$), 3.48 (s, 6H, C*H*$_3$COOCH$_2$), 3.83 (q, 4H, pyrrole-C*H*$_2$CH$_3$), 4.04 (t, 4H, pyrrole-C*H*$_2$CH$_2$CH$_2$), 4.20 (s, 6H, COOC*H*$_3$), 4.36 (t, 4H, C*H*$_2$OOCCH$_3$), 9.65 (s, 2H, *meso*-H), 9.70 (s, 2H, *meso*-H); ^{13}C NMR ($CDCl_3$), δ, ppm: 11.4, 18.3, 19.5, 21.1, 22.6, 31.4, 52.3, 63.8, 99.2, 99.6, 133.5, 134.7, 136.5, 137.5, 142.9, 143.2, 143.7, 167.2, 171.2. UV/vis (DCM), λ_{max}, nm: 402, 519, 677. CI-MS (M^+): 687. Anal. Calcd. for $C_{38}H_{46}N_4O_8$, %: C, 66.45; H, 6.75; N, 8.16; Found, %: C, 66.32; H, 6.80; N, 8.14. *Spectroscopic data* for **4**: ^{1}H NMR ($CDCl_3$): δ −3.78 (s, 2H, NH pyrrole), 1.88 (t, 6H, C*H*$_3$CH$_2$), 2.17 (s, 6H, pyrrole-C*H*$_3$), 2.63 (p, 4*H*, CH$_2$C*H*$_2$CH$_2$), 3.66 (s, 6H, C*H*$_3$COOCH$_2$), 4.01 (q, 4H, pyrrole-C*H*$_2$CH$_3$), 4.21 (t, 4H, pyrrole-C*H*$_2$CH$_2$CH$_2$), 4.40 (t, 4H, C*H*$_2$OCOOCH$_3$), 4.78 (s, 6H, OC*H*$_3$), 10.06 (s, 4H, *meso*-H); ^{13}C NMR ($CDCl_3$), δ, ppm: 11.4, 14.1, 18.5, 21.1, 22.6, 29.4, 31.7, 62.6, 96.3, 96.6, 99.2, 133.3, 134.6, 136.9, 137.2, 144.0, 145.0, 167.3, 171.2. UV/vis (DCM), λ_{max}, nm: 394, 497, 530, 565, 619. CI-MS (M^+): 655. Anal. Calcd. for $C_{38}H_{46}N_4O_6$, %: C, 69.70; H, 7.08; N, 8.56; Found, %: C, 69.82; H, 7.10; N, 8.54.

§ *Crystallographic data* for **2** (dark plates and prisms, 0.35 × 0.30 × 0.10 mm): $C_{38}H_{46}N_4O_8$, M = 686.79, triclinic, a = 9.7740(3), b = 12.2750(4), c = 16.3590(5) Å, α = 69.217(2), β = 84.584(2), γ = 82.626(2)°, T 123(2) K, U = 1817.27(10) Å^3, Z = 2, μ (Mo-Kα) = 0.088 mm^{-1}, 13040 reflections collected, 8267 independent reflections (R_{int} = 0.029), 5372 with $I \geqslant 2\sigma(I)$, R_1 = 0.0498, 0.0941 (all data), $wR(F^2)$ = 0.0981, 0.114 (all data). CCDC 160558. See http://www.rsc.org/suppdata/cc/b1/b102139g/ for crystallographic files in .cif format.

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