A facile and versatile preparation of bilindiones and biladienones from tetraarylporphyrins†

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Received (in Cambridge, UK) 16th September 2004, Accepted 6th December 2004
First published as an Advance Article on the web 21st January 2005
DOI: 10.1039/b414299c

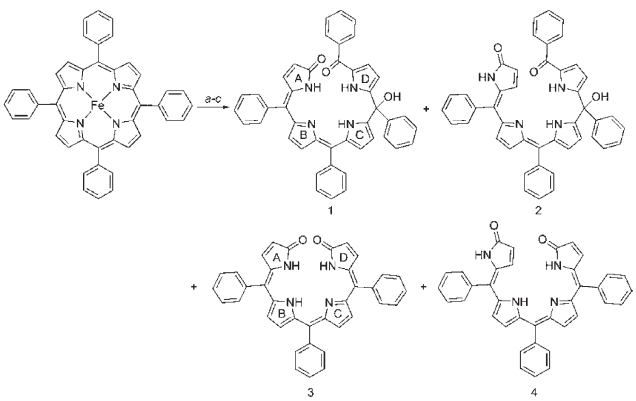
Bilindiones and biladienones carrying aryl groups at the *meso* positions were prepared using coupled oxidation reactions of iron tetraarylporphyrins in 20–63% yield.

Linear tetrapyrroles such as bilindiones are a family of compounds that have various biological and chemical functions due to their redox activity,[1] photochemical isomerisation and energy transfer,[2] coordinating ability,[3] and conformational flexibility, and a chiral framework applicable to various enantioselective processes.[4] In nature, these compounds are biosynthesized from porphyrin *via* enzymatic oxidation catalysed by heme oxygenase.[5] Phytochromobilin is one of such compounds that undergo photochemical *cis–trans* isomerisation and act as a sensory chromophore in a photoreceptor protein.[6] Although bilindiones have potential multi-functional properties, the synthesis of bilindiones requires a multi-step route owing to the low symmetry of the molecule.[7] This is one of the reasons that the compounds are less frequently employed as a scaffold for functional materials compared to well-studied porphyrins. Because a variety of tetraarylporphyrins have been prepared as models for photosynthesis and redox enzymes, a synthetic procedure converting tetraarylporphyrins to bilindiones should be a versatile and efficient route to these compounds. In this paper we report the oxidation of iron tetraarylporphyrin by dioxygen in the presence of a reductant as the new synthetic route to a series of bilindiones and biladienones. Oxidation of metalloporphyrins by dioxygen is also important as a degradation pathway of porphyrin catalysts during cytochrome P-450 type oxidations. Therefore, investigation of reactivity of iron porphyrin with dioxygen is important for its application as a catalyst and an oxygen carrier.

As a typical reaction, a solution of [5,10,15,20-tetraphenylporphyrinato]iron(II) in chloroform was treated with pyridine, ascorbic acid and dioxygen at room temperature for 30 min. The oxidation proceeded smoothly, and usual work-up, *i.e.* precipitation with $NaBF_4$ and treatment with HCl, afforded a violet spot and a more polar red spot on silica gel TLC.

After silica gel column purification, the violet fraction was isolated as the major product in 63% yield. Its spectroscopic data coincided with that for biladienone **1**, which had been obtained in the photochemical oxidation of the tetraphenylporphyrin dianion by Cavaleiro and co-workers.[8] The second red fraction was obtained in 15% yield. Its mass spectrum was almost identical with that of **1** and the ^{13}C NMR spectrum showed one sp^3 carbon resonance (C-20) at 76.4 ppm, while the ^{13}C NMR spectrum of **1** showed one at 75.0 ppm. The ^1H NMR spectrum is similar to that of **1**, except for one upfield shifted NH resonance and one downfield shifted β-pyrrole resonance, that are ascribed to the $N_{21}H$ proton and H-3 of the lactam A-ring, respectively. These NMR data suggest that the red isomer is (*EZ*)-biladienone **2**. The structural assignment was corroborated by comparisons of the ^1H NMR with that of *EZ*-15-butylbiladienone reported by Callot *et al.*.[9] Biladienone **2** can be photochemically isomerised to **1**, while the reverse isomerisation from **1** to **2** did not proceed.‡

When the coupled oxidation was carried out in refluxing chloroform for 1.5 h, more polar fractions **3** and **4** appeared as blue spots on silica gel TLC, in addition to **1** and **2**. The FAB mass spectrum of **3** showed an M^+ peak at *m*/*z* 558, suggesting that it is bilindione. Compound **3** showed a simple ^1H NMR spectrum exhibiting only four β-pyrrole proton resonances, implying that the product has a symmetrical framework. On the basis of COSY, NOESY, and HMBC spectra, we identified this product as (*ZZZ*)-bilindione **3**, the yield of which was 20%. The simple NMR spectrum can be attributable to the fast proton tautomeric isomerisation of the NH proton on the B-ring pyrrole.



Scheme 1 Reagents: (a) O_2, ascorbic acid, pyridine in $CHCl_3$, 30 min, rt, (b) $NaBF_4$, (c) 1 M HCl.

A slightly more polar, blue fraction **4**, was obtained in an equal amount to **3**. Compound **4** showed a UV-visible spectrum and a mass spectrum almost identical to those of **3**, while the ^1H NMR spectrum of **4** was complex, exhibiting eight β-pyrrole resonances. The diagnostic resonances are one NH proton at 9.11 ppm, shifted downfield relative to that of **3**, which showed an NOE with the

† Electronic supplementary information (ESI) available: experimental details and NMR data and spectra for **1–4**. See http://www.rsc.org/suppdata/cc/b4/b414299c/

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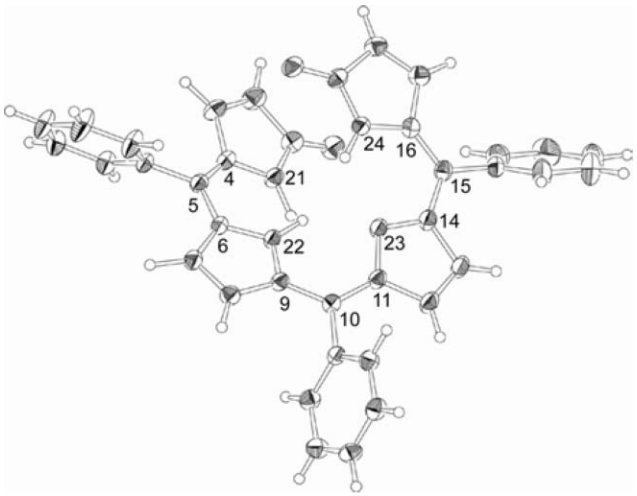


Fig. 1 ORTEP view of **3** with thermal ellipsoids at 30% probability.

most downfield resonance of the β-pyrrole protons appearing at 7.58 ppm. These features can be best explained by assuming that the A-ring pyrrole is connected *via* a double bond with the *E* configuration, and the NH proton at 7.1 ppm and the β-proton at 7.58 ppm are assigned to those of the A-ring pyrrole. Then the β-pyrrole proton on the A-ring should be close to the NH proton of the D ring, resulting in the observed NOE. The COSY and HMBC spectra also support the assignment and the structure of **4** shown in Scheme 1.

Illumination with visible light converts **3** to **4** and *vice versa*. The ^{1}H NMR spectrum of the illuminated sample indicated that the steady-state mixture contains **3** and **4** in a 0.9 to 1 ratio. Molecular orbital calculations at the B3LYP/6-31G* level indicated that the *ZZZ* isomer of etiobiliverdin was more stable than the *EZZ* isomer by 5.0 kcal mol^{-1}, while **3** was more stable than **4** only by 0.3 kcal mol^{-1}. The energy difference between the *ZZZ* and *EZZ* isomer of etiobiliverdin is ascribed to the steric repulsion between the β-alkyl groups and the pyrrole ring. Lack of such steric repulsion in **4** lead to almost equal distribution of the isomers in triphenylbilindiones.

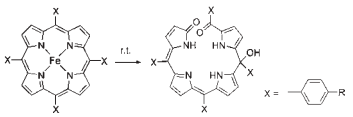
Compared to the photo-oxidation and the oxidation with metal salts (Ce and Tl), the coupled oxidation described here gave the products in a higher yield with less by-products.[10] Preparation of **2–4** has not been reported before.

A crystal of **3** suitable for the single-crystal X-ray crystallographic analysis was obtained by diffusion of hexane to a chloroform solution of **3**. The crystal structure of **3** demonstrated that it is a *ZZZ,syn,syn,syn* diketo[11] isomer with a helicoidal conformation (Fig. 1).§ The dihedral angles of exocyclic single and double bonds are 9.9 (N_{21}–C_4–C_5–C_6), 15.9 (C_4–C_5–C_6–N_{22}), 9.6 (N_{22}–C_9–C_{10}–C_{11}), 9.9 (C_9–C_{10}–C_{11}–N_{23}), 7.4 (N_{23}–C_{14}–C_{15}–C_{16}), 1.1° (C_{14}–C_{15}–C_{16}–N_{24}), showing that the A-ring pyrrole is distorted from coplanarity with the D-ring pyrrole. This can be attributed to the repulsion of the N–H dipoles of the A- and B-ring pyrroles. In the crystal, the NH group of the A-ring is hydrogen bonded to the D-ring carbonyl group of the neighboring molecule, to form a homochiral column. The three NH protons were located in the difference Fourier maps. In a unit cell, there are four bilindione molecules and two are *P*- and the other two are *M*-helix. The bilindione molecules with the same chirality are stacked to form a column of helix in the crystal. Compared to the bilindiones with alkyl substituents at the β-positions of pyrrole, **3** has a narrower helix with a larger helix pitch. The distance between C5 and C15 is 6.17 Å, shorter than that of biliverdin (6.70 Å). Introduction of phenyl groups at the *meso* position makes the bond angles of C4–C5–C6, C9–C10–C11, and C14–C15–C16, smaller than those of biliverdin,[12] leading to better spatial overlap of the terminal A, D pyrroles. The average of the three bond angles of **3** was 123.1°, while that of biliverdin was 126°[12a] and 127.8°[12b] on the basis of X-ray crystallographic structures. This difference should be important in bilindione chemistry such as the dynamic process of helix inversion[13] and the coordination to metal ions.

Table 1 Substituent effects on the reaction yield of *ZZ*-biladienone[a]

para-Substituent R	Yield (%)	Reaction time (min)
H	63	30
OMe	73	15
n-$C_{12}H_{25}$	72	30
CN	31	90

[a]



The reaction is applicable to tetraarylporphyrins with various substituents on the aryl groups. The effects of *para*-substituents on the aryl groups on the reactivity are summarized in Table 1. Electron-withdrawing groups such as a cyano group lowered the yield while an electron-donating group improved the yield. The coupled oxidation of [5,10,15,20-tetramesitylporphyrinato]iron did not proceed even in refluxing chloroform, with the starting porphyrin recovered. Thus, introduction of *ortho*-substituents strongly inhibited the oxidation. These observations imply that the oxidation occurs *via* intramolecular electrophilic attack of the coordinated oxygen on the *meso* carbon. We previously demonstrated that the coupled oxidation of β-substituted porphyrin occurs selectively at the electron-rich *meso* carbon, by using a trifluoromethyl group as a directing substituent.[14]

In summary, the coupled oxidation of iron tetraarylporphyrins afforded products with different oxidation levels. The reaction mechanism leading to **1–4** is not known, and further investigation is necessary to elucidate it, which should shed light on the reaction of heme oxygenase.

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Notes and references

‡ Geometry optimisation of **1** by molecular orbital calculations at the B3LYP/6-31G* level indicated that the 15-hydroxy group is hydrogen bonded to the 1*O*-carbonyl group, while this is not the case for **2**. This

hydrogen bond and the hydrogen bond between N_{21}–H–N_{22} can stabilise **1** compared to **2**, to result in one-way isomerisation.

§ Crystal data. $C_{37}H_{26}N_4O_2$, M = 558.64, monoclinic, a = 5.905 (1), b = 22.765 (4), c = 21.913 (4) Å, β = 100.031 (4), U = 2900 (1) Å^3, T = 243.2 K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo–K_α) = 0.081 mm^{-1}, 6541 reflections measured, 4036 unique which were used in all calculations. The final $wR(F^2)$ was 0.0659 (all data). CCDC 251472. See http://www.rsc.org/suppdata/cc/b4/b414299c/ for crystallographic data in .cif or other electronic format.

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