

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

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

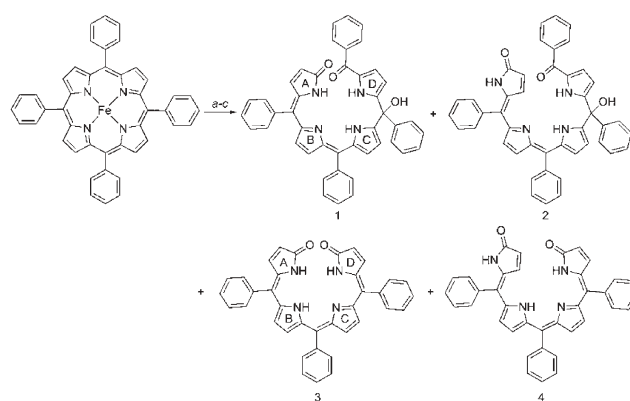
Linear tetrapyrroles such as bilindiones are a family of compounds that have various biological and chemical functions due to their redox activity,¹ photochemical isomerisation and energy transfer,² coordinating ability,³ and conformational flexibility, and a chiral framework applicable to various enantioselective processes.⁴ In nature, these compounds are biosynthesized from porphyrin *via* enzymatic oxidation catalysed by heme oxygenase.⁵ Phytychromobilin 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 NaBF₄ 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 ¹³C NMR spectrum showed one sp³ carbon resonance (C-20) at 76.4 ppm, while the ¹³C 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 N₂H 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) O₂, ascorbic acid, pyridine in CHCl₃, 30 min, rt, (b) NaBF₄, (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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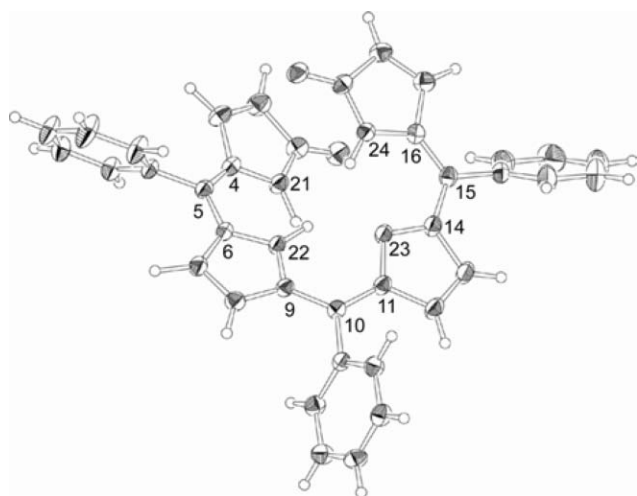


Fig. 1 ORTEP view of **3** with thermal ellipsoids at 30% probability.

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 ^1H 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.

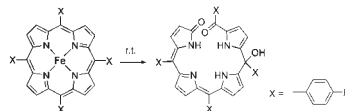
Compared to the photo-oxidation and the oxidation with metal salts (Ce and Tl), the coupled oxidation described here gave the products in a higher yield with less by-products.¹⁰ Preparation of **2–4** has not been reported before.

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* diketo¹¹ isomer with a helicoidal conformation (Fig. 1).§ The dihedral angles of exocyclic single and double bonds are 9.9 (N₂₁–C₄–C₅–C₆), 15.9 (C₄–C₅–C₆–N₂₂), 9.6 (N₂₂–C₉–C₁₀–C₁₁), 9.9 (C₉–C₁₀–C₁₁–N₂₃), 7.4 (N₂₃–C₁₄–C₁₅–C₁₆), 1.1° (C₁₄–C₁₅–C₁₆–N₂₄), 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

Table 1 Substituent effects on the reaction yield of ZZ-biladienone^a

<i>para</i> -Substituent R	Yield (%)	Reaction time (min)
H	63	30
OMe	73	15
<i>n</i> -C ₁₂ H ₂₅	72	30
CN	31	90

^a



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 inversion¹³ and the coordination to metal ions.

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 10-carbonyl group, while this is not the case for **2**. This

hydrogen bond and the hydrogen bond between N₂₁-H-N₂₂ can stabilise **1** compared to **2**, to result in one-way isomerisation.

§ Crystal data. C₃₇H₂₆N₄O₂, *M* = 558.64, monoclinic, *a* = 5.905 (1), *b* = 22.765 (4), *c* = 21.913 (4) Å, β = 100.031 (4), *U* = 2900 (1) Å³, *T* = 243.2 K, space group *P2₁/c* (no. 14), *Z* = 4, μ(Mo-Kα) = 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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