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New route to protoporphyrins III and XIII from common starting pyrroles

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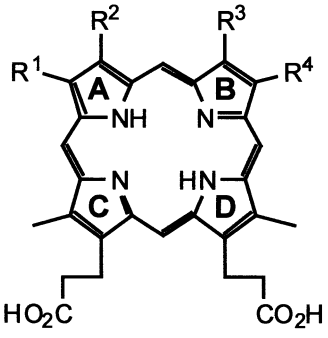
Abstract—A new approach to protoporphyrins III (**2′**) and XIII (**3′**) has been developed based on a single set of starting materials, namely, 2,4-dimethyl-3-(2-chloroethyl)carbethoxypyrrole (**4**) and 3,3′-di(2-methoxycarbonylethyl)-4,4′-dimethyldipyrromethane-5,5′-dicarboxylic acid (**5**) for both targets. The biladiene route was adopted for the preparation of **2′** (five steps, 18% overall yield) while the coupling of two pyrromethenes was used to synthesize **3′** (four steps, 11% overall yield). © 2002 Published by Elsevier Science Ltd.

Myoglobin is a small protein responsible for oxygen fixation in muscle tissues. It consists of two components; the peptide and hemin moieties. The hemin consists of the native protoporphyrin IX (**1**) in which a Fe^{2+} cation is inserted; interestingly, both components as well as the hemin itself can be chemically dissociated from each other into the peptidic and the hemin parts on one hand and into the protoporphyrin **1** and the metal cation parts on the other hand, and then all together recombined back to the original myoglobin without affecting its biological activity.

We have recently reported[1–3] the electrochemical results obtained using the cyclic voltametric technique with some reconstituted myoglobins where the hemin moiety, derived from the native protoporphyrin **1**, was modified at the hemin backbone (i.e. monoazahemin),[1] at the side-chain groups (i.e. octamethyhemin, meso- and deutero-hemins),[2] and at the metal cation center (i.e. Co^{2+}, Mn^{2+}, Ru^{2+}, Zn^{2+} versus Fe^{2+}).[3] The results we obtained drove us to further pursue this study by modifying the structure of the protoporphyrin itself; we therefore began an investigation of the two symmetrical regioisomers (**2**) and (**3**) that are protoporphyrins III and XIII, respectively (Fig. 1).

We first tried to prepare **2** and **3** via their dimethylesters (**2′** and **3′**, respectively) using procedures largely inspired by previously reported syntheses of either **1**, **2** and/or **3**.[4]



	R^1	R^2	R^3	R^4
1: Protoporphyrin IX	Me	CH_2=CH	Me	CH_2=CH
2: Protoporphyrin III	Me	CH_2=CH	CH_2=CH	Me
3: Protoporphyrin XIII	CH_2=CH	Me	Me	CH_2=CH

Figure 1.

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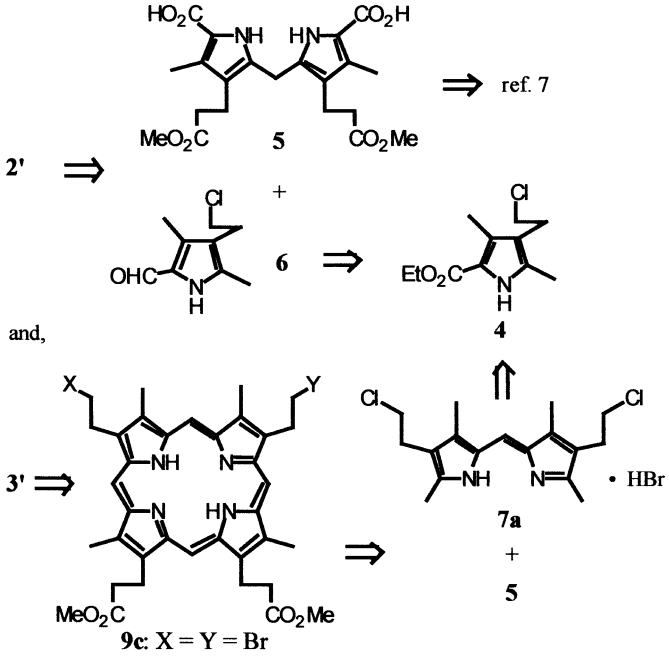
However, these routes required starting materials which were themselves laborious to synthesize and our efforts to prepare **2′** and **3′** on preparative scale using these existing methodologies were eventually abandoned. Noteworthy is that the synthesis of **3** frequently implies the use of 2,3-dimethylpyrrole, the preparation of which remains extremely inefficient and impractical.[4]

Therefore, it goes without saying that the development of a new strategy based upon readily available starting materials would greatly enhance the field of porphyrin synthetic chemistry. Scheme 1 illustrates our two convergent retrosynthetic analyses that utilize a single set of easily available starting pyrrole derivatives for the syntheses of **2** and **3** and this approach indeed proved to be fruitful.

One key starting material (**4**) was smoothly prepared according to a recent report[5] that, in our hands, had to be slightly modified.[6] The C,D-ring precursor (**5**) was smoothly synthesized following the standard reported procedure.[7] With **4** in hand, we first started the preparation of **2** and then moved on to the synthesis of **3** according to the pyrromethenes coupling approach.[8]

Preparation of 2-dimethylester (2′)

For the synthesis of **2′** we used the previously reported biladiene route which required the preparation of aldehyde **6** which has been previously described.[4b] In our case, treatment of **4** with 70% H_2SO_4 in water (v/v) at room temperature (rt) for 14 h, yielded after work-up, a red oil that was treated with trifluoroacetic acid (TFA) for 2–3 min at 50°C; to the resulting mixture, cooled to 0°C, was added trimethylorthoformate and the reaction was allowed to stir at rt for 2 h.[9] The aldehyde **6** was purified by flash chromatography (SiO_2; CH_2Cl_2–Et_2O elution) and then recrystallized from CH_2Cl_2/C_6H_{14} to give colorless long needles in 67% yield.

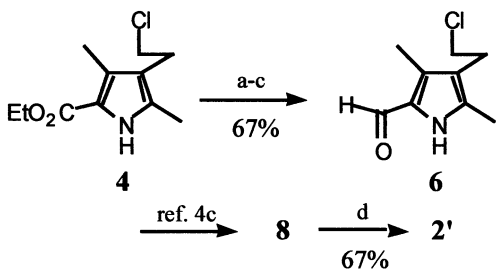


Scheme 1. Convergent retrosynthetic analyses for **2** and **3** leading to pyrrole **4**.

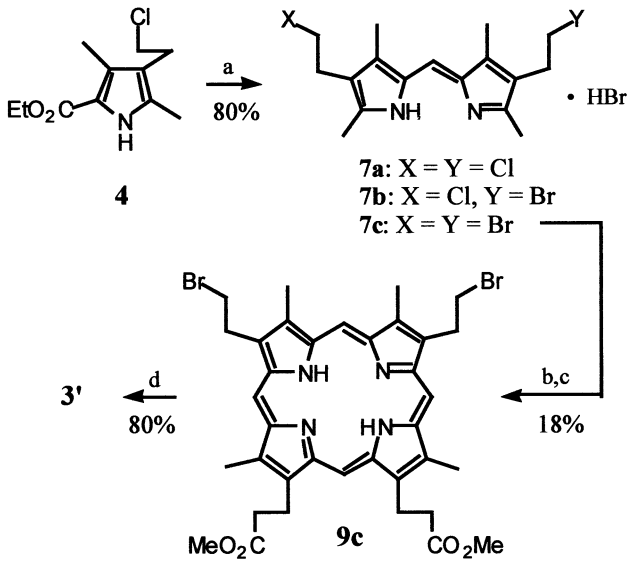
The diacid **5**[7,8] was decarboxylated with TFA (rt, 30 min) and the product transferred at rt into a methanolic solution of **6**; the resulting mixture was immediately treated with 30% HBr in acetic acid and the reaction allowed to stir at rt for 45 min before addition of dry Et_2O to crystallize out the adduct. The red suspension was stirred gently for another 2 h and the biladiene was isolated by filtration, dried in vacuo, then added to a refluxing solution of $CuCl_2 \cdot 2H_2O$ in dry DMF and left to react for about 5 min before extraction of the reaction. Removal of the metal cation together with a secure re-esterification was achieved with TFA/conc. H_2SO_4/MeOH at rt for 14 h to yield the corresponding porphyrin **8** in 41% yield after flash chromatography. The final β-elimination step was achieved by treatment of a dry DMF solution of **8** with DBU (10 equiv.) at 100°C for 1 h[10] giving **2′** in 67% yield after flash chromatography followed by recrystallization. Spectroscopic data of **2′** were in accordance with those previously reported[4c] (Scheme 2).

Preparation of 3-dimethylester (3′)

For the synthesis of the A,B-ring fragment (**7a**), the pyrrole **4** was dissolved in hot 99% formic acid. Our preliminary homocoupling gave upon treatment with aqueous 48% HBr (1.75 equiv.) for 3 h at 80–90°C,[4d] a mixture of three components characterized by mass spectroscopy as the dichloro- (**7a**), chlorobromo- (**7b**) and the dibromo-pyrromethene (**7c**) hydrobromides where the chlorobromo-derivative was largely predominant. To simplify the stoichiometrical requirements of the subsequent step, we next focussed our efforts on the simplification of this mixture. Fortunately, reaction of **4** in formic acid with 10 equiv. of aqueous 48% HBr at 100°C for 2 h then at rt for 14 h yielded the dibromopyrromethene hydrobromide salt **7c** exclusively as judged by proton NMR and mass spectrometry.[11] Thus, **7c** was obtained in 80% yield as a golden solid after paper filtration and washing with cold MeOH then Et_2O:[11] compound **7c** is unprecedented and critical for our new route to protoporphyrin XIII.



Scheme 2. Synthesis of protoporphyrin III dimethylester (**2′**). *Reagents and conditions*: (a) 70% aqueous H_2SO_4 (v/v), rt, 14 h; (b) TFA, 50°C, 3 min; (c) $HC(OMe)_3$ (co-solvent), 0°C then rt, 2 h; (d) DBU (10 equiv.), DMF, 100°C, 1 h.



Scheme 3. Synthesis of protoporphyrin XIII dimethylester (**3′**). *Reagents and conditions*: (a) 48% HBr (10 equiv.) HCO_2H, 100°C, 2 h then rt 14 h; (b) Mix **5** and HCO_2H, addition of Br_2 (1 equiv.) then reflux for 2.5 h before distillation of the solvent to dryness; (c) conc. H_2SO_4–MeOH, rt, 14 h; (d) DBU (10 equiv.), CH_2Cl_2, rt, 3 days.

The coupling between **7c** and **5**[8] in refluxing formic acid yielded, after distillation of the formic acid to dryness and re-esterification with conc.H_2SO_4–MeOH at rt for 14 h, the porphyrin **9c** in 18% yield after recrystallization from CH_2Cl_2/MeOH. The final vinylation step was performed by treating a CH_2Cl_2 solution of **9c** with DBU (10 equiv.) at rt for 3 days giving **3′** as a dark purple shiny solid in 80% yield after flash chromatography (Scheme 3); it was then recrystallized from CH_2Cl_2/MeOH; the proton NMR as well as the UV absorption spectra were in excellent agreement with those reported.[4]

In conclusion, protoporphyrin III and XIII dimethyl esters have been synthesized according to two retrosynthetic analyses that converged to a single set of starting materials **4** and **5**. The simplicity of the schemes, the considerable improvement in the availability of the materials employed together with the overall yields, underline the efficiency and practicality of our method which has been used in our laboratory to prepare large amounts of **2′** and **3′** in order to record their electrochemical responses. The results of these studies will be reported in due course.

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6. In order to obtain the reported yield in the reduction of the Friedel–Crafts adduct, precursor of **4**, we used 2.1 equiv. of $NaBH_4$ and 2.8 equiv. of $Et_2O{\cdot}BF_3$, see: Morgan, B.; Dolphin, D. *J. Org. Chem.* **1987**, *52*, 5364–5374.
7. For the preparation of the CD-ring fragment see: Ref. 4c and also Fuhrhop, J.-H.; Smith, K. M. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed. Laboratory methods; Amsterdam, 1975; pp. 761–764.
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9. It was necessary to conduct the whole process under an inert atmosphere (N_2) to achieve a good yield. For the reaction with the trimethyl orthoformate, see: Helms, A.; Heiler, D.; McLendon, G. *J. Am. Chem. Soc.* **1992**, *114*, 6227–6238.
10. The reaction in neat DBU at rt for 4 days cleanly returned the starting material.
11. The obtention of an orange non-shiny solid is characteristic of a mixture consisting of **7a**–**c**: this can be smoothly converted into the desired **7c** upon further treatment with HCO_2H–HBr.
    Compound **7c**: golden shiny solid that gradually turned into a black tar upon heating above 130°C. ^{1}H NMR ($CDCl_3$; 300 MHz) δ (ppm) 8.00 (s, 1H); 7.10 (s, 1H); 3.41 (t, 4H, *J* 7.15 Hz); 3.00 (t, 4H, *J* 7.15 Hz); 2.71 (s; 6H); 2.32 (s, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz) δ (ppm) 154.4; 142.9; 126.1; 125.7; 31.1; 27.4; 12.9; 10.4.