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# Synthesis of a new bis-pyridyl crown-capped porphyrin

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**Abstract**—The synthesis of a new porphyrin bearing both two pyridyl residues and two *ortho*-nitrophenyl groups in *meso* position is reported. The reduction of the nitro functions provides the points of anchoring for a crown ether maintained in a cofacial conformation. 

Cationic porphyrins such as 5,15-di(*N*-methyl-4-pyridyl)-10,20-di(3-nitrophenyl)-porphyrin chloride bind to quadruplex DNA and exhibit an anti-human telomerase activity.[1] Additionally, such porphyrins could be useful for the design of new water-soluble chelatants for large cations such as lanthanides in order to be used as contrast agents[2] provided the fact that the nitro functions were in the *ortho* positions to tightly link a second macrocycle in a cofacial conformation. Indeed, this type of porphyrin has already been described more than 20 years ago, with an analogue known as 'crowned porphyrin',[3] but the possibility of using them as an alternative solution to expanded porphyrins remains to be explored.[4]

Recently, we have published the easy synthesis of a simple bis-crown ether porphyrin targeting the coordination of the bismuth(III) cation.[5] Unfortunately, this porphyrin was too rigid to allow such a coordination. Indeed, the crystal structure of the zinc analogue clearly indicates that the presence of one crown ether molecule on each side of the porphyrin generates an excessive steric hindrance—inducing the distortion of the porphyrin itself—for an easy access of the metal to the center of the cage. On the other hand, the synthetic analogues of **1** (Scheme 4) with only one crown-ether attached on a porphyrin by longer linkers but lacking the pyridyl moieties already exist, but their coordination properties towards large cations such as lanthanides have not been reported yet.[6] However, it is likely that their cavity should be too large to stabilize such cations.

In our continuing effort to design new macrotricyclic porphyrin-based ligands, we report herein the synthesis of porphyrin **2** and its derivatization in the mixed macrotricycle **1**.

Obviously, the starting material for the synthesis of compound **1** is porphyrin **3**αα, namely the αα atropisomer of 5,15-di(2-aminophenyl)-10,20-di(4-pyridyl) porphyrin (Scheme 3). To reach this compound, two major synthetic strategies are possible. The first one consists of the statistical reaction between stoichiometric amounts of two aldehydes and pyrrole where the second is achieved by the condensation of a dipyrrylmethane on a aldehyde, both reactions being catalyzed by an acidic medium.

In the case of the first strategy, again two different methods are well known: either the Adler method,[7] performed in propionic or acetic acid, or the Lindsey method with a reactant concentration of 0.01 M.[8] However, in this latter case, to obtain ca. 1 g of porphyrin, the low concentration conditions would require about 20 L of solvents.

The second strategy consists in the 2+2 MacDonald coupling[9] modified with the Lindsey methodology,[10] and is considered as the method of choice for the synthesis of *trans*-$A_2B_2$-type tetra *meso*-substituted porphyrins. To apply such conditions, possible dipyrrylmethanes to be used are either the *meso*(2-nitrophenyl)-dipyrrylmethane[11] or the *meso*(4-pyridyl)dipyrrylmethane **4** (Scheme 2). The synthesis of **4** had been described via the one-flask room-temperature condensation of 4-pyridinecarboxaldehyde with an excess of pyrrole either in the presence of TFA[12] or without acid but at high-temperature.[13]

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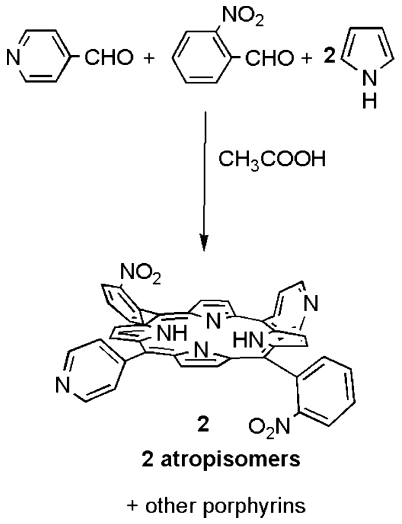
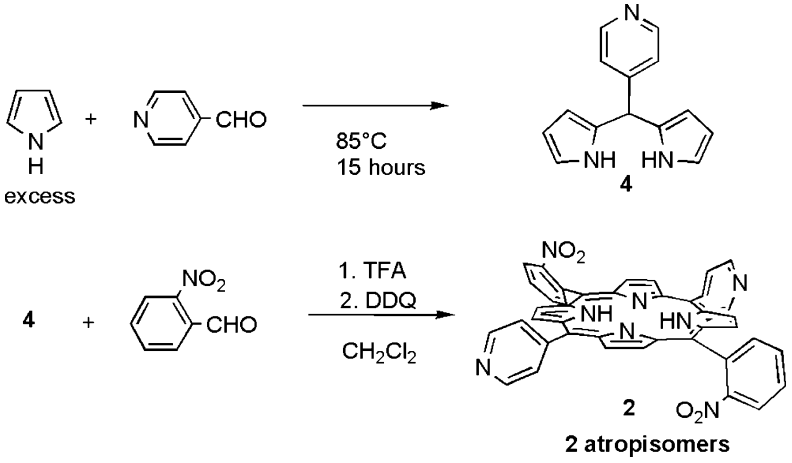



**Scheme 1.** One-pot direct synthesis of **2**.

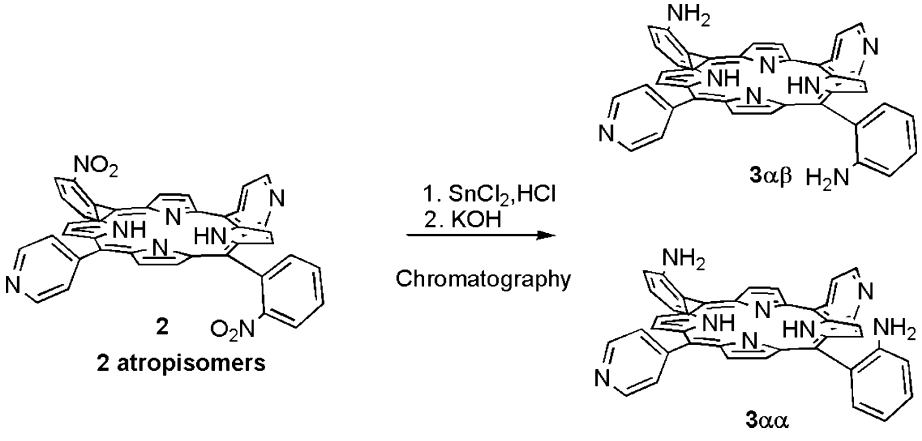
Thus, to investigate the first strategy, 1 equiv. of 2-nitrobenzaldehyde (25.66 g, 0.17 mol), 1 equiv. of 4-pyridinecarboxaldehyde (16.23 mL, 0.17 mol) and 2 equiv. of pyrrole (23.58 mL, 0.34 mol) were refluxed for 1 h in an acetic acid solution to give the 5,15-bis-pyridyl-10,20-bis-(*o*-nitrophenyl)porphyrin **2**. As a result, **2** was obtained (1.14 g, yield = 1%) after purification and separation of the other porphyrins by silica gel chromatography ($CH_2Cl_2$/MeOH 100/0.8), as a mixture of two atropisomers that proved to be inseparable in our hands (Scheme 1).

Following the second pathway, firstly *meso*(4-pyridyl)dipyrrylmethane **4** was synthesized by stirring for 15 h at 85°C a mixture of 4-pyridinecarboxaldehyde (1.9 mL, 20 mmol) and pyrrole (20 mL, 280 mmol). Evaporation to dryness, alumina gel chromatography and crystallization (hexane:ethyl acetate) afforded 2.5 g (yield = 56%) of compound **4**. Then a solution of *meso*(4-pyridyl)dipyrrylmethane (1 g, 4.5 mmol) and 2-nitrobenzaldehyde (680 mg, 4.5 mmol) in 450 mL $CH_2Cl_2$ was purged with argon for 10 min, then trifluoroacetic acid (80 μL, 1 mmol) was added. The mixture was stirred for 1 h at room temperature and DDQ (2 g, 9.0 mmol) added. After an additional 1 h period of stirring, the solvent was removed. A column chromatography afforded compound **2** (40 mg, yield = 1.25%) as a mixture of the two atropisomers; the overall yield being 0.7%.

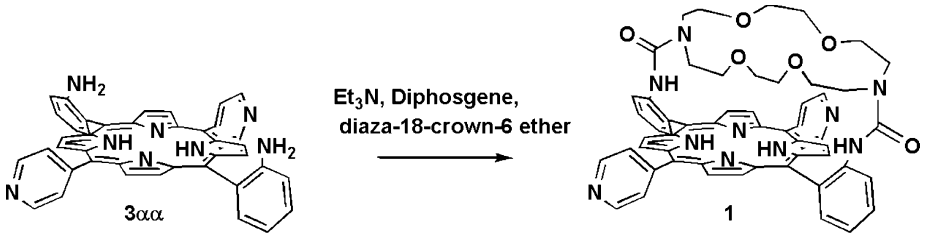
The amino functions were obtained by reduction of the nitro groups of **2** (800 mg, 1.1 mmol) with stannous




**Scheme 2.** Two-step MacDonald type synthesis of **2**.




**Scheme 3.** Reduction of 5,15-bis-(NPh)-10,20-bis-(Py)$PH_2$.




**Scheme 4.** Preparation of macrotricycle **1**.

chloride in acidic medium (HCl 37%) for 3 h at 65°C. After purification and separation by silica gel chromatography, two atropisomers were isolated: the αβ-5,15-bis-(APh)-10,20-bis-(Py)$PH_2$ **3**αβ (410 mg, yield = 58%, eluted with a mixture 1.2% MeOH/$CH_2Cl_2$) and the αα-5,15-bis-(APh)-10,20-bis-(Py)$PH_2$ **3**αα (250 mg, yield = 35%, eluted with a mixture 1.6% MeOH/$CH_2Cl_2$).

As the two atropisomers of 5,15-bis-(APh)-10,20-bis-(Py)$PH_2$ **3** had no spectroscopic difference, it was necessary to perform a chemical derivatization in a strapped-type compound to distinguish them. In our case, we used the *p*-phenylene dipropionic acyl chloride that Momenteau et al.[14] had already employed for the preparation of bis-strapped porphyrins. Indeed, where the αα atropisomer affords a strapped porphyrin under high dilution conditions (MALDI-TOF *m/z* calcd: 833.71 [M+H] for $C_{54}H_{40}N_8O_2$ found: 832.33), the αβ atropisomer is expected to yield oligomers.

Additionally, the desired atropisomer αα can easily be obtained from the αβ one by using a method of enrichment similar to that described by Lindsey[15] for the tetrakis-*ortho*-aminophenyl porphyrin ($TAPPH_2$). This method, applied to the αβ atropisomer in toluene or benzene led to a 75/25 mixture of αα and αβ.

The atropisomer αα (70 mg, 0.11 mmol) was then activated by reaction of diphosgene (26 μL, 0.20 mmol) and $Et_3N$ (119 μL, 0.8 mmol) in dry THF as described in a previously published method,[16] and then condensed with 2 equiv. of the diaza-18-crown-6 ether (56 mg, 0.22 mmol). After evaporation of the reaction mixture, the new macrotricycle **1** was purified by flash chromatography on 15 μm silica gel and eluted as the major band (315 mg, yield = 29%).

In conclusion, we have reported the preparation of a new porphyrin which bears the appropriate groups to both render the compound water-soluble and to functionalize a single side of the aromatic macrocycle. Unexpectedly, the statistical method proved to be the most efficient in terms of yield. A direct application of this raw material is illustrated with the straightforward synthesis of a new macrotricycle. The coordination properties of this latter one, in comparison with non related ligands are under investigation and will be reported elsewhere.

## Notes

All the new compounds described in this work gave satisfactory spectroscopic data ($^1H$ NMR, MS) and consistent elemental analyses. The chemical shifts are given in ppm versus TMS.

**αα-5,15-DUPCE-DPy$PH_2$ 1** (αα-diurea phenyl crown ether-dipyridyl porphyrin): $^1H$ NMR (500 MHz, $CDCl_3$, 300 K): $\delta = 9.08$ (broad s, 4H, 3,5-Py); 8.96 (d, 4H, $J = 4.4$ Hz, pyrrole); 8.85 (d, 4H, $J = 4.4$ Hz, pyrrole); 8.55 (d, 2H, $J = 7.83$ Hz, 6-APh); 8.15 (broad s, 4H, 2,6-Py); 7.95 (d, 2H, $J = 7.83$ Hz, 3-APh); 7.80 (dd, 2H, $J = 7.34$ Hz, $J = 7.83$ Hz, 5-APh); 7.60 (dd, 2H, $J = 7.34$ Hz, $J = 7.83$ Hz, 4-APh); 5.78 (s, 2H, NH amide); 2.58 (broad s, 8H, $(CH_2)_{crown\ ether}$); 1.98 (broad s, 8H, $(CH_2)_{crown\ ether}$); 1.70 (broad s, 8H, $(CH_2)_{crown\ ether}$); −2.53 (s, 2H, *N*-pyrrole); $^{13}C$ NMR ($CDCl_3$): $\delta = 50.2$ $(CH_2)_{crown\ ether}$; 68.1 $(CH_2)_{crown\ ether}$; 69.7 $(CH_2)_{crown\ ether}$; 116.2; 117.4; 122.1; 122.6; 129.8; 130.1; 131.3; 131.7; 133.9; 141.4; 148.9; 149.9; 156.9 (CO); UV–vis ($CH_2Cl_2$): $\lambda_{max}$ (log ε): 418 (59.5), 512 (3.5), 545 (1.3), 587 (1.3), 642 (0.7) nm; HR-MS (LSI-MS) *m/z* calcd: 961.4150 $[M+H]^+$ for $C_{56}H_{53}N_{10}O_6$ found: 961.4136.

**5,15-Bis-(NPh)10,20-bis-(Py)$PH_2$ 2**: $^1H$ NMR (200 MHz, $CDCl_3$, 300 K): $\delta = 9.03$ (AA′BB′m, 4H, 3,5-Py); 8.79 (d, 4H, $J = 4.4$ Hz, pyrrole); 8.69 (d, 4H, $J = 4.4$ Hz, pyrrole); 8.48 (m, 2H); 8.25 (m, 2H); 8.16 (AA′BB′m, 4H, 2,6-Py); 8.00 (m, 4H); −2.74 (s, 2H, *N*-pyrrole).

**αβ-5,15-Bis-(APh)10,20-bis-(Py)$PH_2$ 3αβ**: $R_f$ (TLC, 1% MeOH/$CH_3Cl$) = 0.8; $^1H$ NMR (500 MHz, $CDCl_3$, 300 K): $\delta = 9.07$ (AA′BB′m, 4H, 3,5-Py); 9.00 (d, 4H, $J =$ 4.4 Hz, pyrrole); 8.84 (d, 4H, $J = 4.4$ Hz, pyrrole); 8.18 (AA′BB′m, 4H, 2,6-Py); 7.88 (d, 2H, $J = 7.21$ Hz, 6-APh); 7.65 (t, 2H, $J = 7.95$ Hz, 4-APh); 7.22 (t, 2H, $J = 7.21$ Hz, 5-APh); 7.17 (d, 2H, $J = 7.21$ Hz, 3-APh); 3.58 (s, 4H, -$NH_2$); −2.76 (s, 2H, *N*-pyrrole); MALDI-TOF *m/z* calcd: 646.26 [M+H] for $C_{42}H_{30}N_8$ found: 646.83.

**αα-5,15-Bis-(APh)10,20-bis-(Py)$PH_2$ 3αα**: $R_f$ (TLC, 1% MeOH/$CH_3Cl$) = 0.6; $^1H$ NMR (500 MHz, $CDCl_3$, 300 K): $\delta = 9.06$ (AA′BB′m, 4H, 3,5-Py); 9.00 (d, 4H, $J =$ 4.4 Hz, pyrrole); 8.85 (d, 4H, $J = 4.4$ Hz, pyrrole); 8.18 (AA′BB′m, 4H, 2,6-Py); 7.90 (d, 2H, $J = 7.21$ Hz, 6-APh); 7.65 (t, 2H, $J = 7.95$ Hz, 4-APh); 7.23 (t, 2H,

$J=7.21$ Hz, 5-APh); 7.16 (d, 2H, $J=7.21$ Hz, 3-APh); 3.55 (s, 4H, -$NH_2$); −2.76 (s, 2H, *N*-Pyrrole). Anal. calcd for $C_{42}H_{30}N_8 \cdot 1/2H_2O$: C, 76.93; H, 4.76; N, 17.09; found: C, 76.98; H, 4.77; N, 16.92; MALDI-TOF $m/z$ calcd: 646.26 [M+H] for $C_{42}H_{30}N_8$ found: 646.83.

**5-(4-Pyridyl)dipyrrylmethane 4**: $^1$H NMR (200 MHz, DMSO, 300 K): $\delta=10.62$ (s, 2H, *N*-pyrrole); 8.41 (AA′BB′m, 2H, 2,6-Py); 7.09 (AA′BB′m, 2H, 3-5-Py); 6.60 (m, 2H, m, pyrrole); 5.88 (m, 2H, pyrrole); 5.66 (m, 2H, pyrrole); 5.34 (s, 1H); $^{13}$C NMR (DMSO): $\delta=43.64$; 107.30; 107.95; 118.15; 124.29; 132.37; 150.29; 153.21. Anal. calcd for $C_{14}H_{13}N_3 \cdot 1/2H_2O$: C, 72.39; H, 6.08; N, 18.09; found: C, 71.65; H, 5.85; N, 17.59; HRMS (LSIMS): $m/z$ (%): 223.11095 calcd for $C_{14}H_{13}N_3$ [$M^+$], found 223.11092 (100).

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