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Short synthesis of chiral tentacled porphyrins using pyrrolylmagnesiumbromide and (3*R*)-(+)-citronellal

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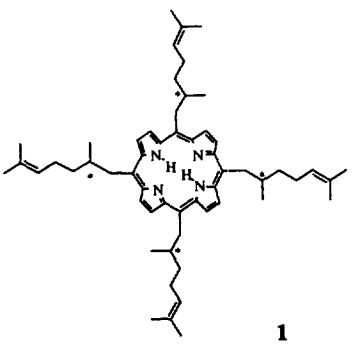
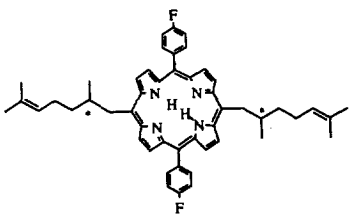
Abstract: The reaction between pyrrolylmagnesiumbromide and (3*R*)-(+)-citronellal produced porphyrin **1** with four chains at the meso carbons, each one bearing a stereogenic centre at C-2 and a double bond at C-5. 4′-Fluoro-phenyldipyrrylmethanebismagnesiumbromide **4** with (3*R*)-(+)-citronellal gave rise to porphyrin **2** with two stereogenic chains. © 1997 Published by Elsevier Science Ltd

The construction of superstructured porphyrins with different types of functionalities in the same molecule can provide them with new and useful properties in many fields such as photodynamic therapy, molecular recognition, and structure–activity studies.[1]

Recently, we have become interested in the synthesis of water-soluble and amphiphilic compounds by producing a series of C-*glyco*-porphyrins.[2] We believe that the introduction of a double bond in the meso substituents is important because of its possible transformation either into two hydroxyls, that could confer amphiphilic properties on the whole molecule, or into an aldehydic group, that could be functionalized to give thiosemicarbazone compounds, of which antitumor and antiviral activities are known.[3]



1



2

The reaction between pyrrole and a natural aldehyde such as (3*R*)-(+)-citronellal unexpectedly occurred in low yield with $BF_3 \cdot OEt_2$ under Lindsey's conditions,[4] while, by using pyrrolylmagnesiumbromide and (3*R*)-(+)-citronellal in CH_2Cl_2 under argon and subsequent air oxidation, porphyrin **1**, bearing at the meso carbons four tentacles with a stereogenic carbon at C-2 and a double bond at C-5, was obtained in one step and in acceptable yield (7.8%, Scheme 1).[5] The reaction mechanism is analogous to those proposed in our previous studies on the selective arylation and hetero-arylation of protected carbohydrates.[2]

Due to its acidity and to its strong coordinating capability, $MgBr^+$ is an ideal promoter to enhance the electrophilic power of the aldehydic carbon, the nucleophilicity of the pyrrole C-2 carbon, and,

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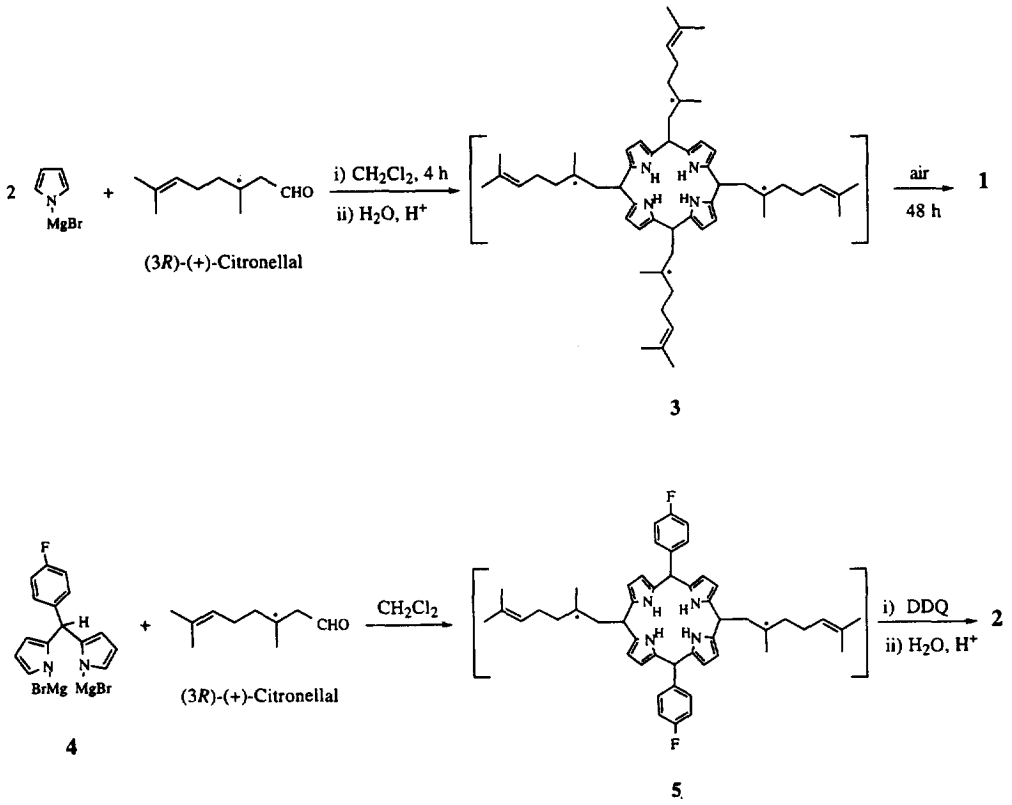

Scheme 1. Reaction strategy to porphyrins **1** and **2**.

last but not least, minimize attack at N by ensuring the C-2 regioselectivity. Moreover, $MgBr^+$ is able to coordinate four or five electron-rich atoms, so that the complex geometry can favour, as in this particular case, the direct formation of the porphyrinogen. In fact pyrrolylmagnesiumbromide (10 mmol) and (3*R*)-(+)-citronellal (5 mmol, 1:2 molar ratio with respect to pyrrolylmagnesiumbromide) in 100 ml of CH_2Cl_2, under argon, afforded, after 4 h and by quenching the magnesiumbromide salt with H_2O/H^+, porphyrinogen **3** (not isolated), and after a 48 h air oxidation compound **1** was obtained (Scheme 1).

We needed to apply a different strategy to obtain porphyrin **2**.[6] The known compound 4′-fluoro-phenyldipyrrylmethane[6] was converted to 4′-fluoro-phenyldipyrrylmethanebismagnesiumbromide **4** using EtMgBr (2:1 molar ratio compared to the dimeric compound) in dry Et_2O (30 ml); the solvent was subsequently removed under vacuum, and anhydrous CH_2Cl_2 (60 ml) was added. Compound **4** (0.4 mmol) gave in the presence of (3*R*)-(+)-citronellal (0.4 mmol, 1:1 molar ratio), in 90 ml of CH_2Cl_2, under an argon stream, porphyrinogen **5** (not isolated), that, by DDQ oxidation and following H_2O/H^+ quenching, afforded the porphyrinic macrocycle **2**[7] in 4.7% yield (Scheme 1).

In conclusion, $MgBr^+$ appears to be an efficient promoter for the synthesis of new chiral porphyrins bearing at the meso carbons two or four chains able to be modified to obtain tetrapyrrolic macrocycles with different and potentially useful functions.

Acknowledgements

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5. Analytical data of 5α,10β,15α,20β-tetrakis-[(2*R*)-2,6-dimethyl-5-eptenyl]-porphyrin (**1**): blue-fluorescent red brown powder (7.8% yield). $[\alpha]^{20}_{546}$ −309.5; $[\alpha]^{20}_{589}$ −166.7 (*c*=0.84, $CHCl_3$). UV-vis ($CHCl_3$) λ_{max} 421 nm (ε=47771 cm^{-1} M^{-1}), 522 (ε=1831), 558 (ε=1406), 602 (ε=647), 660 (ε=825). ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz) 9.48 (8H, s, H-β), 5.10 (4H, m, H-5), 5.06 (4H, dd, *J*=14.3, *J*=6.4, H-1α), 4.69 (4H, dd, *J*=14.6, *J*=8.5, H-1β), 2.62 (4H, m, H-4α), 2.32 (4H, m, H-2), 2.15 (4H, m, H-4β), 1.78 (4H, m, H-3α), 1.71 (4H, m, H-3β), 1.69 and 1.61 (24H, 2s, 12H each, CH_3C=C), 1.02 (12H, s, CHCH_3), −2.65 (2H, bs, NH). MS (CI, CH_4) 807 (M+1). Anal. calcd for $C_{56}H_{78}N_4$: C 83.32, H 9.74, N 6.94; found: C 83.45, H 9.88, N 6.67.
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7. Analytical data of 5,15-di-[p-fluoro-phenyl]-10α,20β-di-[(2*R*)-2,6-dimethyl-5-eptenyl]-porphyrin (**2**): blue-fluorescent red brown powder (4.7% yield). $[\alpha]^{20}_{546}$ −598.2; $[\alpha]^{20}_{589}$ −424.8 (*c*=0.11, $CHCl_3$). UV-vis ($CHCl_3$) λ_{max} 414 nm (ε=25038 cm^{-1} M^{-1}), 514 (ε=2401), 549 (ε=1544), 590 (ε=1239), 646 (ε=883). ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz) 9.50 (2H, d, *J*=5.0, H-β), 8.91 (2H, d, *J*=5.0, H-β), 8.83 (2H, s, H-β), 8.78 (2H, s, H-β), 8.16 (4H, m, H *ortho* phenyl), 7.68 (2H, m, H-1α), 7.52 2H, m, H-1β), 7.43 (4H, m, H *meta* phenyl), 4.89 (2H, m, H-5), 4.31 (2H, m, H-4α), 4.21 (2H, m, H-2), 4.04 (2H, m, H-4β), 3.62 (4H, m, H-3α+H-3β), 1.82 and 1.62 (12H, 2s, 6H each, CH_3C=C), 1.33 (6H, s, CHCH_3), −1.50 (2H, bs, NH). MS (CI, CH_4) 746 (M+1). Anal. calcd. for $C_{50}H_{52}N_4F_2$: C 80.40, H 7.02, N 7.5; found: C 80.56, H 7.14, N 7.38.

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