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Development of Strategies for the Regiocontrolled Synthesis of *meso*-5,10,20-Triaryl-2,3-chlorins

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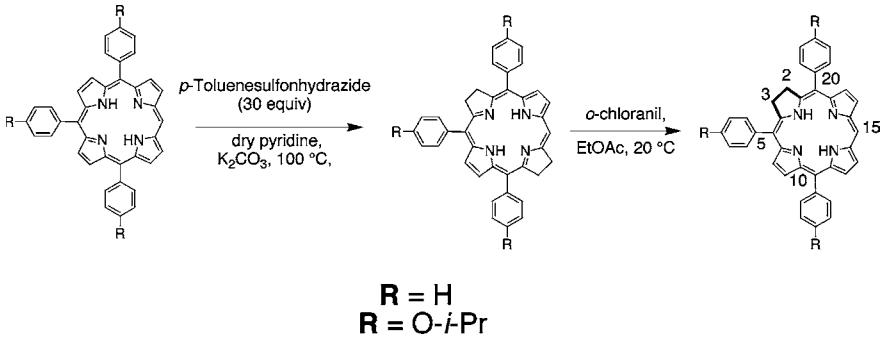
ABSTRACT



Triglycoconjugated photosensitizers show promise for use in the photodynamic therapy-based treatment of cancer. Two different routes have been studied for the regioselective preparation of 5,10,20-*meso*-triphenyl-2,3-chlorin, 9a, and 5,10,20-*meso*-tri(4-isopropyloxyphenyl)-2,3-chlorin, 9b. The main issue was to control the placement of the partially reduced pyrrole ring in the more hindered environment in the triarylchlorin products.

There is increasing interest in photodynamic therapy (PDT), as an anti-cancer strategy for the treatment of shallow small localized tumors. In this approach a highly focused light source is used in combination with a systemic or topical administration of a light-activated molecule.[1] Among the different porphyrin-/chlorin-based photosensitizers currently available, the *meso*-tetra-(*m*-hydroxyphenyl)chlorin **1** (FOSCAN) has received approval for the palliative treatment of head and neck tumors[2] and curative for Barrett esophagus.[3] In a recent study of the glycoconjugates of closely related tri-(*m*-hydroxyphenyl)chlorin derivatives, we showed that the uptake, localization and phototoxicity of the triglucocongugated chlorins **3** in HT29 tumor cells is modified compared to FOSCAN, leading to increased photoefficiency.[4]

These glucoconjugated chlorins were prepared by partial reduction of the corresponding unsymmetrical porphyrin **2** according to the protocol developed by Whitlock et al. (Scheme 1).[5] In this two-step process, which involves sequential reaction with diimide (generated in situ from *p*-toluenesulfonhydrazide ($TsNHNH_2$) in the presence of pyridine and potassium carbonate) followed by *o*-chloranil, the regioisomeric chlorins **3a** and **3b** were obtained as a

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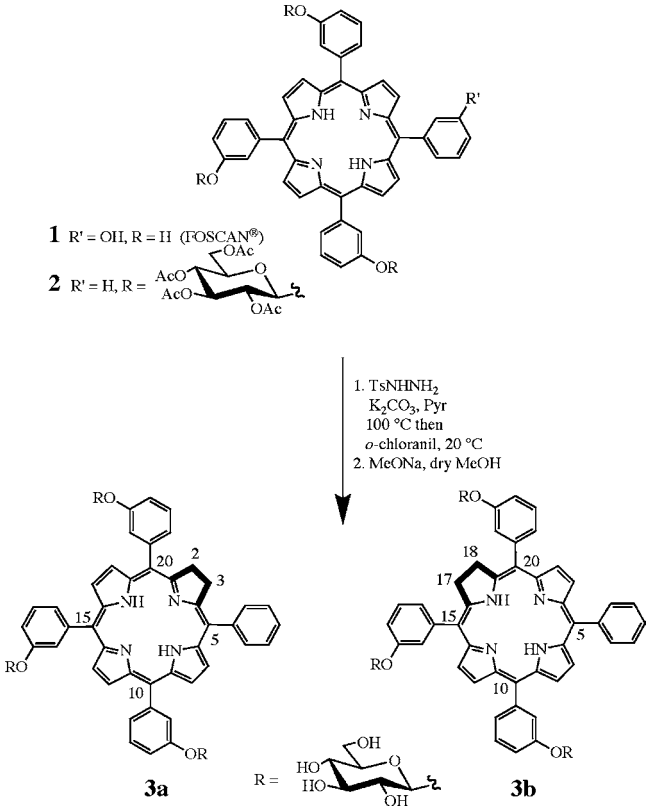
Scheme 1. Preparation of Triglucosylated Chlorins



nonseparable 1/1 mixture. This situation has complicated the study of the stability and photoefficiency of these systems and, consequently, their preclinical assessment relative to the reference molecule FOSCAN.[6]

To continue the development of triglycoconjugated chlorins for PDT, we have explored two new synthetic routes to 5,10,20-triarylsubstituted 2,3-chlorins in which there is a higher level or complete control in the positioning of the dihydropyrrole ring.

In the first approach, illustrated by the preparation of 5,10,20-triphenyl-2,3-chlorin, **9a,** and the corresponding tri-(4-O-isopropoxy)-substituted chlorin **9b** (Scheme 2), the problem of regiocontrol in the porphyrin to chlorin reduction step was avoided by carrying out the operation on the symmetrical 5,15-diarylporphyrins **5a** and **5b** (obtained in multigram quantities in 54−57% yields through condensation of dipyrromethane **4** with benzaldehyde and 4-isopropoxybenzaldehyde, respectively). In this way the chlorins **6a** (93%) and **6b** (77%) were obtained in high yield.

The second, and more challenging operation was to then introduce a bromine atom selectively onto the C-20 *meso* position next to the dihydropyrrole ring without competing or preferred bromination at the *meso* bridge C-10. In the experiment, however, it was found that reaction of compound **6a** with NBS (1 equiv) at 20 °C for 4 h (CH_2Cl_2−pyridine 0.5%) led to formation of two products, the desired 20-bromo-5,15-diaryl-2,3-chlorin, **7a** (26%), as the major product and the less polar 12,20-dibromo-5,15-diaryl-2,3-chlorin derivative **8a** (20%) The corresponding reaction of **6b** in THF (better solubility) resulted in formation of porphyrin **7b** in 44% yield and the dibromo compound **8b** (12%) as the more minor product (see Supporting Information[SI] for NMR data). Interestingly, the 10-bromo-substituted chlorins were not detected in the reaction mixture. The formation of the unexpected dibromo compounds **8a** and **8b** could not be eliminated by varying either the reaction conditions (time, °C, solvent, presence or absence of ambient light) or the quantities of *N*-bromosuccinimide.

Fortunately, compounds **7a**/**8a** and **7b**/**8b** could be separated by silica gel column chromatography (CH_2Cl_2/heptane, 7/3, v/v for **7a** and **8a**, $R_{f7a} = 0.35$ and $R_{f8a} = 0.47$; toluene for **7b** and **8b**, $R_{f7b} = 0.67$ and $R_{f8b} = 0.84$). The structures of compounds **7a**, **7b**, **8a**, and **8b** were determined by ^{1}H, ^{13}C NMR spectroscopy (HMQC, HMBC, and 1D nuclear Overhauser difference spectroscopy). The subsequent, and regiocontrolled Pd(0)-catalyzed Suzuki coupling of compounds **7a** and **7b** with phenyl and 4-isopropoxyphenyl boronic acid, respectively, provided the target *meso*-triarylchlorins **9a** and **9b** in 44% and 62% yields, respectively. The presence of singlet ^{1}H NMR resonance for the protons H_2 and H_3 of compounds **9a** and **9b** (4.18 ppm, see SI) shows that these protons see the same environment induced by C5 and C20 aryl moieties, confirming the strutures. Note that Dolphin et al. selectively prepared 10-iodo-5,15-diphenylporphyrin by treatment of the 5,15-diphenylporphyrin **5** with [bis(fluroacetoxy)iodo] benzene in 70% yield (after chromatographic separation from other iodinated products).[7] However, in the application of this method to the 5,15-diphenylchlorin **6a** only the 12-iodo compound was isolated (35% yield; SI).

In the second approach (Scheme 3), the idea was to see whether the regiochemistry of the reduction of 5,10,15-triarylporphyrins **10** and **13** could be controlled to produce 2,3-chlorins **9a** and **9b**, and not the isomeric and less hindered 12,13-chlorins **11**/**14** as the unique reaction products. Porphyrin **10** was conveniently prepared in 67% yield by addition of phenyllithium to 5,15-diphenyl porphyrin **5a** in THF.[8] In a related manner porphyrin **13** was obtained in two steps from **5b** [(i) 4-hydroxyphenyllithium, THF, 87%;[9] (ii) isopropyl bromide, DMF, 84%]. Under the reduction conditions developed by Whitlock, porphyrins **10** and **13** were converted in high yields (90−93%) to mixtures of chlorins **9a**/**11** and **9b**/**14**, in which the "more hindered" chlorins **9a** and **9b** were the dominant products (86/14 ratio, analytical HPLC;[10] 7:3 ratio by ^{1}H NMR). As for chlorins **3a**,**b**, characterization of the reaction components by ^{1}H

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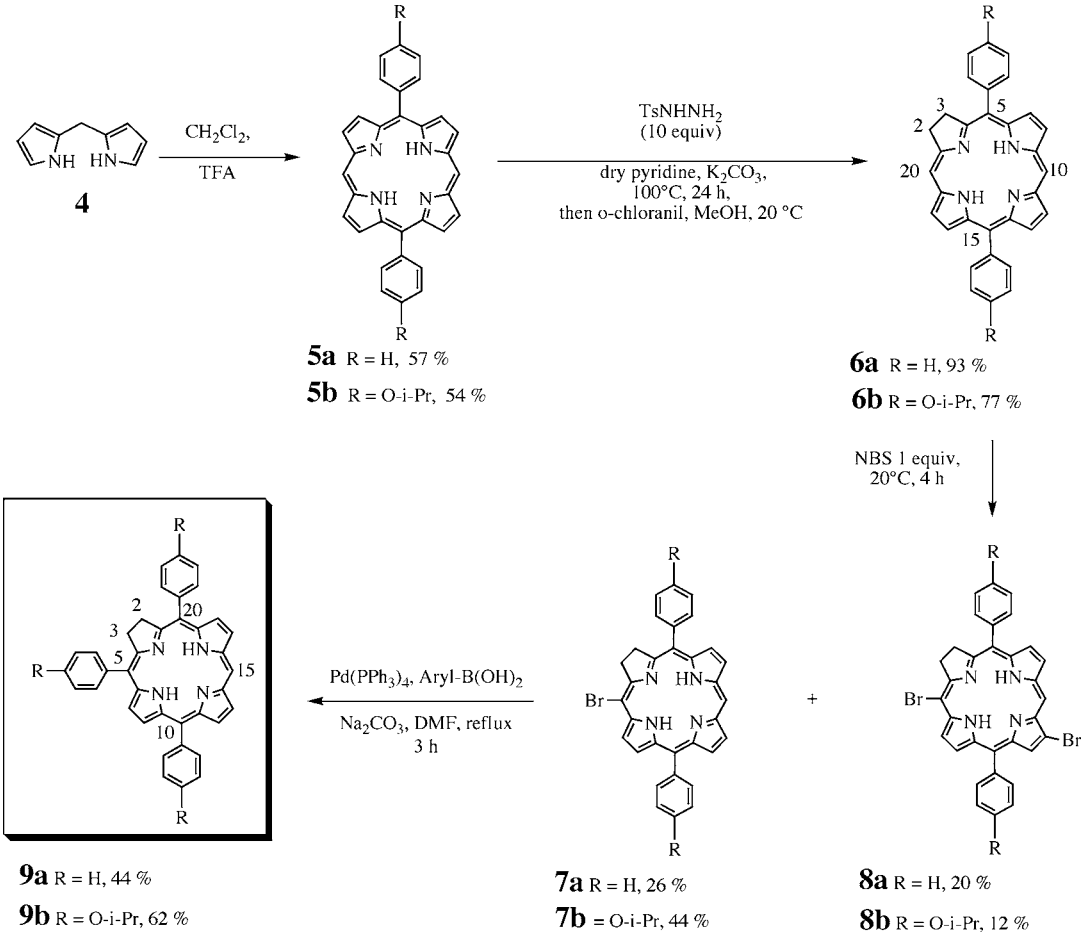
(10) Apparatus : Waters P600 PDA-996, column: Lichrospher 100 SiO_2 5 μm, 250 mm × 4 mm; solvents: methylene chloride/heptane, 1/1, v/v, 1 mL/min.

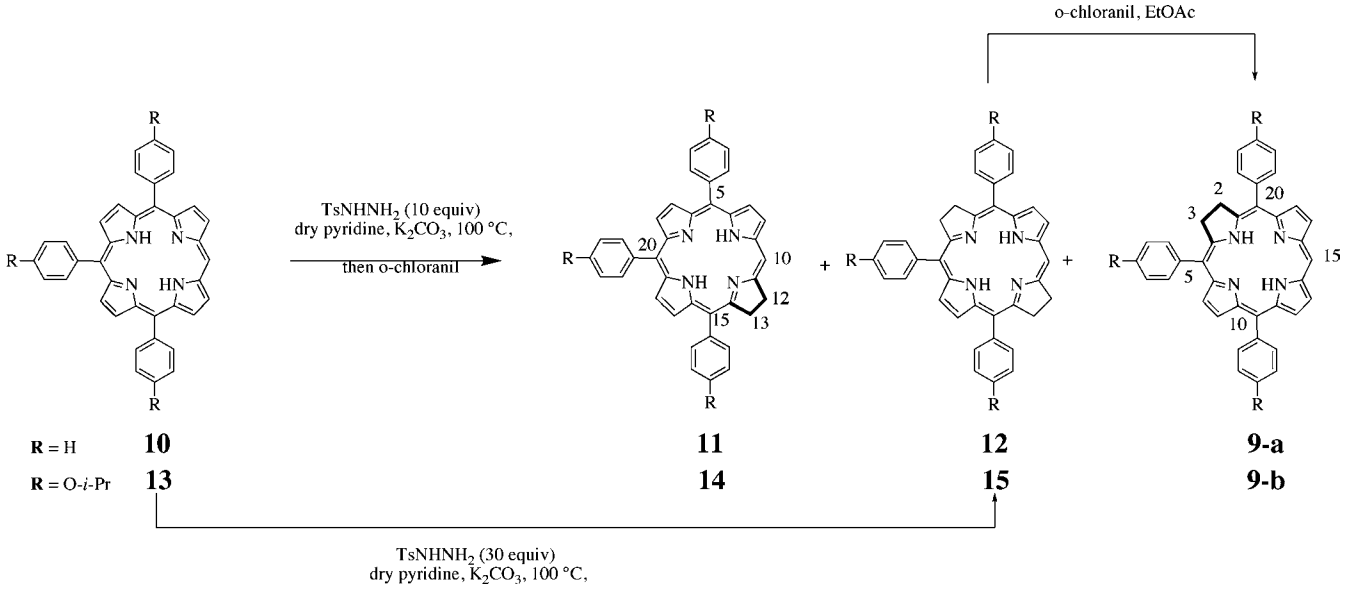
Scheme 2. Synthesis of 5,10,20-Triaryl-2,3-chlorins **9a** and **9b**

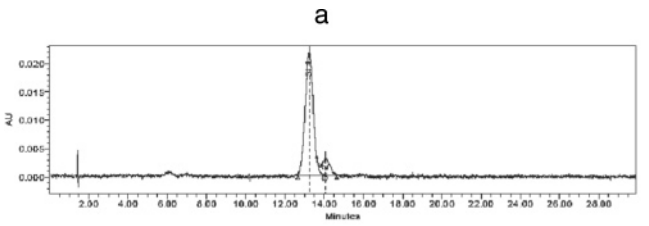


NMR was made on the individual product mixtures.[11] ^{1}H and ^{13}C NMR spectra of compounds **9a**, **9b** obtained by the two strategies were identical.

The fact that the "least hindered" chlorins **11** and **14** were the minor products in these reactions and that a higher level of selectivity was achieved relative to the conversion of

Scheme 3. Selective Synthesis of 5,10,20-Triaryl-2,3-chlorin





Peak results

	RT	Area	%Area
1	13 228	639 206	87.74
2	14 071	89 303	12.26

Figure 1. HPLC profile (a) and UV visible spectra (b) of products obtained from reduction of porphyrin **13** with a large excess of the diimide reagent (30 equiv), SI 1 corresponding to compound **9b** and SI 2 compound **14**. Column Sphinx C18 4.6 mm × 150 mm; conditions: isocratic mode A 5%, B 9 5%, solvent A: ammonium acetate−water, pH 7.1, and solvent B: methanol.

porphyrin **2** to chlorins **3a**,**b** was important. Under Whitlock's conditions, the first step involves reaction of the starting porphyrins **10** and **13** with diimide, generated in situ by decomposition of excess (10 equiv) of *p*-toluenesulfonhydrazide in pyridine containing potassium carbonate. This reaction can lead to formation of both the isomeric chlorins **9a**/**11** or **9b**/**14** as well as to the bacteriochlorins **12** or **15**. Building on the assumption that the rate of formation of **11** and **14** is faster than for the isomeric chlorin products **9a** and **9b**, one can expect that their concentration will build up rapidly in the medium, and one can further expect that in the presence of the large excess of reducing agent they will undergo essentially complete conversion to the bacteriochlorins **12** and **15**.

In this scenario, the subsequent role played by *o*-chloranil will be to oxidize the doubly reduced bacteriochlorins **12**/**15** back to the chlorin level. Again, one can assume that the more accessible dihydropyrrole will be the more reactive, producing the observed products **9a**/**9b**. Taking into account that chlorins **11**/**14** are unreactive under these conditions, the presence of these materials as the minor contaminant in the product mixture from **10**/**13** suggests in the reaction that (i) there is not total conversion of the initially formed chlorin **11**/**14** to bacteriochlorin **12**/**15** or that (ii) the oxidizing agent *o*-chloranil is not sufficiently selective.

In an attempt to verify these points, triarylporphyrins **10** and **13** were reacted with a very large excess of the diimide-generating reagent (30 equiv) in order to push the first step toward complete conversion to **12** and **15** (under these "forcing" conditions only trace amounts of unreacted chlorin could be detected by UV). Rapid workup of these reactions was followed by treatment of the crude reaction mixtures with *o*-chloranil for 15 min at room temperature.

In the reaction of porphyrin **10** there was almost (<10%) exclusive formation of the desired chlorin **9a**, and in the reaction of porphyrin **13** compounds **9b** and **14** were formed in essentially the same ratio as before (88/12 ratio by HPLC) (Figure 1). From this result it was suspected that the loss of specificity still observed arises during the oxidation step. That both isomeric chlorins can be obtained from the intermediate bacteriochlorin **15** was demonstrated by using molecular oxygen as the oxidant (vigorous bubbling for 24 h). This reaction was much slower, and as anticipated, under these conditions the two isomeric chlorins **14** and **9b** were obtained in a 45/55 ratio (50%).

In conclusion, by the two routes that were investigated, the 5,15,20-triaryl-2,3-chlorin system can be prepared with a high degree of regiocontrol in the positioning of the dihydropyrrole ring component. Work is in progress to further optimize the yield and selectivity for the key steps in each approach, and in particular efforts will be directed to the development of more bulky quinone reagents with the requisite redox potential to effect partial oxidation of bacteriochlorin systems.

Acknowledgment. We thank Ms. M.-T. Adeline and F. Pélissier for help concerning HPLC analysis (ICSN, CNRS, 91405, Gif sur Yvette, France) and Ms. M. Bombled for ESI MS analysis.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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