

Synthesis of amphiphilic and non-aggregating chlorins from hematoporphyrin using the Diels-Alder reaction

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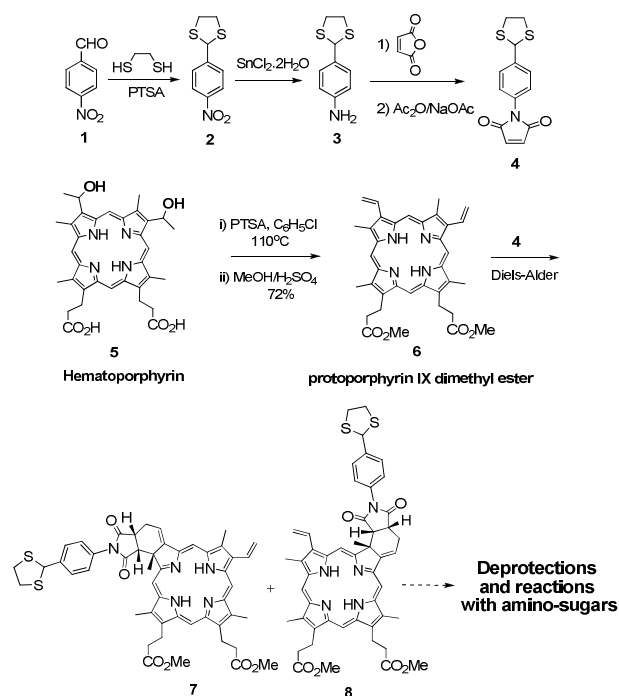
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INTRODUCTION

Hematoporphyrin (**5**) (Scheme 1) and its derivatives have been extensively studied since the discovery of their potential application as photosensitizers in Photodynamic Therapy (PDT).¹ This technique is nowadays very promising for treating several diseases such as skin cancer, internal malignant tumors, viral, bacterial and dermatological diseases. Essentially, PDT treatments employ the combined action of a photosensitizer, light, and molecular oxygen to cause selective cellular damage, in which singlet oxygen, generated through a series of photo-induced processes, is believed to be the major cytotoxic agent.² We are exploring the synthesis of new photosensitizers using protoporphyrin IX dimethyl ester (**6**) obtained from natural hematoporphyrin (**5**) (Scheme 1).³ Porphyrin **6** has been used as diene in the Diels-Alder reaction with phenylmaleimides in order to obtain amphiphilic and non-aggregating compounds.²

RESULTS AND DISCUSSION

First compound **1** was protected with ethanedithiol/PTSA (89% yield) and then reduced with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (93% yield) (Scheme 1). The protected amine **3** was added to maleic anhydride (84% yield) and the amide-ester was converted to **4** using $\text{Ac}_2\text{O}/\text{NaOAc}$ with heating (90 °C) (92% yield). Protoporphyrin IX dimethyl ester (**6**) was synthesized from hematoporphyrin (**5**) performing a double elimination (PTSA/ $\text{C}_6\text{H}_5\text{Cl}$, reflux, 2h) and a double esterification ($\text{MeOH}/\text{H}_2\text{SO}_4$, overnight) (73% global yield). The Diels-Alder reaction between porphyrin **6** and phenylmaleimide **4** was performed in toluene at 120 °C (sealed tube). The *endo*-adducts **7** and **8** were purified in silica gel (both 14% yield) and characterized by ^1H and ^{13}C NMR and UV-Vis. We will perform deprotection of **7** and **8** and reaction with some amine-sugars in order to synthesize amphiphilic chlorin derivatives.



Scheme 1. Synthesis of new chlorin derivatives.

CONCLUSION

Syntheses of new chlorin derivatives starting from natural hematoporphyrin were performed through the Diels-Alder reaction. The use of the synthesized phenylmaleimides is strategic for the obtainment of adducts with a large group in axial position of the macrocycle, allowing low aggregation in solutions.

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