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Synthesis of β-functionalized Temoporfin derivatives for an application in photodynamic therapy

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ABSTRACT

The synthesis of novel β-functionalized derivatives of the clinically used photosensitizer Temoporfin has been achieved by nucleophilic addition reactions to a corresponding diketo chlorin. The β-substituted dihydroxychlorin products exhibit a strong absorption in the red spectral region, a high singlet oxygen quantum yield, and were found to be highly effective in in vitro assays against HT-29 tumor cells.

Photodynamic therapy (PDT) is a well established modality for selective destruction of malignant cells. After administration of the photosensitizer it is locally activated with laser light. Thus, cytotoxic singlet oxygen is produced resulting in cell damage or cell death.[1] The first generation sensitizers were based on a porphyrin core system but their efficacy is limited by the weak absorbance in the red spectral region. However, chlorins and other second generation sensitizers possess significantly stronger absorptions at longer wavelengths, thus increasing both the efficacy and the depth of effect.[2]

Chlorins can principally be obtained either by reduction or oxidation of one of the β-pyrrolic double bonds of porphyrins. For instance, simple β-unsubstituted chlorins are synthesized by reduction with in situ formed diimide.[3] However, the resulting chlorins are oxidation-susceptible and are often not easily separable from the starting porphyrin and by-products.[4] A β-unsubstituted chlorin is Temoporfin (Foscan®) which carries *meta*-hydroxyphenyl groups in *meso*-positions (Fig. 1). It is a clinically approved photosensitizer in Europe for the palliative treatment of head and neck cancer. An example for the oxidative functionalization of the porphyrin double bond is the *cis*-dihydroxylation. Although expensive and very toxic, osmium tetroxide has been established as the standard oxidizing agent for the synthesis of such β-dihydroxy-substituted chlorins.[5] Other reagents proved insufficient. We here report the 'osmium free' synthesis of novel β-substituted Temoporfin derivatives[6] by nucleophilic addition reactions to a corresponding diketo chlorin. In addition, in vitro studies were carried out to preliminarily assess the PDT efficacy of these new chlorins against HT-29 tumor cells.

Our synthetic strategy is related to a route developed by Crossley and co-workers.[7] In the present case, this approach involved preparation of the common dicarbonyl precursor **5**. Its synthesis was accomplished in four steps starting from known porphyrin **1**[8] (Scheme 1). First, selective mononitration and copper complex-

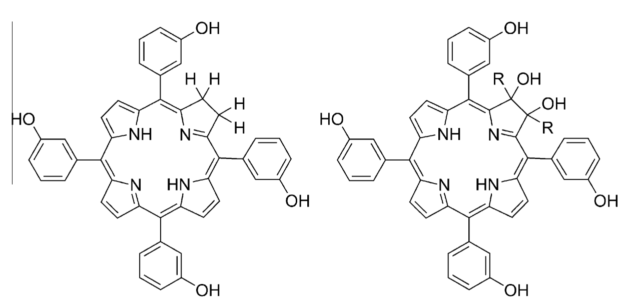

Figure 1. Structure of Temoporfin and its novel derivatives.

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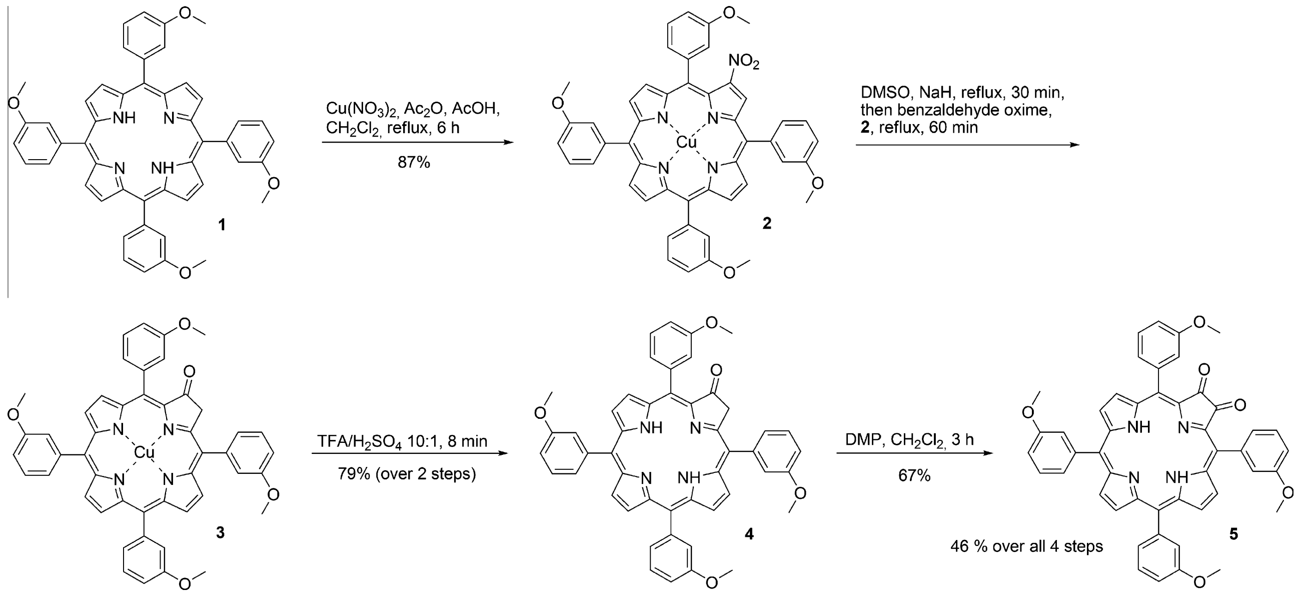


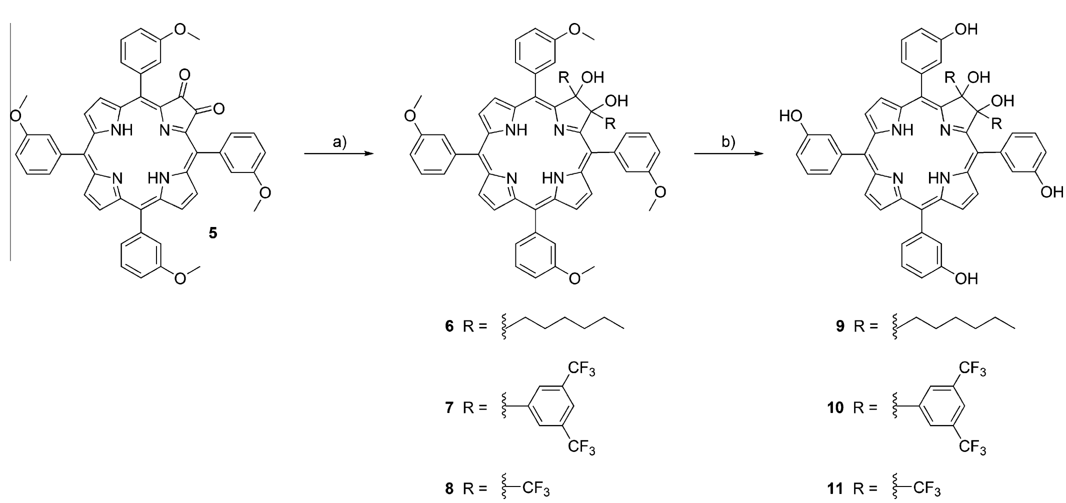
Scheme 1. Synthesis of precursor-chlorin **5**.

ation of porphyrin **1** was achieved in one step using $Cu(NO_3)_2$ in a mixture of acetic anhydride and acetic acid.[9] The nitroporphyrin copper(II)-complex **2** was obtained in 87% yield and subsequently converted to the 2-hydroxyporphyrin derivative **3** by treatment with benzaldoxime in a solution of sodium methyl-sulfinylmethanide.[10] The following decomplexation of copper(II)-porphyrin **3** using concentrated sulfuric acid in dichloromethane failed[11] and led to sulfonated products. Instead, a 10:1 mixture of trifluoroacetic acid and sulfuric acid afforded the copper-free *meta*-methoxyphenyl-substituted porphyrin derivative **4** in 79% yield over two steps. Finally, oxidation using Dess-Martin periodinane (DMP)[11] yielded the diketo chlorin **5** in 67% yield. Thus, porphyrin **1** was efficiently converted to the diketo chlorin **5** in four steps with an overall yield of 46% (Scheme 1).

With common precursor **5** in hand, the addition of nucleophilic agents was investigated. In a first experiment chlorin **5** was reacted with hexyl magnesium bromide affording the dialkylated chlorin **6** in 53% yield (Scheme 2). No mono-addition product was detected. Pleasingly, the desired double addition product was formed as a single diastereoisomer. Selective formation of the presumed *trans*-diol is believed to be favored due to steric reasons.[12]

We next focused on fluoro-substituted dihydroxy-chlorins for mainly two reasons: (i) Generally, fluorinated porphyrins exhibit higher triplet quantum yields[13] and singlet oxygen quantum yields, respectively, and (ii) the substitution with electron-withdrawing groups in β-position stabilizes the vicinal diol against pinacol–pinacolone rearrangement.[14] We therefore treated diketone **5** with 3,5-bis(trifluoromethyl)phenyl magnesium bromide and surprisingly only the two-fold addition product **7** was obtained. However, the use of the electron-deficient and very bulky Grignard reagent led to a reduced yield of only 44% (Scheme 2). In order to minimize the steric stress we inserted trifluoromethyl groups directly without any spacer by using the Ruppert–Prakash reagent CF_3SiMe_3/TBAF (Scheme 2).[15] This reaction afforded a mixture of the dihydroxychlorin and the corresponding trimethylsilyl ether. After treatment with additional TBAF the clean diol product **8** was isolated in 78% yield.[16]

Finally, chlorins **6**, **7**, and **8** were subjected to boron tribromide mediated cleavage of the phenolic methyl ethers. The corresponding *meta*-hydroxyphenyl-substituted products **9**, **10**, and **11** were obtained in yields of 57–87%.[17,18] These β-substituted chlorins were found to consist of a mixture of atropisomers because the



Scheme 2. Synthesis of Temoporfin derivatives. Reagents and conditions: (a) For the synthesis of product **6**: *n*-HexMgBr, THF, −45 °C, 3 h, 53%; for the synthesis of product **7**: $(CF_3)_2$PhMgBr, THF, −45 °C, 3 h, 44%; for the synthesis of product **8**: Me_3SiCF_3/TBAF, THF, −40 °C, 8 h, 78%. (b) **9**, **10**, **11** BBr_3, CH_2Cl_2, −50 °C, 16 h, 57–87%.