DOI: 10.1002/ejoc.201001209

Carbohydrate–Porphyrin Conjugates with Two-Photon Absorption Properties as Potential Photosensitizing Agents for Photodynamic Therapy

Sylvain Achelle,[a,b] Pierre Couleaud,[c] Patrice Baldeck,[d] Marie-Paule Teulade-Fichou,[a,b] and Philippe Maillard*[a,b]

Keywords: Porphyrinoids / Photodynamic therapy / Two-photon absorption / Carbohydrates / Conjugation

We report the synthesis of a series of conjugated zinc porphyrin oligomers designed as photodynamic therapy agents. These compounds exhibit exceptionally high two-photon absorption cross-sections, redshifted linear absorption spectra, and high singlet oxygen quantum yields, making them ideal for one-photon- and two-photon-excited photodynamic therapy. These products are substituted by three α-mannose units on each chromophore with the aim to target tumor cells with over-expressing lectin-type membrane receptors.

Introduction

Photodynamic therapy (PDT) is a promising light-activated treatment that is used clinically to destroy locally diseased tissues.[1] When exposed to light, the photosensitizer (PS) transfers its excitation energy to ground-state triplet oxygen to generate highly reactive singlet oxygen and other cytotoxic reactive oxygen species, inducing oxidative damage to the cell that causes localized cell death and ultimately tissue apoptosis or necrosis. A major advantage of PDT in comparison with other treatments such as chemotherapy is that, in the absence of light, the PS is benign.

The most common photosensitizers used in PDT are porphyrin compounds thanks to their long triplet excited-state lifetime.[2] Amongst them, Photofrin currently used in the clinic has one-photon absorption peaks in the visible wavelength range. However due to the significant absorption in this region by biological tissues, this PS cannot be used to treat deep cancers. Designing a PS excitable in the near-infrared or infrared region between 700–1100 nm may reduce this limitation, as the absorption and diffusion of tissues are much lower in this range currently named the optical window of biological tissues.[3] This can be achieved either by a redshifted absorbing PS, by exciting the PS using sequential discrete absorption (up-conversion), or by simultaneous two-photon absorption (TPA).[4] In this nonlinear optical process, two photons of lower excitation energy whose combined energy is sufficient to induce the transition are simultaneously absorbed. The real advantage is that the excitation in the near-infrared (NIR) region avoids tissue absorbing or scattering and induces a deeper light penetration in the tissue. Consequently, it is a better treatment for deep or large-sized tumors. Porphyrin compounds have a strong one-photon absorption between 400 and 500 nm (Soret band) corresponding to the combined energy of two photons in the wavelength range from 800 to 1000 nm. This is just within the biological optical window. Because porphyrin monomers exhibit relatively small TPA values using femtosecond pulse lasers (less than 50 GM where 1 GM = 10^{-50} $cm^4 s molecule^{-1}$),[5] dimers and oligomers of conjugated porphyrins have been shown to exhibit very strong TPA with δ_{max} values up to 500 times those of monomeric analogues.[6] To obtain conjugated porphyrin oligomers, monomers should be linked with bridges that do not twist out of plane with the porphyrin macrocycle. Because of steric hindrance, alkynyl bridges are one of the most effective ways of making connections to the *meso* position of a porphyrin. Indeed, butadiyne,[7] diethynylbenzene,[8] diethynylthiophene,[9] diethynylanthracene,[10] diethynyltetrathiafulvalene,[11] diethynylsquaraine,[12] and triethynylphenylamine[13] π-conjugated cores have been described in the literature. Recently, in vivo experiments have shown that PDT performed with PS exhibiting high TPA was able to treat tumors more than 0.8 cm in diameter with a total irradiation time of less than 30 min. Excellent regression or total disappearance of the tumor was observed during the week following the treatment.[14] TPA PDT should allow greater precision than is achieved by conventional one-pho-

[a] UMR 176 CNRS/Institut Curie, Institut Curie, Bât 110, Univ. Paris-Sud,
91405 Orsay, France
[b] Institut Curie, Section de Recherches, Centre Universitaire, Univ. Paris-Sud,
91405 Orsay, France
[c] Laboratoire Réactions et Génie des Procédés, UPR 3349, Nancy Université,
1 rue Grandville, B. P. 20451, 54001 Nancy, cedex, France
[d] Laboratoire de Spectrométrie Physique, UMR 5588, Université Joseph Fourier/CNRS,
140 rue de la physique, B.P. 87, 38402 Saint Martin d'Hères, cedex, France

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001209.

ton excitation, as a consequence of the quadratic dependence of two-photon excitation on the local light intensity.[15]

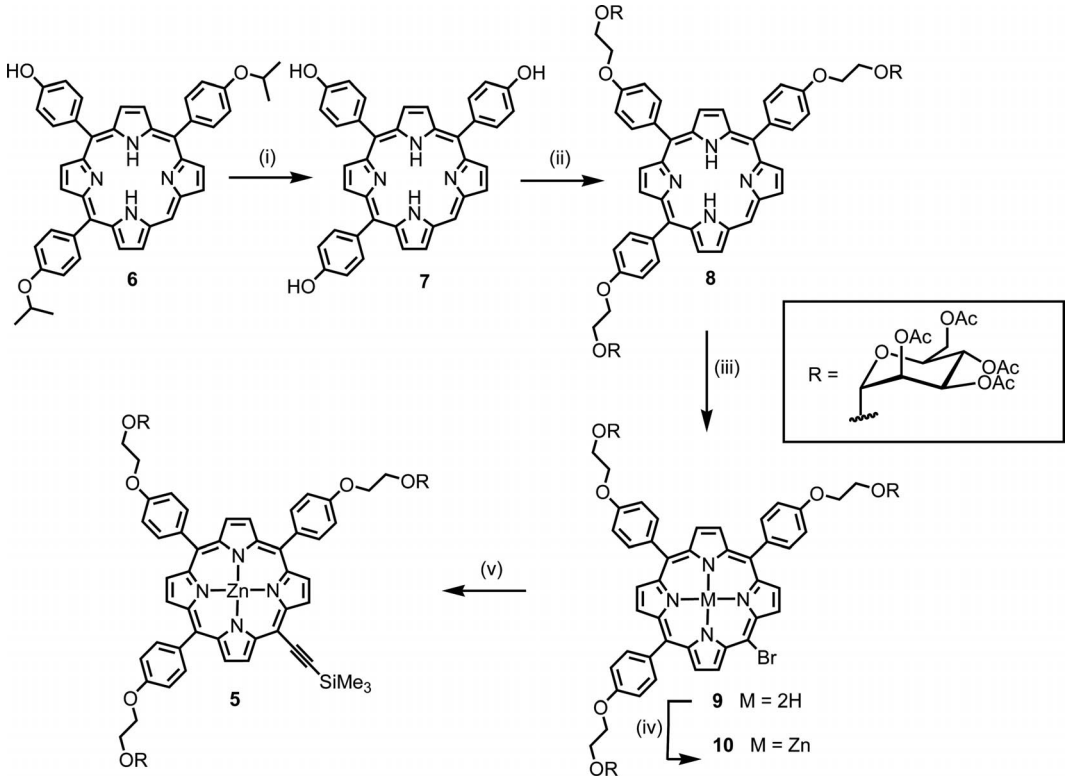
Another limitation of PDT is the low selectivity and specificity of the PS for tumor cells. High doses of the drug and light are thus required to compensate for this, leading to the damage of healthy tissues. Active targeting of membrane receptors represents an obvious improvement.[16] However, only a few examples of cell-targeted TPA PSs are described in the literature.[14,17] It has been reported that lectin-type receptors are over-expressed in certain malignant cells[18] and that carbohydrates such as α-mannose and β-galactose have a specific interaction with these receptors.[19] For over a decade we have focused our efforts on the preparation, as well as, the in vitro and in vivo evaluation of the phototoxicity of glycoconjugated tetrapyrrolic macrocycles. Several of our studies have contributed to establish the proof of the concept.[20,21]

The aim of the present article is to describe the synthesis of new α-mannose-conjugated zinc porphyrin oligomers having remarkable TPA as well as singlet oxygen generating properties. Various neutral π-conjugated cores, ethynyl, butadiyne, diethynylbenzene, and electron-donor triphenylamine, have been incorporated between porphyrin moieties. Using a convergent pathway, this has led to the synthesis of four linear (dimeric) and octupolar (trimeric) structures (i.e., **1**–**4**) from a single parent molecule (i.e., **5**).

Results and Discussion

Porphyrin **5** (Scheme 1) bearing a protected ethynyl group is the key parent molecule for the synthesis of conjugated zinc porphyrin oligomers **1**–**4** (Figure 1). Porphyrin **5** was obtained in five steps starting from trisubstituted porphyrin **6** (Scheme 1).[22] The first step involved deprotection with the removal of the two isopropyloxy groups with BBr_3 (85%). The second step was a Williamson reaction with 2-bromoethoxy-*O*-2′,3′,4′,6′-tetraacetyl-α-D-mannose[23] leading to glycoconjugated porphyrin **8** with a moderate yield (58%). Then, monobromination with *N*-bromosuccinimide (NBS) followed by metalation with zinc acetate quantitatively afforded zinc porphyrin **10**. Sonogashira cross-coupling with trimethylsilylacetylene (TMSA), led to porphyrin **5** in good yield (92%).

Oligomer synthesis started with the deprotection of the trimethylsilyl group of monomer **5** with tetrabutylammonium fluoride (TBAF)[24] leading to compound **11**, which was not isolated due to its instability, and was immediately engaged in the following reaction (Scheme 2). Butadiyne core dimer **1** was obtained by Glaser–Hay oxidative coupling in good yield (72%). Dimers **2** and **3** as well as trimer **4** were obtained by Heck cross-coupling reactions with the corresponding halogenated derivatives in moderate to good yields (31, 42, and 80%, respectively). Deprotection of compounds **1** and **4** (Scheme 3), selected among the four oligo-



Scheme 1. Reagents and conditions: (i) BBr_3, CH_2Cl_2, 15 h, room temp., 85%; (ii) 2-bromoethoxy-*O*-2′,3′,4′,6′-tetraacetyl-α-D-mannose, Cs_2CO_3, dimethylformamide (DMF), 60 °C, 15 h, 58%; (iii) NBS, pyridine, $CHCl_3$, 15 min, 0 °C, 97%; (iv) $Zn(OAc)_2$, $CHCl_3$/MeOH, 5 min, Δ, 99%; (v) TMSA, CuI, $Pd(PPh_3)_2Cl_2$, tetrahydrofuran (THF)/triethylamine (Et_3N), 15 h, 78°K → room temp., 92%.

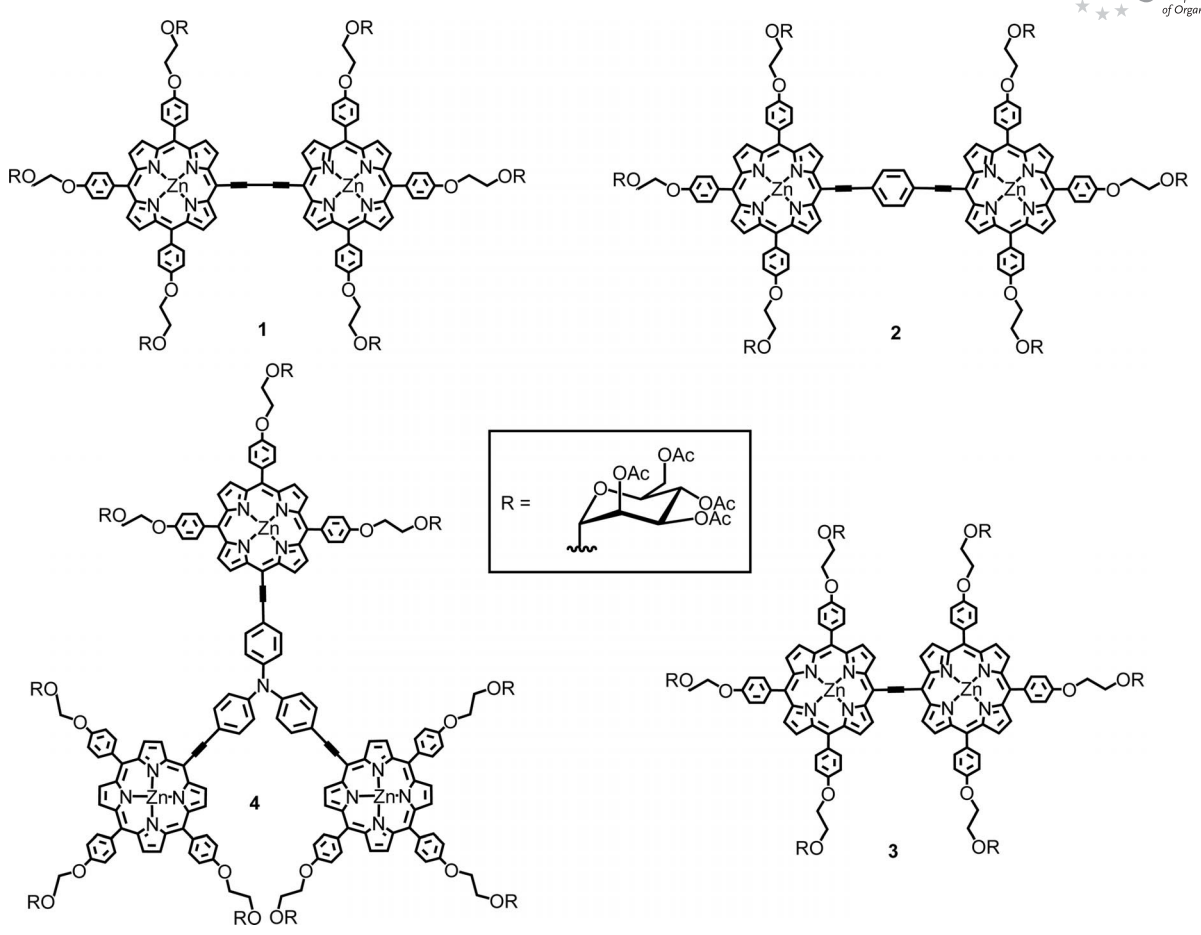
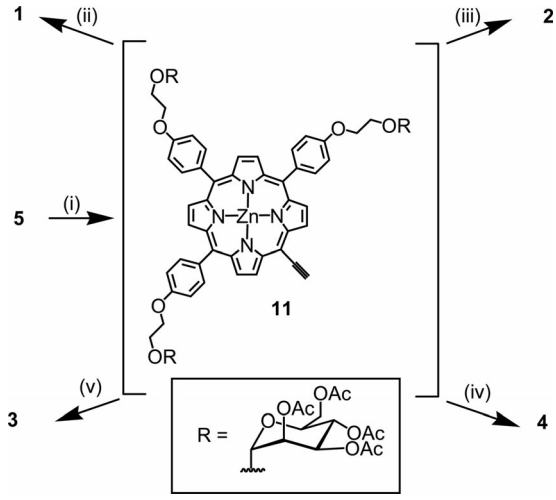


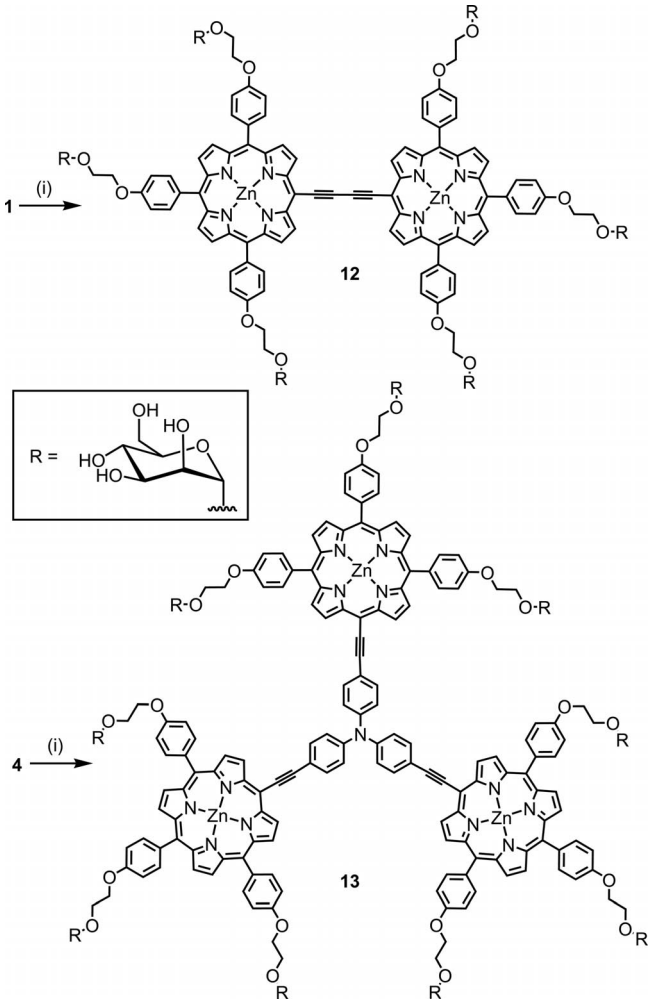
Figure 1. Structures of conjugated zinc porphyrin oligomers.

mers because of their ease of synthesis, was carried out using Zemplén conditions[25] and led to compounds **12** and **13** in 73 and 85% yield, respectively. ^{1}H NMR, ^{13}C NMR, and, UV/Vis spectroscopy, MALDI-TOF analyses, and microanalyses were used to characterize compounds **1**–**4**. Assignments of the resonance to individual protons were based on integration and selective homonuclear correlation (COSY). Heteronuclear multiple coherence (HMQC, HMBC) spectra were obtained for all compounds and the carbon resonances were assigned. Due to insolubility, we were unable to record any interpretable NMR spectra for compounds **12** and **13**.

All photophysical analyses were carried out with protected compounds due to the low solubility of the deprotected derivatives. It was assumed that their optical properties were similar in the absence of aggregation. Figure 2 shows the one-photon UV/Vis absorption spectra of oligomers **1**–**4** and corresponding monomer **5** in CH_2Cl_2. As expected based upon literature precedence,[6,26] for all oligomeric compounds the typical Soret band (around 400–440 nm) is remarkably broadened in comparison to that of the monomer with absorption maxima at similar wavelengths − or slightly redshifted. Also as expected for oligomeric structures, the Q-Bands (590–690 nm range) of the oligomer compounds were stronger, as the molar absorption coefficient of the conjugated dimers (Table 1) was significantly higher (2- to 5-fold) than that of the monomer. In addition, the lowest-energy vibronic shoulder was redshifted, especially in the case of dimer **1** compared to mono-



Scheme 2. Reagents and conditions: (i) TBAF, THF/CH_2Cl_2, room temp., 30 min, not isolated. (ii) CuCl, tetramethylethylenediamine (TMEDA), CH_2Cl_2, room temp., 20 min, 72% in two steps. (iii) *p*-diiodobenzene, $AsPh_3$, $Pd_2(dba)_3$, THF/Et_3N, Δ, 15 h, 31%. (iv) tris(4-iodophenyl)amine, $AsPh_3$, $Pd_2(dba)_3$, THF/Et_3N, Δ, 15 h, 80%. (v) **10**, $AsPh_3$, $Pd_2(dba)_3$, THF/Et_3N, Δ, 15 h, 42%.



Scheme 3. Reagents and conditions: (i) NaOMe/MeOH, THF, room temp., 1 h.

mer **5**. As described above, the ground-state absorptions of oligomers differ remarkably from that of the reference monomer, indicating a higher conjugation of the former. The absorption of the conjugated dimers (Table 1) compares favorably with the well-known PDT sensitizers, for example, $\varepsilon \approx 4 \times 10^4\ cm^{-1}\,M^{-1}$ for Foscan at 654 nm, for chlorin e6 at 664 nm, and for verteporfin at 690 nm.[27]

The large NIR extinction coefficients of new oligomers **1**–**4** indicate that they have potential as one-photon PDT agents. UV/Vis spectra of deprotected compounds **12** and **13** were recorded in a mixture of polyethyleneglycol (PEG)400/EtOH/H_2O (3:2:5), the mixture generally used for in vivo injection of PS.[21b,28] The spectra obtained, characteristic of monomer species, were similar to the corresponding protected derivatives with a small solvatochromic effect and molar extinction coefficients in the same range (see Supporting Information).

Emission spectra of monomer **5** and oligomers **1**–**4** in CH_2Cl_2 are presented in Figure 3 and photophysical parameters are summarized in Table 1. Interestingly, the fluorescence quantum yield (Φ_F) of the four oligomers is significantly lower (1.5–2-fold) than that of monomer **5** (0.14).

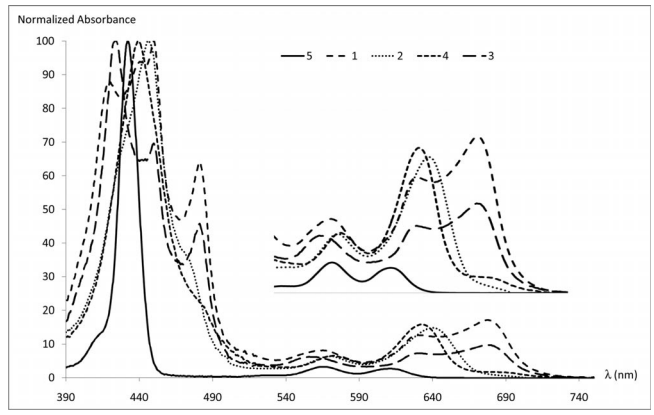


Figure 2. Normalized absorption of monomer **5** and oligomers **1**–**4** in CH_2Cl_2 (6×10^{-6} to 2×10^{-5} M).

Table 1. Photophysical parameters of porphyrins: monomer **5** and oligomers **1**–**4** in CH_2Cl_2.[a]

	λ_{abs} [nm]	ε [$10^{-3}\ M^{-1}cm^{-1}$]	λ_{em} [nm]	Φ_F	Φ_Δ	TPA λ_{max} [nm]	δ_{max} (GM)
5	432	470	630	0.14	nd	790	50
	566	15	679				
	611	13					
1	419	215	619	0.07	0.75	790	8000
	450	244	712				
	481	157					
	565	22					
	630	35					
	677	48					
2	446	294	655	0.10	0.61	820	260
	570	19					
	640	44					
3	424	242	707	0.08	0.43	790	4200
	450	168					
	481	111					
	558	20					
	631	23					
	677	31					
4	440	535	647	0.05	0.47	790	1300
	573	36	698				
	632	88					

[a] λ_{abs} = absorption peak wavelength; ε = molar extinction coefficient; λ_{em} = emission peaks (λ_{exc} = 450 nm); Φ_F = emission quantum yield vs. Rhodamine 101 in ethanol (1.00);[1] Φ_Δ = singlet oxygen quantum yield vs. tetraphenylporphyrin (0.60);[26] TPA λ_{max} = wavelength for which the highest recorded TPA cross-section is obtained; δ_{max} = TPA cross-section.

This is a good indication for a favored intersystem crossing (ISC) de-excitation pathway. Monomer **5** and trimer **4** exhibit two emission bands that are shifted to the red in the case of **4**. In the case of compound **1**, two emission bands are observed at 619 and 712 nm. On the basis of reports of similar dimers, these two emission peaks can be assigned to the two excited-state conformations of **1**, defined by different torsional angles around the central butadiyne bridge.[29]

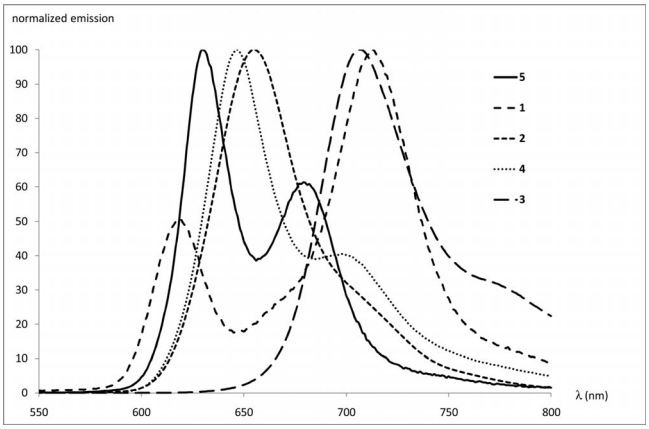


Figure 3. Normalized emission spectra of monomer **5** and oligomers **1**–**4** in CH_2Cl_2 (6×10^{-6} to 2×10^{-5} M; λ_{exc} = 450 nm).

The singlet oxygen quantum yields of all porphyrin oligomers in dichloromethane have been determined after one-photon excitation and are given in Table 1. High $^1O_2$ quantum yields (Φ_Δ from 0.43 up to 0.75) were obtained. These values, measured in organic solvent with protected glycosylated compounds **1**–**4**, are highly encouraging for future use in PDT, even if values in water for deprotected compounds will probably be lower.

TPA cross-sections of monomer **5** and oligomers **1**–**4** were established by detecting the up-converted fluorescence following excitation between 790 and 950 nm (Table 1). The dependence of the fluorescence intensity on the power was almost quadratic rather than linear, indicating that the values obtained are mainly due to TPA. As expected, high TPA cross-sections were obtained for porphyrin oligomers, in particular for dimers **1** and **3** and trimer **4** (8000, 4200 and 1300 GM, respectively). These values are considerably higher than that of monomer **5** (50 GM), validating the oligomeric design.[6] In addition, this indicates that the presence of the protected carbohydrate units does not significantly affect the capacity of the structure for TPA. The comparison of the four oligomer compounds shows that ethynyl and butadiyne linkers are the most efficient in terms of TPA. This is consistent with the literature data that emphasizes the importance of electronic conjugation between the two porphyrin units.[26] Indeed, compound **2** displays a dramatic decrease in TPA cross-sections as compared to dimers **1** and **3**, probably due to the nonplanarity of the two porphyrin moieties providing lower conjugation within the structure. Finally trimeric scaffold **4**, although showing a strong enhancement in TPA cross-sections compared to the monomer, appears less efficient than dimers **1** and **3**. This could be attributed to the propeller shape of the triphenylamine core, which is less favorable to electronic conjugation between the porphyrin units. The TPA cross-sections of this series of conjugated porphyrin oligomers compare favorably with the values of other potential photosensitizers designed for two-photon excited PDT.[7d]

Conclusions

In summary we have described the synthesis of four carbohydrate–porphyrin oligomers. The high TPA efficiencies of these compounds at wavelengths within the optical window of biological tissues, combined with their high singlet oxygen quantum yields, highlights the potential of these products as promising PS for two-photon excited PDT to treat tumor cells with overexpressing lectin-type receptors. Evaluation of the in vitro phototoxicity of free glycoconjugated PS is currently in progress.

Experimental Section

General Methods: All solvents were reagent grade. The starting materials were acquired from Sigma–Aldrich and used without purification. Tris(4-iodophenylamine) was acquired from TCI Europe and used without purification. Dry MeOH was kept over 3 Å molecular sieves, and dichloromethane (DCM) was distilled from calcium hydride and kept over 4 Å molecular sieves. DMF was distilled under slow argon flow and kept over 4 Å molecular sieves. Dry, amine-free DMF was obtained by bubbling with argon for 30 min. Column chromatography was performed with the indicated solvents using E. Merck silica gel 60 (particle size 0.035–0.070 mm). Macherey–Nagel precoated plates (SIL G-200, 2 mm) were used for preparative thin-layer chromatography. Yields refer to chromatographically and spectroscopically pure compounds. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.3 MHz, respectively, with a Bruker AC-300 spectrometer at ambient temperature by using an internal deuterium lock. Chemical shift values are given in ppm relative to tetramethylsilane (TMS). Acidic impurities in $CDCl_3$ were removed by treatment with anhydrous K_2CO_3. Quantitative UV/Vis spectra were recorded with a UVIKON xm SECOMAM spectrometer. Fluorescence spectra were recorded by using a Spex FluoroMax-3 Jobin–Yvon Horiba apparatus. Microanalyses were obtained from ICSN-CNRS Elemental Analysis Centre at Gif-sur-Yvette, France. MALDI-TOF mass spectra were performed with a MALDI-TOF Voyager Spec equipped with a N_2 Laser emitting at 337 nm. The TPA cross-sections in the range 750–950 nm were obtained by up-conversion fluorescence by using a mode locked Ti/sapphire femtosecond laser (Tsunami Spectra-Physics) with a pulse duration of 100 fs and at a repetition rate of 82 MHz. The measurements were obtained at room temperature in DCM and a concentration of approximately 5×10^{-6} to 10^{-5} M. The excitation beam (5 mm diameter) was focused with a lens (focal length 10 cm) at the middle of the fluorescence cell (10 mm). The fluorescence, collected at 90° to the excitation beam, was focused into an optical fiber (diameter 600 μm) connected to an Ocean Optics S2000 spectrometer. The incident beam intensity was adjusted to 50 mW to ensure an intensity-squared dependence of the fluorescence over the whole range. The detector integration time was fixed to 1 s. The spectra were compared with the published Fluorescein and Rhodamine B two-photon absorption spectra.[30] One-photon singlet oxygen ($^1O_2$) generation was detected by its phosphorescence at 1270 nm through a PTI S/N 1565 monochromator, and the emission was monitored by a liquid nitrogen-cooled Ge-detector model (EO-817L, North Coast Scientific Co). Excitation occurred with a Xe-arc; the light was separated in a SPEX 1680, 0.22 μm double monochromator. The $^1O_2$ quantum yields (Φ_Δ) were calculated by a comparative method using tetraphenylporphyrin in DCM (Φ_Δ = 0.60) as a standard.[26]

5,10,15-Tri(4-hydroxyphenyl)porphyrin (7): A solution of 5,15-bis(4-isopropyloxyphenyl)-10-(4-hydroxyphenyl)porphyrin (800 mg, 1.19 mmol) in DCM (100 mL) was cooled to –20 °C before addition of boron tribromide (2.26 mL, 23.8 mmol). After 15 min, the cold bath was removed and stirring was continued for 15 h at room temperature. The green mixture was poured into a water/ice mixture and neutralized with ammonia. DCM was removed by evaporation, and the porphyrin was extracted with ethyl acetate (4 × 100 mL). The combined organic extracts were washed with diluted ammonia and water and then dried with Na_2SO_4. After filtration, much of the ethyl acetate was removed by evaporation, *n*-heptane was added, and a precipitate formed. Compound **7** (595 mg, 1.01 mmol, 85%) was collected by filtration as a purple solid. $C_{38}H_{26}N_4O_3$ (586.65): calcd. C 77.80, H 4.47, N 9.55; found C 77.69, H 5.14, N 8.74. UV/Vis (acetone): λ_{max} (ε, L mmol^{-1} cm^{-1}) = 412 (420), 509 (15.3), 545 (7.8), 586 (4.5), 642 (3.3) nm. ^{1}H NMR ([D$_6$]DMSO): δ = 10.42 (s, 1 H, 20-H), 9.94 (s, 3 H, OH), 9.52 (d, *J* = 4.8 Hz, 2 H, 2-H and 18-H), 8.98 (d, *J* = 4.8 Hz, 2 H, 3-H and 17-H), 8.89 (d, *J* = 4.8 Hz, 2 H, 7/8-H and 12/13-H), 8.86 (d, *J* = 4.8 Hz, 2 H, 7/8-H and 12/13-H), 8.00 (d, *J* = 8.4 Hz, 4 H, *o*-phenol-H), 7.96 (d, *J* = 8.4 Hz, 2 H, *o*-phenol-H), 7.20 (d, *J* = 8.4 Hz, 4 H, *m*-phenol-H), 7.16 (d, *J* = 8.4 Hz, 4 H, *m*-phenol-H), –3.15 (s, 2 H, NH) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 159.43 (C-*p*-phenol), 159.37 (C-*p*-phenol), 148.7–148.0 (C-1, C-4, C-6, C-9, C-11, C-14, C-16, and C-19), 137.6 (C-*o*-phenol), 137.4 (C-*o*-phenol), 135.5 (C-1-phenol), 134.6 (C-1-phenol), 131.3–129.6 (C-2, C-3, C-7, C-8, C-12, C-13, C-17, and C-18), 122.6, (C-10), 121.5 (C-5 and C-15), 115.8 (C-*m*-phenol), 115.6 (C-*m*-phenol), 106.5 (C-20) ppm.

5,10,15-Tri{*p*-*O*-[2-*O*-(2′,3′,4′,6′-tetraacetyl-α-D-mannosyloxy)-ethoxy]phenyl}porphyrin (8): A mixture of **7** (232 mg, 0.395 mmol), 2-bromoethoxy-*O*-2′,3′,4′,6′-tetraacetyl-α-D-mannose (2.34 g, 5.14 mmol), and cesium carbonate (4.12 g, 12.7 mmol) in dry DMF (60 mL) was stirred under argon at 60 °C overnight. The mixture was concentrated under vacuum, a mixture of water and ethyl acetate (2:1, 150 mL) was added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL), dried with Na_2SO_4, and filtered, and the solvent was evaporated under vacuum. The product was partially purified by crystallization (3×, DCM/*n*-heptane) and preparative TLC (silica; DCM/acetone, 9:1). Another crystallization (DCM/*n*-heptane) produced **8** (392 mg, 229 mmol, 58%) as a deep red solid. $C_{86}H_{92}N_4O_{33}$·6H_2O (1709.66 + 6 H_2O): calcd. C 56.82, H 5.77, N 3.08; found C 57.19, H 5.54, N 2.72. UV/Vis (DCM): λ_{max} (ε, L mmol^{-1} cm^{-1}) = 415 (355), 509 (16.7), 545 (7.3), 586 (5.2), 642 (3.2) nm. ^{1}H NMR ($CDCl_3$): δ = 10.19 (s, 1 H, 20-H), 9.33 (d, *J* = 4.6 Hz, 2 H, 2-H and 18-H), 9.04 (d, *J* = 4.6 Hz, 2 H, 2-H and 18-H), 8.91 (d, *J* = 4.6 Hz, 2 H, 7-H, 13/8-H, and 12-H), 8.89 (d, *J* = 4.6 Hz, 2 H, 7-H, 13/8-H, and 12-H), 8.15 (d, *J* = 8.0 Hz, 2 H, *o*-phenoxy-H), 8.13 (d, *J* = 8.0 Hz, 4 H, *o*-phenoxy-H), 7.31 (d, *J* = 8.7 Hz, 4 H, *m*-phenoxy-H), 7.28 (d, *J* = 8.7 Hz, 2 H, *m*-phenoxy-H), 5.49 (m, 3 H, 3′-H), 5.43 (m, 3 H, 2′-H), 5.38 (m, 3 H, 4′-H), 5.09 (s, 3 H, 1′-H), 4.46 (m, 9 H, 6′-H and CH_2α), 4.27–4.22 (m, 9 H, 6′-H and CH_2β), 4.11 (m, 3 H, 5′-H), 2.23 (s, 9 H, AcO), 2.17 (s, 9 H, AcO), 2.06 (s, 9 H, AcO), 2.04 (s, 9 H, AcO), –2.97 (s, 2 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.6 (C=O, acetyl), 170.0 (C=O, acetyl), 169.8 (C=O, acetyl), 169.7 (C=O, acetyl), 158.3 (C-*p*-phenoxy), 147.5–146.3 (C-1, C-4, C-6, and C-9), 135.6 (C-*o*-phenoxy), 135.43 (C-*o*-phenoxy), 135.36 (C-1-phenoxy), 134.5 (C-1-phenoxy), 131.3–131.0 (C-2, C-3, C-7, C-8, C-12, C-13, C-17, and C-18), 120.1 (C-10), 119.0 (C-5 and C-15), 112.8 (C-*m*-phenoxy), 112.5 (C-*m*-phenoxy), 105.0 (C-20), 97.7 (C-1′), 69.5 (C-2′), 69.0 (C-3′), 68.6 (C-5′), 66.9 (CH_2α), 66.7 (CH_2β), 66.1 (C-4′), 62.4 (C-6′), 20.8 (CH_3, acetyl), 20.7 (CH_3, acetyl), 20.62 (CH_3, acetyl), 20.59 (CH_3, acetyl) ppm.

20-Bromo-5,10,15-tri{*p*-*O*-[2-*O*-(2′,3′,4′,6′-tetraacetyl-α-D-mannosyloxy)ethoxy]phenyl}porphyrin (9): NBS (16.40 mg, 0.092 mmol) was added to a solution of **8** (150 mg, 0.088 mmol) in a mixture of chloroform (35 mL) and pyridine (0.25 mL) at 0 °C. The mixture was stirred at this temperature for 15 min. The reaction was quenched with acetone, and the solvents were evaporated under vacuum. The crude product was washed with water to give **9** (152 mg, 0.085 mmol, 97%) as a purple solid. UV/Vis (DCM): λ_{max} (ε, L mmol^{-1} cm^{-1}): 422 (384), 519 (15.9), 557 (10.6), 597 (4.95), 655 (4.74) nm. ^{1}H NMR ($CDCl_3$): δ = 9.66 (d, *J* = 4.6 Hz, 2 H, 2-H, and 18-H), 8.93 (d, *J* = 4.6 Hz, 2 H, 2-H and 18-H), 8.82 (s, 4 H, 7-H, 13/8-H, and 12-H), 8.09 (d, *J* = 8.0 Hz, 6 H, *o*-phenoxy-H), 7.26 (d, *J* = 8.0 Hz, 6 H, *m*-phenoxy-H), 5.50 (m, 3 H, 3′-H), 5.43 (m, 3 H, 2′-H), 5.39 (m, 3 H, 4′-H), 5.09 (s, 3 H, 1′-H), 4.42 (m, 9 H, 6′-H and CH_2α), 4.32–4.20 (m, 9 H, 6′-H and CH_2β), 4.05 (m, 3 H, 5′-H), 2.23 (s, 9 H, AcO), 2.18 (s, 9 H, AcO), 2.08 (s, 9 H, AcO), 2.05 (s, 9 H, AcO), –2.72 (s, 2 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.2 (C=O, acetyl), 170.6 (C=O, acetyl), 170.4 (C=O, acetyl), 170.3 (C=O, acetyl), 158.9 (C-*p*-phenoxy), 148.2–143.9 (C-2, C-3, C-7, C-8, C-12, C-13, C-17, and C-18), 136.1 (C-1-phenoxy), 136.0 (C-1-phenoxy), 135.2 (C-1-phenoxy), 135.0 (C-1-phenoxy), 132.3–132.1 (C-1, C-4, C-6, C-9, and C-11), 121.1 (C-10), 120.8 (C-5 and C-15), 113.3 (C-*m*-phenoxy), 103.0 (C-20), 98.3 (C-1′), 70.1 (C-2′), 69.6 (C-3′), 69.2 (C-5′), 67.4 (CH_2α), 67.2 (CH_2β), 66.6 (C-4′), 63.0 (C-6′), 21.4 (CH_3, acetyl), 21.3 (CH_3, acetyl), 21.21 (CH_3, acetyl), 21.20 (CH_3, acetyl) ppm.

20-Bromo-5,10,15-tri{*p*-*O*-[2-*O*-(2′,3′,4′,6′-tetraacetyl-α-D-mannosyloxy)ethoxy]phenyl}porphyrinatozinc(II) (10): Zinc acetate (78 mg, 0.425 mmol) was diluted in methanol (45 mL) and added to a solution of **9** (152 mg, 0.085 mmol) in chloroform (90 mL). The mixture was heated to reflux for 5 min. After cooling, the solvents were evaporated under vacuum, and a mixture of water and DCM (100 mL, 1:1) was added. The organic layer was separated, washed with water (2 × 50 mL), and dried with Na_2SO_4. Filtering followed by evaporation of the solvents under vacuum gave the crude product. Crystallization (AcOEt/*n*-heptane) yielded **10** (156 mg, 0.084 mmol, 99%) as a purple solid. $C_{86}H_{89}BrN_4O_{33}Zn$ (1851.95): calcd. C 55.77, H 4.85, N 3.03; found C 55.46, H 5.20, N 2.85. UV/Vis (DCM): λ_{max} (ε, L mmol^{-1} cm^{-1}): 425 (415), 558 (16.1), 600 (7.9) nm. ^{1}H NMR ($CDCl_3$): δ = 9.73 (d, *J* = 4.5 Hz, 2 H, 2-H and 18-H), 9.01 (d, *J* = 4.6 Hz, 2 H, 2-H and 18-H), 8.92 (s, 4 H, 7-H, 13-H, 8-H, and 12-H), 8.09 (d, *J* = 8.1 Hz, 6 H, *o*-phenoxy-H), 7.26 (d, *J* = 8.1 Hz, 6 H, *m*-phenoxy-H), 5.46–5.43 (m, 3 H, 3′-H), 5.37–5.33 (m, 3 H, 2′-H), 5.32–5.31 (m, 3 H, 4′-H), 5.02 (s, 3 H, 1′-H), 4.42–4.31 (m, 9 H, 6′-H and CH_2α), 4.28–4.15 (m, 9 H, 6′-H and CH_2β), 4.07–4.03 (m, 3 H, 5′-H), 2.14 (s, 9 H, AcO), 2.12 (s, 9 H, AcO), 2.03 (s, 9 H, AcO), 1.97 (s, 9 H, AcO) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7 (C=O, acetyl), 170.1 (C=O, acetyl), 169.9 (C=O, acetyl), 169.9 (C=O, acetyl), 158.2 (C-*p*-phenoxy), 150.9 (C-4, C-16/6, C-14/9, and C-11), 150.8 (C-4, C-16/6, C-14/9, and C-11), 150.7 (C-4, C-16/6, C-14/9, and C-11), 149.6 (C-1 and C-19), 135.6 (C-*o*-phenoxy), 135.5 (C-*o*-phenoxy), 135.4 (C-1-phenoxy), 133.1–132.1 (C-2, C-3, C-7, C-8, C-12, C-13, C-17 and C-18), 121.3 (C-10), 121.1 (C-5 and C-15), 112.6 (C-*m*-phenoxy), 104.0 (C-Br), 97.8 (C-1′), 69.6 (C-2′), 69.1 (C-3′), 68.7 (C-5′), 66.9 (CH_2β), 66.7 (CH_2α), 66.1 (C-4′), 62.5 (C-6′), 20.9 (CH_3, acetyl), 20.8 (CH_3, acetyl), 20.73 (CH_3, acetyl), 20.69 (CH_3, acetyl) ppm.

(5,10,15-Tri{*p*-*O*-[2-*O*-(2′,3′,4′,6′-tetraacetyl-α-D-mannosyloxy)-ethoxy]phenyl}-20-trimethylsilylethenylporphyrinato)zinc(II) (5): A

flask containing **10** (147 mg, 0.079 mmol), copper(I) iodide (1.5 mg, 7.94 μmol), and dichlorobis(triphenylphosphanyl)palladium(II) (5.57 mg, 7.94 μmol) was purged with argon, followed by the addition of anhydrous THF (5 mL) and dry Et_3N (1 mL). The solution was frozen with liquid nitrogen, TMSA (0.158 mL, 1.11 mmol) was added, and the mixture was degassed. After stirring for 12 h at room temperature, the mixture was quenched with water, and the organic solvents were evaporated. Upon extracting with DCM, the organic layer was dried with anhydrous Na_2SO_4, filtered, and the solvents evaporated to dryness under reduced pressure. The residue was purified using a silica gel column (DCM and then DCM/acetone, 10:1) to give **5** (137 mg, 0.073 mmol, 92%) as a purple solid. $C_{91}H_{98}N_4O_{33}SiZn{\cdot}3H_2O$ (1869.25 + 3 H_2O): calcd. C 56.83, H 5.45, N 2.91; found C 57.01, H 5.70, N 3.25. UV/Vis (DCM): λ_{max} (ε, L mmol^{-1} cm^{-1}): 432 (470), 566 (15.0), 611 (12.4) nm. ^{1}H NMR ($CDCl_3$): δ = 9.73 (d, J = 4.5 Hz, 2 H, 2-H and 18-H), 9.00 (d, J = 4.6 Hz, 2 H, 2-H and 18-H), 8.90 (s, 4 H, 7-H, 13-H, 8-H, and 12-H), 8.12 (d, J = 8.0 Hz, 2 H, *o*-phenoxy-H), 8.09 (d, J = 8.0 Hz, 4 H, *o*-phenoxy-H), 7.29 (d, J = 8.7 Hz, 4 H, *m*-phenoxy-H), 7.27 (d, J = 8.7 Hz, 2 H, *m*-phenoxy-H), 5.49–5.45 (m, 3 H, 3′-H), 5.38–5.34 (m, 3 H, 2′-H), 5.34–5.31 (m, 3 H, 4′-H), 5.05 (s, 3 H, 1′-H), 4.46–4.35 (m, 9 H, 6′-H and $CH_2\alpha$), 4.29–4.17 (m, 9 H, 6′-H and $CH_2\beta$), 4.09–4.05 (m, 3 H, 5′-H), 2.16 (s, 9 H, AcO), 2.14 (s, 9 H, AcO), 2.05 (s, 9 H, AcO), 1.99 (s, 9 H, AcO), 0.62 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.1 (C=O, acetyl), 170.5 (C=O, acetyl), 170.3 (C=O, acetyl), 170.2 (C=O, acetyl), 158.6 (C-*p*-phenoxy), 153.0 (C-1 and C-19), 151.2 (C-4, C-16/6, C-14/9, and C-11), 150.5 (C-4, C-16/6, C-14/9, and C-11), 150.4 (C-4, C-16/6, C-14/9, and C-11), 135.9 (C-*o*-phenoxy), 135.8 (C-*o*-phenoxy), 134.4 (C-1-phenoxy), 134.3 (C-1-phenoxy), 132.4–131.4 (C-2, C-3, C-7, C-8, C-12, C-13, C-17, and C-18), 122.9 (C-10), 121.7 (C-5 and C-15), 113.0 (C-*m*-phenoxy), 112.9 (C-*m*-phenoxy), 105.6 (C-20), 101.0 (C-triple bond), 99.3 (C-$SiMe_3$), 99.3 (C-1′), 70.0 (C-2′), 69.6 (C-3′), 69.2 (C-5′), 67.4 ($CH_2\beta$), 67.2 ($CH_2\alpha$), 66.6 (C-4′), 63.0 (C-6′), 21.4 (CH_3, acetyl), 21.3 (CH_3, acetyl), 21.19 (CH_3, acetyl), 21.16 (CH_3, acetyl), 0.87 ($SiMe_3$) ppm.

Porphyrinatozinc(II) Dimer (1): Tetrabutylammonium fluoride (1 M in THF, 0.172 mL, 0.172 mmol) was added to **5** (124 mg, 0.066 mmol) dissolved in DCM (15 mL). The reaction was stirred at room temperature for 15 min followed by addition of anhydrous calcium chloride (2 g). The mixture was stirred for 10 min, filtered, and the solvent evaporated. The crude product was dried under vacuum and dissolved in DCM (50 mL). The mixture was stirred vigorously for 15 min to aerate the solution, whereupon copper(I) chloride (197 mg, 1.99 mmol) was added. After an additional 2 min, TMEDA (0.300 mL, 1.990 mmol) was added, and the reaction was followed by TLC. After 20 min, TLC showed no further change, and the reaction was quenched with H_2O (250 mL). The organic layer was washed with water until the aqueous washings were no longer blue. The crude product was purified by filtration through a silica pad (THF) and crystallized (AcOEt/*n*-heptane) to give **1** (86 mg, 0.024 mmol, 72%) as a dark green solid. $C_{176}H_{178}N_8O_{66}Zn_2$ (3592.13): calcd. C 58.85, H 4.99, N 3.12; found C 58.93, H 5.15, N 3.07. UV/Vis (DCM): λ_{max} (ε, L mmol^{-1} cm^{-1}): 419 (215), 450 (244), 481 (157), 565 (22.5), 630 (35.2), 677 (47.7) nm. ^{1}H NMR ($CDCl_3$): δ = 9.99 (d, J = 4.5 Hz, 4 H, 2-H and 18-H), 9.10 (d, J = 4.6 Hz, 4 H, 2-H and 18-H), 8.90 (s, 8 H, 7-H, 13-H, 8-H, and 12-H), 8.16 (d, J = 8.0 Hz, 4 H, *o*-phenoxy-H), 8.12 (d, J = 8.0 Hz, 8 H, *o*-phenoxy-H), 7.32 (d, J = 8.7 Hz, 8 H, *m*-phenoxy-H), 7.29 (d, J = 8.7 Hz, 4 H, *m*-phenoxy-H), 5.52–5.47 (m, 6 H, 3′-H), 5.40–5.38 (m, 6 H, 2′-H), 5.38–5.34 (m, 6 H, 4′-H), 5.08 (s, 6 H, 1′-H), 4.47–4.37 (m, 12 H, 6′-H and $CH_2\alpha$), 4.31–4.20 (m, 12 H, 6′-H and $CH_2\beta$), 4.12–4.07 (m, 6 H, 5′-H), 2.19 (s, 18 H, AcO), 2.16 (s, 18 H, AcO), 2.06 (s, 18 H, AcO), 2.03 (s, 18 H, AcO) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7 (C=O, acetyl), 170.1 (C=O, acetyl), 169.9 (C=O, acetyl), 169.8 (C=O, acetyl), 158.3 (C-*p*-phenoxy), 153.3 (C-1 and C-19), 151.0 (C-4, C-16/6, C-14/9, and C-11), 150.1 (C-4, C-16/6, C-14/9, and C-11), 149.9 (C-4, C-16/6, C-14/9, and C-11), 135.5 (C-*o*-phenoxy), 135.3 (C-*o*-phenoxy), 134.3 (C-1-phenoxy), 134.2 (C-1-phenoxy), 133.3–130.3 (C-2, C-3, C-7, C-8, C-12, C-13, C-17, and C-18), 123.1 (C-10), 122.0 (C-5 and C-15), 112.7 (C-*m*-phenoxy), 112.6 (C-*m*-phenoxy), 104.5 (C-20), 101.0 (C-triple bond), 97.8 (C-1′), 87.5 (C-triple bond), 69.6 (C-2′), 69.1 (C-3′), 68.7 (C-5′), 66.9 ($CH_2\alpha$), 66.7 ($CH_2\beta$), 66.1 (C-4′), 62.5 (C-6′), 20.9 (CH_3, acetyl), 20.8 (CH_3, acetyl), 20.73 (CH_3, acetyl), 20.67 (CH_3, acetyl) ppm. MS: (MALDI-TOF): m/z = 3587.72 [M + H] (requires 3587.94).

General Procedure for the Synthesis of Porphyrinatozinc(II) Dimer 2 and 3 and Porphyrinatozinc(II) Trimer 4: Tetrabutylammonium fluoride (1 M in THF, 2.6 equiv.) was added to **5** (1 equiv.) dissolved in DCM (12 mL). The reaction was stirred at room temperature for 15 min followed by addition of anhydrous calcium chloride (2 g). The mixture was stirred for 10 min, filtered into a flask, and the solvent was evaporated. The product was combined with the iodo or bromo derivative (0.85 equiv. of halogen atom), tris(dibenzylideneacetone)dipalladium(0) (0.3 equiv.), and triphenylarsine (1.5 equiv.) in anhydrous THF (20 mM of **5**) and Et_3N (20 mM of **5**) under argon. The reaction mixture was heated at reflux for 14 h under argon. The solvent was evaporated to dryness under vacuum. The crude product was purified by chromatography and crystallization.

Porphyrinatozinc(II) Dimer 2: Dimer **2** was obtained according to the general procedure, starting from **5** (110 mg, 0.059 mmol) and *p*-diiodobenzene (8.15 mg, 0.025 mmol). The crude product was purified by preparative TLC on silica gel (DCM/acetone, 5:1) and crystallized (AcOEt/*n*-heptane) to give **2** (32 mg, 9.08 μmol, 31%) as a dark green solid. UV/Vis (DCM): λ_{max} (ε, L mmol^{-1} cm^{-1}): 446 (294), 570 (19.4), 640 (44.0) nm. ^{1}H NMR ($CDCl_3$): δ = 9.89 (d, J = 4.5 Hz, 4 H, 2-H and 18-H), 9.08 (d, J = 4.6 Hz, 4 H, 3-H and 17-H), 8.91 (s, 8 H, 7-H, 13-H, 8-H, and 12-H), 8.24 (s, 4 H, Ph-H), 8.16 (d, J = 8.4 Hz, 8 H, *o*-phenoxy-H), 8.12 (d, J = 8.4 Hz, 4 H, *o*-phenoxy-H), 7.33 (d, J = 8.4 Hz, 8 H, *m*-phenoxy-H), 7.29 (d, J = 8.4 Hz, 4 H, *m*-phenoxy-H), 5.51–5.43 (m, 6 H, 3′-H), 5.42–5.35 (m, 12 H, 2′-H and 4′-H), 5.10 (s, 6 H, 1′-H), 4.48–4.37 (m, 18 H, 6′-H and $CH_2\alpha$), 4.31–4.22 (m, 18 H, 6′-H and $CH_2\beta$), 4.13–4.10 (m, 6 H, 5′-H), 2.22 (s, 18 H, AcO), 2.18 (s, 18 H, AcO), 2.08 (s, 18 H, AcO), 2.04 (s, 18 H, AcO) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7 (C=O, acetyl), 170.1 (C=O, acetyl), 169.9 (C=O, acetyl), 169.8 (C=O, acetyl), 158.2 (C-*p*-phenoxy), 152.2 (C-1, C-19/4, C-16/6, C-14/9, and C-11), 151.34 (C-1, C-19/4, C-16/6, C-14/9, and C-11), 151.31 (C-1, C-19/4, C-16/6, C-14/9, and C-11), 150.9 (C-1, C-19/4, C-16/6, C-14/9, and C-11), 135.5 (C-*o*-phenoxy), 135.4 (C-1-phenoxy), 131.9–130.7 (C-2, C-3, C-7, C-8, C-12, C-13, C-17, and C-18), 131.8 (C-2-Ph), 129.3 (C-20), 120.9 (C-10), 119.5 (C-5 and C-15), 112.7 (C-*m*-phenoxy), 112.5 (C-1-Ph), 105.7 (C-triple bond), 104.8 (C-triple bond), 97.8 (C-1′), 69.6 (C-2′), 69.1 (C-3′), 68.7 (C-5′), 67.0 ($CH_2\alpha$), 66.7 ($CH_2\beta$), 66.2 (C-4′), 62.5 (C-6′), 20.9 (CH_3, acetyl), 20.83 (CH_3, acetyl), 20.77 (CH_3, acetyl), 20.7 (CH_3, acetyl) ppm. MS: (MALDI-TOF): m/z = 3662.96 [M + H] (requires 3662.97).

Porphyrinatozinc(II) Trimer (4): Trimer **4** was obtained according to the general procedure, starting from **5** (310 mg, 0.166 mmol) and tris(4-iodophenylamine) (28.9 mg, 0.046 mmol). The crude product was purified by preparative TLC on silica gel (THF/*n*-heptane, 1:1)

and crystallized (AcOEt/*n*-heptane) to give **4** (190 mg, 37 μmol, 80%) as a dark green solid. $C_{282}H_{279}N_{13}O_{99}Zn_3$ (5630.49): calcd. C 60.15, H 4.99, N 3.23; found C 59.93, H 5.15, N 3.07. UV/Vis (DCM): λ_{max} (ε, L mmol^{-1} cm^{-1}): 440 (535), 573 (36.3), 632 (87.7) nm. ^{1}H NMR (C_5D_5N): δ = 10.34 (d, J = 4.3 Hz, 6 H, 2-H and 18-H), 9.37 (d, J = 4.4 Hz, 6 H, 2-H and 18-H), 9.21 (s, 12 H, 7-H, 13/8-H, and 12-H), 8.34–8.31 (m, J = 8.0 Hz, 24 H, *o*-phenoxy-H, *o*-NPh_2-H), 7.64 (d, J = 8.4 Hz, 6 H, *o*-NPh_2-H), 7.48 (d, J = 7.8 Hz, 18 H, *m*-phenoxy-H), 5.94–5.91 (m, 27 H, 3′-H, 2′-H, and 4′-H), 5.41 (s, 9 H, 1′-H), 4.87–4.71 (m, 27 H, 6′-H and $CH_2\alpha$), 4.65 (m, 18 H, $CH_2\beta$), 4.52–4.48 (m, 9 H, 6′-H), 4.30–4.27 (m, 9 H, 5′-H), 2.15 (s, 9 H, AcO), 2.08 (s, 9 H, AcO), 2.05 (s, 9 H, AcO), 2.03 (s, 9 H, AcO) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7 (C=O, acetyl), 170.1 (C=O, acetyl), 169.9 (C=O, acetyl), 169.8 (C=O, acetyl), 158.2 (C-*p*-phenoxy), 152.2–150.0 (C-1, C-4, C-6, C-9, C-11, C-14, C-16, and C-19), 140.7 (C-*p*-NPh_2), 135.44 (C-*o*-phenoxy), 135.4 (C-*o*-phenoxy), 132.9 (C-1-phenoxy), 132.8 (C-1-phenoxy), 132.2–130.7 (C-2, C-3, C-7, C-8, C-12, C-13, C-17, and C-18), 126.1 (C-*m*-NPh_2), 122.2 (C-10), 122.0 (C-5 and C-15), 121.54 (C-1-NPh_2), 121.46 (C-*o*-NPh_2), 112.7 (C-*m*-phenoxy), 106.0 (C-20), 102.9 (C-triple bond), 100.4 (C-triple bond), 97.7 (C-1′), 69.5 (C-2′), 69.0 (C-3′), 68.6 (C-5′), 66.9 ($CH_2\alpha$), 66.7 ($CH_2\beta$), 66.0 (C-4′), 62.5 (C-6′), 20.84 (CH_3, acetyl), 20.76 (CH_3, acetyl), 20.71 (CH_3, acetyl), 21.64 (CH_3, acetyl) ppm. MS: (MALDI-TOF): *m*/*z* = 5623.56 [M + H] (requires 5623.51).

Porphyrinatozinc(II) Dimer (3): Dimer **3** was obtained according to the general procedure, starting from **5** (50 mg, 0.027 mmol) and **10** (56 mg, 0.030 mmol). The crude product was purified by preparative TLC on silica gel (AcOEt/*n*-hexane, 3:1) and crystallized (DCM/*n*-heptane) to give **3** (38 mg, 11 μmol, 42%) as a dark green solid. UV/Vis (DCM): λ_{max} (ε, L mmol^{-1} cm^{-1}): 424 (242), 450 (168), 481 (11.1), 558 (19.9), 631 (23.3), 677 (31.1) nm. ^{1}H NMR ($CDCl_3$): δ = 9.99 (d, J = 4.5 Hz, 4 H, 2-H and 18-H), 9.10 (d, J = 4.6 Hz, 4 H, 2-H and 18-H), 8.90 (s, 8 H, 7-H, 13-H, 8-H, and 12-H), 8.17–8.10 (m, 12 H, *o*-phenoxy-H), 7.32–7.26 (m, 12 H, *m*-phenoxy-H), 5.52–5.48 (m, 6 H, 3′-H), 5.41–5.35 (m, 12 H, 2′-H and 4′-H), 5.09 (s, 6 H, 1′-H), 4.47–4.40 (m, 18 H, 6′-H and $CH_2\alpha$), 4.32–4.21 (m, 18 H, 6′-H and $CH_2\beta$), 4.11–4.08 (m, 6 H, 5′-H), 2.21 (s, 18 H, AcO), 2.17 (s, 18 H, AcO), 2.07 (s, 9 H, AcO), 2.03 (s, 18 H, AcO) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7 (C=O, acetyl), 170.0 (C=O, acetyl), 169.9 (C=O, acetyl), 169.8 (C=O, acetyl), 158.1 (C-*p*-phenoxy), 150.9 (C-1, C-19/4, C-16/6, C-14/9, and C-11), 150.5 (C-1, C-19/4, C-16/6, C-14/9, and C-11), 150.1 (C-1, C-19/4, C-16/6, C-14/9, and C-11), 149.8 (C-1, C-19/4, C-16/6, C-14/9, and C-11), 135.5 (C-*o*-phenoxy), 135.4 (C-*o*-phenoxy), 135.2 (C-1-phenoxy), 133.1–131.6 (C-2, C-3, C-7, C-8, C-12, C-13, C-17, and C-18), 121.7 (C-10), 121.6 (C-5 and C-15), 112.6 (C-*m*-phenoxy), 112.5 (C-*m*-phenoxy), 107.2 (C-20), 100.9 (C-triple bond), 97.7 (C-1′), 69.5 (C-2′), 69.0 (C-3′), 68.6 (C-5′), 66.9 ($CH_2\alpha$), 66.7 ($CH_2\beta$), 66.1 (C-4′), 62.5 (C-6′), 20.9 (CH_3, acetyl), 20.8 (CH_3, acetyl), 20.71 (CH_3, acetyl), 20.66 (CH_3, acetyl) ppm. MS (MALDI-TOF): *m*/*z* = 3562.93 [M + H] (requires 3562.94).

General Procedure for the Synthesis of Porphyrinatozinc(II) Dimers 12 and 13: To a solution of acetylated carbohydrate compounds in anhydrous THF (20 mL) was added 10 drops of a freshly prepared solution of sodium methoxide in methanol. The solution was stirred at room temperature for 1 h. Then, IWT ion-exchange resin (500 mg) was added, and the mixture was carefully stirred for an additional 30 min. The resin was filtered, washed with a mixture of pyridine and water (1:1), and the solvents were evaporated under vacuum.

Deprotected Porphyrinatozinc(II) Dimer (12): Starting with **1** (25 mg, 6.96 μmol) and following the general procedure, dimer **12** was obtained as a dark green solid (13 mg, 5.03 μmol, 73%). $C_{128}H_{130}N_8O_{42}Zn_2 \cdot 18H_2O$ (2583.69 + 18 H_2O): calcd. C 53.54, H 5.69, N 3.90; found C 53.53, H 6.11, N 4.18. UV/Vis (PEG400/EtOH/H_2O, 3:2:5): λ_{max} (ε, L mmol^{-1} cm^{-1}): 429 (286), 453 (189), 481 (157), 568 (15.8), 648 (26.2), 706 (38.5) nm. MS: (MALDI-TOF): *m*/*z* 2579.76 [M + H] (requires 2579.69).

Deprotected Porphyrinatozinc(II) Trimer (13): Starting from **4** (32 mg, 5.68 μmol) and following the general procedure, trimer **13** was obtained as a dark green solid (20 mg, 4.86 μmol, 85%). $C_{210}H_{207}N_{13}O_{63}Zn_3 \cdot 15H_2O$ (4117.17): calcd. C 57.49, H 5.44, N 4.15; found C 57.25, H 5.63, N 3.95. UV/Vis (PEG400/EtOH/H_2O, 3:2:5): λ_{max} (ε, L mmol^{-1} cm^{-1}): 443 (485), 580 (28.2), 648 (84.5) nm. MS: (MALDI-TOF): *m*/*z* = 4110.95 [M + H] (requires 4111.13).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR of **1**–**4** and **7**–**10** and UV visible spectra of **12** and **13**.

Acknowledgments

We thank Mr. Jean Bernard for TPA measurements and Vincent Guérineau for MALDI-TOF analyses. This work was supported by the Institut Nationale du Cancer (INCa 2009–1-RT-08-IC-1) and the non-profit French organization Rétinostop (http://www.retinostop.org), S. A. also thanks the foundation Pierre-Gilles de Gennes for a postdoctoral fellowship.

[1] a) T. J. Dougherty, C. J. Gomer, B. W. Henderson, G. Jori, D. Kessel, M. Korbelik, J. Moan, Q. Peng, *J. Nat. Canc. Inst.* **1998**, *90*, 889–905; b) R. Bonnet, *Chemical Aspects of Photodynamic Therapy*, Gordon and Breach Science Publishers, Amsterdam, **2000**; c) I. J. MacDonald, T. J. Dougherty, *J. Porphyrins Phthalocyanines* **2001**, *5*, 105–129; d) D. E. J. G. J. Dolmans, D. Fukumura, R. K. Jain, *Nature Rev.* **2003**, *3*, 380–386; e) C. A. Robertson, D. Hawkins Evans, H. Abrahamse, *J. Photochem. Photobiol. B: Biology* **2009**, *96*, 1–8.

[2] R. Bonnett, *Chem. Soc. Rev.* **1995**, *24*, 19–33.

[3] R. W. Waynant, M. N. Ediger (Eds.), *Electrooptics Handbook*, McGraw-Hill, New York, **1993**, ch. 24.

[4] a) M. Pawlicki, H. A. Collins, R. G. Denning, H. L. Anderson, *Angew. Chem.* **2009**, *121*, 3292; *Angew. Chem. Int. Ed.* **2009**, *48*, 3244–3266; b) K. Ogawa, Y. Kobuke, *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 269–279.

[5] a) M. Drobizhev, A. Karotki, M. Kruk, A. Rebane, *Chem. Phys. Lett.* **2002**, *355*, 175–182; b) A. Karotki, M. Khurana, J. R. Lepock, B. C. Wilson, *Photochem. Photobiol.* **2006**, *82*, 443–452.

[6] a) M. Drobizhev, Y. Stepanenko, Y. Dzenis, A. Karotki, A. Rebane, P. N. Taylor, H. L. Anderson, *J. Am. Chem. Soc.* **2004**, *126*, 15352–15353; b) A. Karotki, M. Drobizhev, Y. Dzenis, P. N. Taylor, H. L. Anderson, A. Rebane, *Phys. Chem. Chem. Phys.* **2004**, *6*, 7–10; c) M. Drobizhev, V. Stepaznenko, Y. Dzenis, A. Karotki, A. Rebane, P. N. Taylor, H. L. Anderson, *J. Phys. Chem. B* **2005**, *109*, 7223–7236; d) H. M. Kim, B. R. Cho, *Chem. Commun.* **2009**, 153–164; e) G. S. He, L.-S. Tan, Q. Zheng, P. N. Prasad, *Chem. Rev.* **2008**, *108*, 1245–1330; f) K. S. Kim, J. M. Lim, A. Osuka, D. Kim, *J. Photochem. Photobiol. C: Photochem. Rev.* **2008**, *9*, 13–28.

[7] a) D. P. Arnold, A. W. Johnson, M. Mahendran, *J. Chem. Soc. Perkin Trans. 1* **1978**, 366–370; b) D. P. Arnold, D. A. James, *J. Org. Chem.* **1997**, *62*, 3460–3469; c) H. L. Anderson, *Chem. Commun.* **1999**, 2323–2330; d) M. Balaz, H. A. Collins, E. Dahlstedt, H. L. Anderson, *Org. Biomol. Chem.* **2009**, *7*, 874–888; e) M. K. Kuimova, H. A. Collins, M. Balaz, E. Dahlstedt, J. A. Levitt, N. Sergent, K. Suhling, M. Drobizhev, N. S. Mak-

arov, A. Rebane, H. L. Anderson, D. Phillips, *Org. Biomol. Chem.* **2009**, *7*, 889–896.

[8] a) D. P. Arnold, L. J. Nitschinsk, *Tetrahedron Lett.* **1993**, *34*, 693–696; b) D. P. Arnold, D. A. James, *J. Org. Chem.* **1997**, *62*, 3460–3469.

[9] D. P. Arnold, D. A. James, C. H. L. Kennard, G. Smith, *J. Chem. Soc., Chem. Commun.* **1994**, 2131–2132.

[10] P. N. Taylor, A. P. Wylie, J. Huuskonen, H. L. Anderson, *Angew. Chem.* **1998**, *110*, 1033; *Angew. Chem. Int. Ed.* **1998**, *37*, 986–989.

[11] K. Ogawa, Y. Nagatsuka, *J. Porphyrins Phthalocyanines* **2009**, *13*, 114–121.

[12] S. A. Odom, S. Webster, L. A. Padilha, D. Peceli, H. Hu, G. Nootz, S.-J. Chung, S. Ohira, J. D. Matichak, O. V. Przhonska, A. D. Kachkovski, S. Barlow, J.-L. Brédas, H. L. Anderson, D. J. Hagan, E. W. Van Stryland, S. R. Marder, *J. Am. Chem. Soc.* **2009**, *131*, 7510–7511.

[13] J.-W. Seo, S. Y. Jang, D. Kim, H.-J. Kim, *Tetrahedron* **2008**, *64*, 2735–2739.

[14] J. R. Starkey, A. K. Rebane, M. A. Drobizhev, F. Meng, A. Gong, A. Elliott, K. McInnerney, C. W. Spangler, *Clin. Cancer Res.* **2008**, *14*, 6564–6573.

[15] H. A. Collins, M. Khurana, E. H. Moriyama, A. Mariampillai, E. Dahlstedt, M. Balaz, M. K. Kuimova, M. Drobizhev, V. X. D. Yang, D. Phillips, A. Rebane, B. C. Wilson, H. L. Anderson, *Nature Photonics* **2008**, *2*, 420–424.

[16] a) M. Hamblin, J. L. Miller, B. Ortel, *Photochem. Photobiol.* **2000**, *72*, 533–540; b) W. M. Sharman, J. E. van Lier, C. M. Allen, *Adv. Drug Delivery Rev.* **2004**, *56*, 53–76; c) J. T. C. Wojtyk, R. Goyan, E. Gudgin-Dickson, R. Pottier, *Med. Laser Appl.* **2006**, *21*, 225–238; d) X. Zheng, R. K. Pandey, *Anti Cancer Agents Med. Chem.* **2008**, *8*, 241–268; e) M. B. Bakar, M. Oelgemöller, M. O. Senge, *Tetrahedron* **2009**, *65*, 7064–7078; f) R. Schneider, L. Tirand, C. Frochot, R. Vanderesse, N. Thomas, J. Gravier, F. Guillemin, M. Barberi-Heyob, *Curr. Med. Chem.* **2006**, *6*, 469–488; g) J.-P. Taquet, C. Frochot, V. Manneville, M. Barberi-Heyob, *Curr. Med. Chem.* **2007**, *14*, 103–112.

[17] V. Lebret, L. Raehm, J.-O. Durand, M. Smaïhi, M. H. V. Werts, M. Blanchard-Desce, D. Méthy-Gonnod, C. Dubernet, *J. Sol-Gel Sci. Technol.* **2008**, *48*, 32–39.

[18] a) M. Monsigny, A. C. Roche, C. Kieda, P. Midoux, A. Obrenovitch, *Biochimie* **1988**, *70*, 1633–1649; b) R. Lotan, A. Raz, *Ann. N. Y. Acad. Sci.* **1988**, *551*, 385–396; c) S. Griegel, M. F. Rajewsky, T. Ciesiolka, H. J. Gabius, *Anticancer Res.* **1989**, *9*, 723–730; d) S. Sakuma, T. Yano, Y. Masaoka, M. Kataoka, K. Hiwatari, H. Tachikawa, Y. Shoji, R. Kimura, H. Ma, Z. Yang, L. Tang, R. M. Hoffman, S. Yamashita, *J. Controlled Release* **2009**, *134*, 2–10.

[19] a) S. Ballut, A. Makky, B. Loock, J.-Ph. Michel, Ph. Maillard, V. Rosilio, *Chem. Commun.* **2009**, 224–226; b) Y. K. Park, B. Bold, B. C. Cui, W. Lee, Y. K. Shim, *Bull. Korean Chem. Soc.* **2008**, *29*, 130–134.

[20] a) Ph. Maillard, J.-L. Guerquin-Kern, M. Momenteau, S. Gaspard, *J. Am. Chem. Soc.* **1989**, *111*, 9125–9127; b) M. Momenteau, Ph. Maillard, M.-A. de Bélinay, D. Carrez, A. Croisy, *J. Biomed. Opt.* **1999**, *4*, 298–318; c) I. Laville, T. Figueiredo, B. Loock, S. Pigaglio, Ph. Maillard, D. S. Grierson, D. Carrez, A. Croisy, J. Blais, *Bioorg. Med. Chem.* **2003**, *11*, 1643–1652; d) I. Laville, S. Pigaglio, J.-C. Blais, F. Doz, B. Loock, Ph. Maillard, D. S. Grieson, J. Blais, *J. Med. Chem.* **2006**, *49*, 2558–2567; e) Ph. Maillard, B. Loock, D. S. Grierson, I. Laville, J. Blais, F. Doz, L. Desjardins, D. Carrez, J.-L. Guerquin-Kern, A. Croisy, *Photodiagn. Photodynamic Ther.* **2007**, *4*, 261–268.

[21] a) M. Lupu, C. D. Thomas, Ph. Maillard, B. Loock, B. Chauvin, I. Aerts, A. Croisy, E. Beloir, A. Volk, J. Mispelter, *Photodiagn. Photodynamic Ther.* **2009**, *6*, 214–220; b) B. Di Stasio, C. Frochot, D. Dumas, P. Even, J. Zwier, A. Müller, D. Didelon, F. Guillemin, M. L. Viriot, M. Barberi-Heyob, *Eur. J. Med. Chem.* **2005**, *40*, 1111–1122.

[22] M. Varamo, B. Loock, Ph. Maillard, D. S. Grierson, *Org. Lett.* **2007**, *9*, 4689–4692.

[23] J. Dahmen, T. Frejd, G. Groenberg, T. Lave, G. Magnusson, G. Noori, *Carbohydr. Res.* **1983**, *116*, 303–307.

[24] a) D. P. Arnold, R. D. Hartnell, *Tetrahedron* **2001**, *57*, 1335–1345; b) C. Maeda, S. Yamaguchi, C. Ikeda, H. Shinokubo, A. Osuka, *Org. Lett.* **2008**, *10*, 549–552; c) M. Fathalla, J. Jayawickramarajah, *Eur. J. Org. Chem.* **2009**, 6095–6099.

[25] G. Zemplén, *Ber. Dtsch. Chem. Ges.* **1927**, 1555–1564.

[26] M. Drobizhev, Y. Stepanenko, Y. Dzenis, A. Karotki, A. Rebane, P. N. Taylor, H. L. Anderson, *J. Phys. Chem. B* **2005**, *109*, 7223–7236.

[27] G. Jori, *J. Photochem. Photobiol. B: Biology* **1996**, *36*, 87–93.

[28] M.-C. Desroches, A. Bautista-Sanchez, C. Lamotte, B. Labèque, D. Auchère, R. Farinotti, Ph. Maillard, D. S. Grierson, P. Prognon, A. Kasselouri, *J. Photochem. Photobiol. B: Biology* **2006**, *85*, 56–64.

[29] a) M. U. Winters, J. Kärnbratt, M. Eng, C. J. Wilson, H. L. Anderson, B. Albinsson, *J. Phys. Chem. C* **2007**, *111*, 7192–7199; b) M. K. Kuimova, M. Balaz, H. L. Anderson, P. R. Ogilby, *J. Am. Chem. Soc.* **2009**, *131*, 7948–7918.

[30] N. S. Makarov, M. Drobizhev, A. Rebane, *Proc. SPIE* **2008**, *6891*, 689105.

Received: August 26, 2010
Published Online: January 18, 2011

