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Synthesis of new amphiphilic chlorin derivatives from protoporphyrin-IX dimethyl ester

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ABSTRACT

A simple synthesis of new amphiphilic chlorin derivatives from protoporphyrin-IX dimethyl ester is reported. The preparation of such compounds is based in a straightforward methodology, which involves the Diels–Alder reaction of protoporphyrin-IX dimethyl ester with maleic anhydride followed by addition of nucleophilic species to the initially formed cycloadducts, a transformation, which is highly regioselective. Preliminary photophysical studies with the new compounds show that they meet adequate features for PDT applications.

1. Introduction

The chemistry of the protoporphyrin-IX (**1**) and its derivatives has been extensively studied since the discovery of their potential application as photosensitizers in Photodynamic Therapy (PDT).[1,2] An exceptional combination of advantages, such as optimal photophysical properties, low systemic toxicity, and a great affinity for hyperproliferating tissues, makes protoporphyrin-IX and particularly its chlorin-type derivatives (Fig. 1) very promising compounds for use in the diagnosis and therapy of cancer and eye diseases, as well as in cardiology, cosmetology, and in other medicinal fields.[1,2] The same applies to photosensitizers derived from chlorophyll-a.[2d]

The use of natural porphyrins, whose properties, mechanisms of biosynthesis/metabolism and low systemic toxicity are well known, can be strategic in the search for new drugs with higher activity and lower side effects that may be used in PDT.[1,3] In the last years, several transformations of protoporphyrin-IX (**1**) have been performed, involving reactions such as reduction, oxidation, addition, substitution, elimination, and pericyclic ones.[1a] In some cases, the coupling of pharmacophoric groups can be carried out.[1a] Particularly, the synthesis of chlorins through the Diels–Alder reaction of protoporphyrin-IX dimethyl ester (**2**) with activated dienophiles has drawn the attention of several research groups. In 1973 Callot et al.[4] reported the Diels–Alder reaction of porphyrin **2** with some activated dienophiles. Later, Dolphin[5] published a more detailed study concerning the synthesis and structural assignment of the two resulting monoadducts (chlorins). One of these monoadducts is the precursor of a mixture of compounds currently being commercialized as Visudyne®. Smith and Pandey[6] also published a wide-ranging work on the synthesis and biological evaluation of numerous benzoporphyrin derivatives from hematoporphyrin dimethyl ester. In particular, the compound corresponding to the replacement of the vinyl group by a 1-(hexyloxy)ethyl group showed an enhanced activity. In this way, the greatest challenge of the photosentitizers chemistry is the synthesis of new compounds fulfilling several specific structural requirements, such as an easy and reproducible synthesis, good solubility in physiologic solutions, adequate photophysics, pharmacokinetic and pharmacodynamic features, amongst others.[3] In general, amphiphilic photosensitizers are considered to be the most potent ones to induce cell death.[7,8] Amphiphilic porphyrin PEG derivatives obtained from *meso*-tetraaryl- and vinyl-substituted porphyrins have recently been reported.[9] In this article we describe the preparation of amphiphilic chlorins derived from protoporphyrin-IX dimethyl ester (**2**); such chlorins are functionalized with ester or amide groups, some of them also containing ethylene glycol moieties. Our methodology involves the Diels–Alder reaction between porphyrin **2** and maleic anhydride (**3**) followed by the addition of nucleophiles to the resulting anhydride cycloadducts (Scheme 1).

2. Results and discussion

The Diels–Alder reaction between porphyrin **2** and maleic anhydride (**3**) was performed by using a saturated solution of **3** (50 equiv) in dry/deoxygenated toluene at reflux, under a N_2

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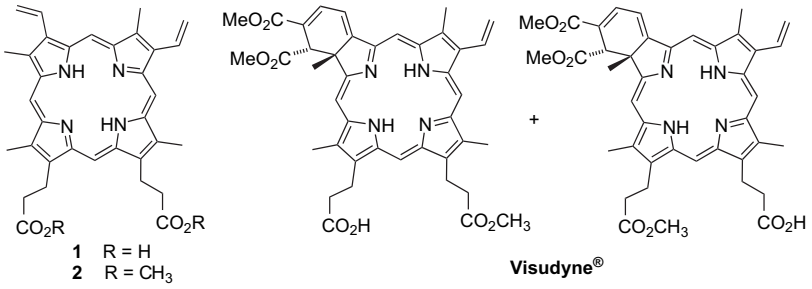
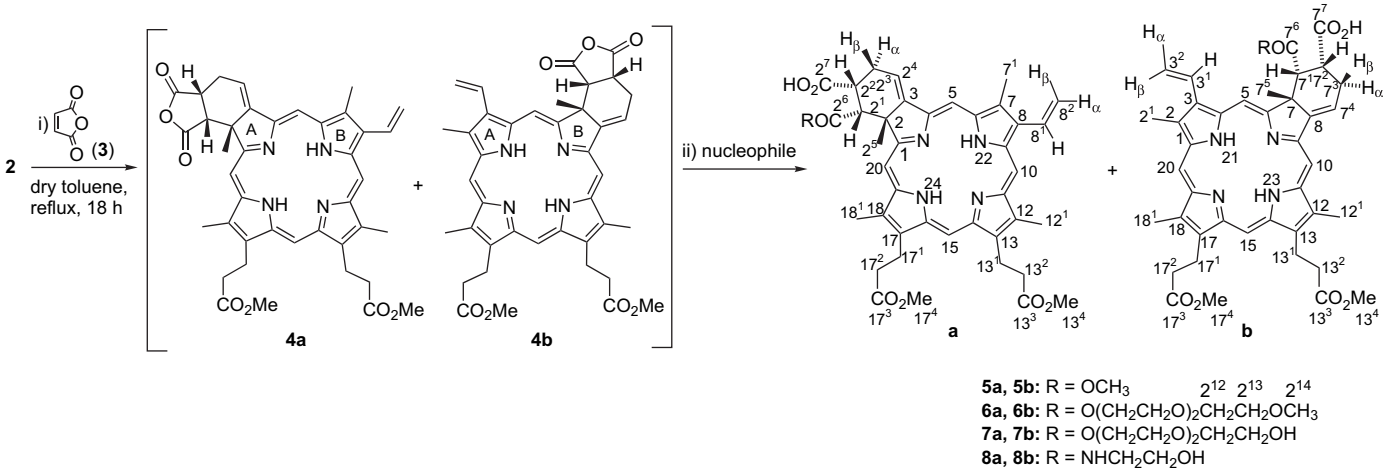


Figure 1. Protoporphyrin-IX and derivatives.



Scheme 1. Synthesis of new amphiphilic chlorins.

atmosphere. The reaction was monitored by TLC and UV–vis (chlorins **4a**/**4b** show a strong absorption band at ca. 665 nm). When the total conversion of porphyrin **2** to the corresponding adducts was observed (after 18 h at reflux), a nucleophilic species was added to the reaction mixture in order to obtain the esters **5**–**7** or the amides **8**.[10] For each nucleophile, it was expected the formation of four isomeric products; however, in each case, the TLC of the reaction mixture shows only two major spots. This indicates that the nucleophilic attack to each anhydride is highly regioselective, occurring preferentially at one of the carbonyl groups. Purification of the reaction mixture by column chromatography (silica) and by preparative TLC (silica) afforded the two major products. The NMR spectra confirm that each spot corresponds to a single compound. The reason for this regioselectivity is not obvious, since it cannot be attributed to steric hindrance. A plausible explanation for the observed selectivity is the establishment of an electronic interaction between the nucleophile and the chlorin macrocycle **4a** or **4b,** resulting in a directing effect to the carbonyl group closer to the macrocycle.

The methyl esters **5a** and **5b** were prepared to confirm the viability of the synthetic route and to be used as model compounds for the NMR studies. They were obtained by addition of dry methanol to the mixture of cycloadducts **4a** and **4b** and refluxing the reaction mixture for 2 h. Compounds **5a** and **5b** were separated from the maleic acid monomethyl ester by column chromatography (silica) and were further purified (and separated) by preparative TLC (silica) using a 6:4 mixture of $CHCl_3$/AcOEt as the eluent. The two isomers were obtained in a global 70% yield in a 1.4:1 ratio, being the main product the one with lower R_f value.

Compounds **5a** and **5b** were fully characterized by 1D (^{1}H, ^{13}C{^{1}H}, and DEPT-135) and 2D (HMBC, HSQC, COSY, NOESY) NMR techniques and also by HRMS-ESI, UV–vis, and microanalysis. The site selectivity of the Diels–Alder reaction (reaction in ring A or B) was deduced from the NOESY spectra. The nuclear Overhauser effect (NOE) correlations observed for **5a** and **5b** are shown in Figure 2. The NOE correlations between H-5 and H-3^1/H-7^5(CH$_3$)/H-7^1 confirm unequivocally that the isomer with higher R_f value resulted from the D–A reaction in ring B (**5b**). In addition, the NOE correlations between H-7^1 and H-7^2/H-7^5(CH$_3$) confirm the *cis-endo* configuration of this isomer (**5b**). Other NOE correlations useful in the complete assignment of the structure of **5b** are shown in Figure 2. On the other hand, compound **5a** (lower R_f) presents NOE correlations between H-20 and H-2^1/H-2^5(CH$_3$) confirming its structure. Furthermore, the NOE correlations between H-2^1 and

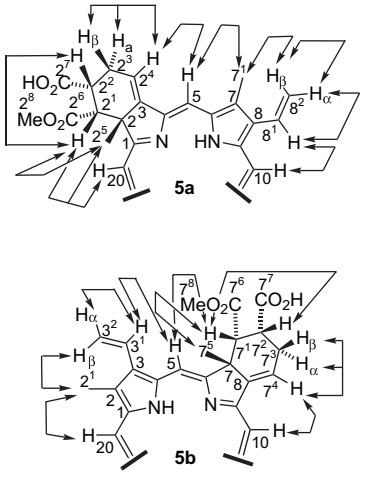


Figure 2. More representative NOE in compounds **5a** and **5b**.

H-2^2/H-2^5 confirm the *cis-endo* configuration of isomer **5a**. Also, proton H-2^4 gives NOE correlation with H-5 but H-5 does not give NOE correlations with the vinylic hydrogens H-8^1 and H-8^2, confirming the correct assignment of **5a**. To find, which regioisomers were formed in the reaction of anhydrides **4a** and **4b** with methanol, HMBC[11] spectra (long-range coupling constants optimized to 7.0, 3.3, and 2.5 Hz) were acquired. These spectra show several C/H correlations ($^2J_{CH}$ and $^3J_{CH}$), which were decisive for the structural assignment of these isomers.

The HMBC spectrum (long-range J_{CH} of 7.0 Hz) of the isomer with higher R_f value (**5b**) revealed a correlation between H-7^1 and C-7^7 ($^3J_{CH}$), but not with C-7^6 ($^2J_{CH}$), and a correlation between the CO_2Me group and C-7^6 ($^3J_{CH}$). On the other hand, the HMBC spectrum with long-range J_{CH} of 3.3 Hz revealed a correlation between H-7^1 and C-7^6 ($^2J_{CH}$) but not with C-7^7 ($^3J_{CH}$). Additionally, the spectrum with long-range J_{CH} of 3.3 Hz showed a correlation between H-$7^{3\beta}$ and C-7^7 (CO_2H), confirming unequivocally that the CO_2Me group is linked to C-7^1. The assignment of the position of CO_2Me group in **5a** was performed in a similar way. The HMBC spectrum (long-range J_{CH} of 7.0 Hz) shows correlation between H-2^1 and C-2^7 but not with C-2^6. Among other correlations, the spectrum with long-range J_{CH} of 2.5 Hz shows a correlation between H-2^1 and C-2^6, confirming the structural assignment of **5a**. The HMBC spectra and the other 2D NMR analysis enabled a complete assignment of all protons and carbons of the two isomers.

Due to their intense absorption bands at 668 nm (Fig. 3), the new chlorins **5a** and **5b** are remarkable if one considers their future potential applications in PDT.

The synthetic methodology described above was also used to prepare derivatives **6a** and **6b** and **7a** and **7b** using triethyleneglycol monomethyl ether or triethyleneglycol as nucleophiles, respectively. However, since the reaction of these alcohols with the anhydride intermediates was very slow, in both cases, we used Et_3N as catalyst.[12] With this modification, compounds **6a** and **6b** and **7a** and **7b** were obtained just by stirring the reaction mixture for 2 h at room temperature. Work-up followed by column chromatography and preparative TLC afforded **6a** (lower R_f) and **6b** (higher R_f) in 1.4:1 ratio (53% global yield, two steps). Similarly, compounds **7a** (lower R_f) and **7b** (higher R_f) were isolated in 1.4:1 ratio (45% global yield, two steps). Similarly, compounds **8a** and **8b** were prepared by using ethanolamine as the nucleophilic species.

After work-up and purification by column chromatography, compounds **8a** and **8b** were separated by preparative TLC. The two isomers were obtained in 62% global yield (two steps) in 1.4:1 ratio (**8a**/**8b**). All chlorins were fully characterized using several NMR techniques, mass spectroscopy and UV–vis, as described for **5a** and **5b**.

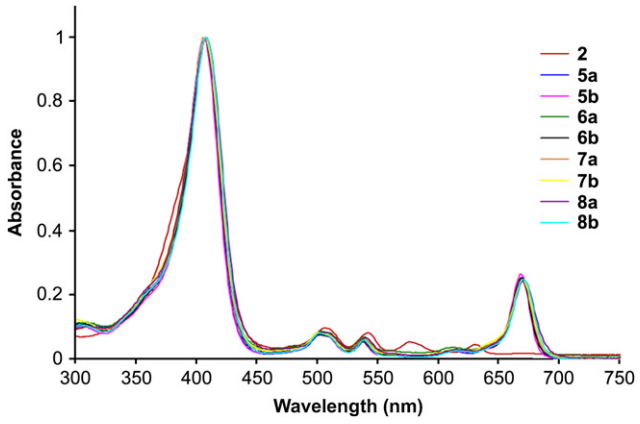


Figure 3. Normalized UV–vis spectra of protoporphyrin dimethyl ester (**2**) and of the products **5**–**8**.

2.1. Photodynamic activity evaluation (uric acid test)

In order to verify the photodynamic activity of the new synthesized chlorins, it was decided to carry out the uric acid test[13] with compounds **5a** and **5b**. Uric acid (UA) has been found to be an excellent scavenger of singlet oxygen ($^1O_2$). Its concentration decrease can be monitored at 294 nm. The decrease of UA can be considered as an indirect measure of the generated singlet oxygen when the photosensitizer is irradiated with visible light. The photodynamic activity scale (PA) obtained for the chlorin derivatives can be determined by using the modified Fischer expression (Eq. 1)[14]

$$\mathrm{PA} = \Delta A_{\mathrm{UA}} \times 10^5 / W \times t \times A_{\mathrm{PS}(\lambda \mathrm{irr})} \quad (1)$$

with ΔA_{UA} being the UA absorbance decrease at 294 nm in solution after irradiation, W the laser power (mW), t the irradiation time (seconds) and $A_{PS(\lambda irr)}$ the absorbance of the photosensitizer (PS) after irradiation.

These experiments were carried out in a 1 cm path length cell containing an ethanolic solution of chlorin **5a** or **5b** (6.0×10^{-6} mol L^{-1}) and uric acid (6.4×10^{-4} mol L^{-1}). The solution was irradiated with a red laser (661 nm; 150 mW) and stirred under saturated air conditions. The absorbance measurements were performed directly on the cell at pre-determined time intervals (0–300 s). The uric acid degradation, in presence of chlorins **5a** and **5b**, is shown in Figures 4–6. The photodynamic activities of **5a** and **5b**, determined by Eq. 1, are shown in Table 1. It can be observed that the PA obtained for compound **5a** is about two times that of **5b**.

Considering the PA reported for photofrin II (PA=24),[13a] the values obtained for chlorins **5a** and **5b** show that these compounds are excellent singlet oxygen generators, and thus potentially useful as photosensitizers for use in PDT.

2.2. Direct singlet oxygen quantum yield measurement

The direct measurement of the singlet oxygen quantum yield (Φ_Δ)[15] was carried out to validate the high efficiency of the new compounds **5a** and **5b** to generate $^1O_2$ (Fig. 7). The analysis was performed by time-resolved near infrared luminescence technique (NIR) and the photoexcitation experiments of **5a** and **5b** were performed with laser pulses at 532 nm (10 mJ/pulse, 1–10 Hz). All the NIR emission data were acquired at 5 Hz. The measurements were performed using acetonitrile as solvent adjusting the absorbance to 0.2. All the measurements were performed by

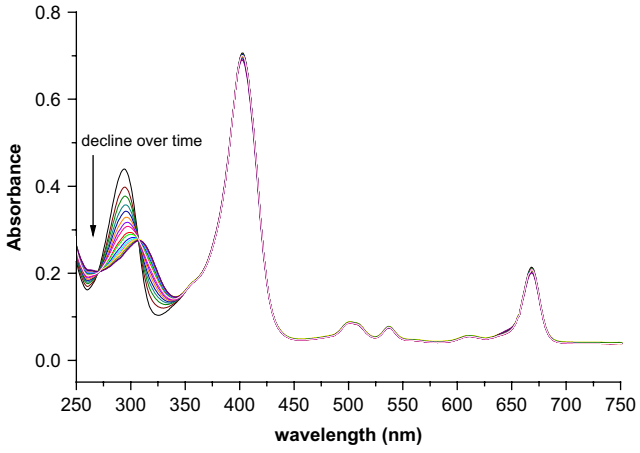


Figure 4. Degradation of uric acid in the presence of **5a**.

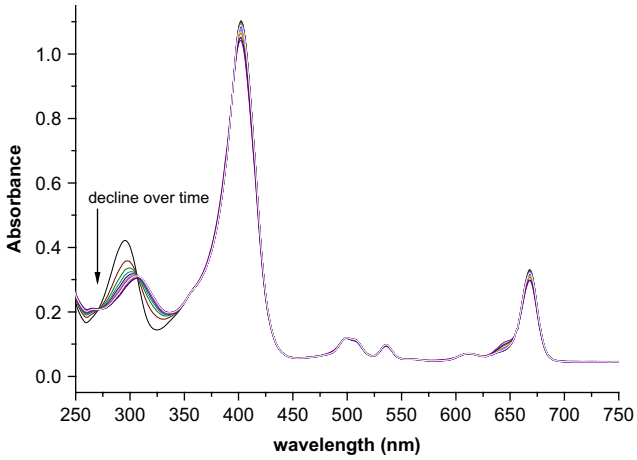


Figure 5. Degradation of uric acid in the presence of **5b**.

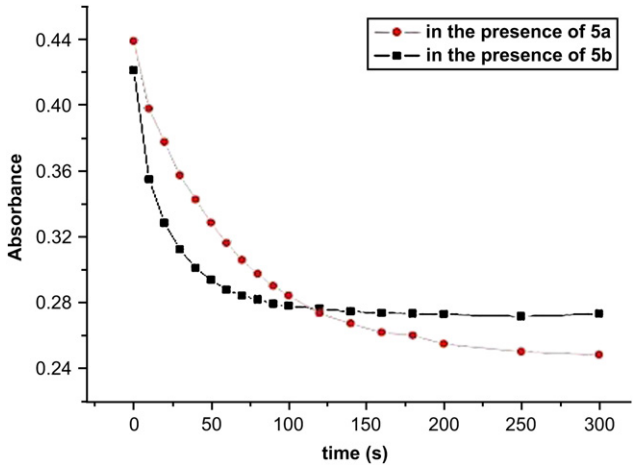


Figure 6. Decrease of the uric acid absorbance in the presence of **5a** and **5b**.

accumulation of 10 spectra in triplicate. The reference used was methylene blue (Φ_{Δ}=0.52)[16] and the laser was a Nd:YAG from Continuum (Surelite III, 10 ns light pulses with frequency varying from 1 to 10 Hz) that excites the sample into a time-resolved fluorometer (Edinburgh Analytical Instruments), which is connected to an NIR-PMT (R5509 from Hamamatsu Co). The emission wavelength was selected using a silicon cutoff filter and a monochromator. The equipment is calibrated weekly and checked for expected emission spectra and lifetime of $^1O_2$ in different conditions.

The Φ_{Δ} values obtained for **5a** and **5b** were 0.54 and 0.25, respectively, which are in agreement with the uric acid test. These results are in line with those reported for the benzoporphyrin derivatives BPD-MA and BPD-MB,[3c,17] where the singlet oxygen quantum yield for BPD-MA is greater than that for BPD-MB. Hioka et al.[17] reported that B-ring derivatives exhibit higher aggregation tendency, resulting in nonhomogeneous solutions and decreasing singlet oxygen formation. In general, these preliminary results

Table 1
Photodynamic activity of compounds **5a** and **5b**

PS	ΔA_{UA}	$A_{PS(\lambda irr)}$	PA
5a	0.19	0.15	139
5b	0.15	0.23	72

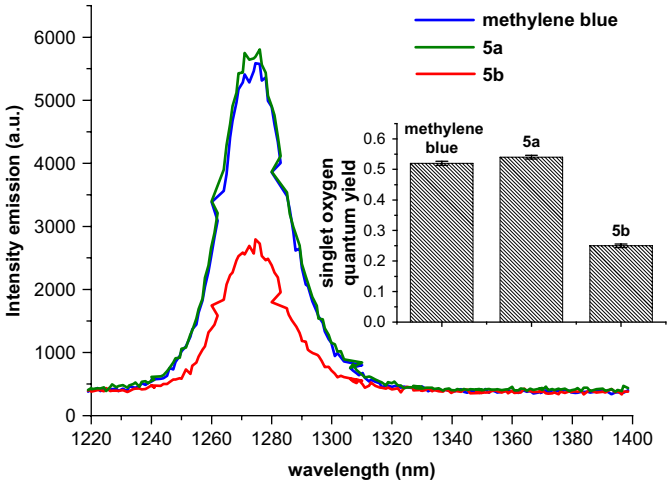


Figure 7. Emission spectra of singlet oxygen and singlet oxygen quantum yield comparison.

indicate that the new chlorins are promising candidates for application in PDT.

3. Conclusion

The results presented in this work demonstrate that the Diels–Alder reaction of protoporphyrin-IX dimethyl ester with maleic anhydride, followed by the addition of a nucleophile to the anhydride moiety, is a versatile approach for the preparation of amphiphilic chlorin derivatives. This two-step synthetic methodology not only gives rise to new chlorins but also it is anticipated that it can also be used for the addition of pharmacophoric groups, which might increase the cellular affinity and the photodynamic activity of such compounds.

4. Experimental section

4.1. General

All reactions were carried out under a N_2 atmosphere. Anhydrous solvents were distilled according to standard procedures:[18] toluene from sodium, dichloromethane and triethylamine from calcium hydride. The maleic anhydride was recrystallized in toluene and the ethylene glycol derivatives were dried with activated molecular sieves 4 Å. Other commercially available reagents were used without further purification. Ultrasound was used for the deoxygenation of toluene. ^{1}H NMR spectra were recorded at 300.13 MHz or 500.13 MHz and ^{13}C NMR spectra at 75.47 or 125.77 MHz, using $CDCl_3$, or mixtures of $CDCl_3/CD_3OD$ as solvent and TMS as internal reference. Unequivocal ^{1}H assignments were made with aid of 2D gCOSY (^{1}H/^{1}H) and NOESY spectra (mixing time of 800 ms), while ^{13}C assignments were made on the basis of 2D gHSQC (^{1}H/^{13}C) and gHMBC experiments (delay for long-range J C/H couplings were optimized to 7.0, 3.3 and 2.5 Hz). Mass spectra and HRMS were recorded using ESI and LD-MS techniques. Microanalyses were obtained with a CHNS analyser. The UV–vis spectra were recorded using $CHCl_3$ as solvent. Flash chromatography was carried out using silica gel Merck (230–400 mesh) and the preparative thin layer chromatography was carried out on 20 cm×20 cm glass plates coated with Merck silica gel 60 (1 mm thick). Analytical TLC was carried out on precoated sheets with silica gel (0.2 mm thick, Merck).

4.2. General procedure for the Diels–Alder reaction

To a saturated solution of recrystallized maleic anhydride (209 mg, 2.12 mmol or 418 mg, 4.24 mmol) in dry/deoxygenated toluene (2 or 4 mL) was added protoporphyrin-IX dimethyl ester (25.0 mg, 42.3 μmol or 50.0 mg, 84.6 μmol) and the mixture was heated at reflux for 18 h under a N_2 atmosphere. After that, the addition of nucleophiles was performed according to the following procedures.

*4.2.1. 2^1-Methoxycarbonyl-13,17-bis[2-(methoxycarbonyl)ethyl]-2,7,12,18-tetramethyl-8-vinyl-2,2^1,2^2,2^3-tetrahydrobenzo-[b]porphyrin-2^2-carboxylic acid (**5a**) and 2^1-methoxycarbonyl-8,12-bis[2-(methoxycarbonyl)ethyl]-2,7,13,17-tetramethyl-18-vinyl-2,2^1,2^2,2^3-tetrahydrobenzo[b]porphyrin-2^2-carboxylic acid (**5b**)*[9]

Dry methanol (10 mL) was added to the crude mixture of adducts **4a** and **4b** prepared from 50.0 mg of protoporphyrin-IX dimethyl ester and the solution was refluxed for 2 h. After that, CH_2Cl_2 (100 mL) was added and the reaction mixture was washed with brine. The organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The products were pre-purified by column chromatography (silica gel, chloroform/ethyl acetate 1:1 as the eluent) and then separated by preparative TLC (silica, chloroform/ethyl acetate 6:4 as the eluent) giving **5a** (24.9 mg, 34.5 μmol) and **5b** (17.7 mg, 24.6 μmol) in a global 70% yield. Spectroscopic data for **5a**: ^{1}H NMR ($CDCl_3$, 500.13 MHz) δ (ppm): −3.21 and −2.94 (br s, 2H, H-22 and H-24), 1.79 (s, 3H, CH_3-2^5), 2.65 (t, 2H, J=7.5 Hz, H-13^2), 2.76 (s, 3H, CH_3-12^1), 2.89 (t, 2H, J=8.0 Hz, H-17^1), 3.01–3.10 (m, 2H, H-13^1), 3.12 (ddd, 1H, J=19.3, 7.4, and 3.5 Hz, H-$2^{3\beta}$), 3.36 (s, 3H, CH_3-18^1), 3.38 (ddd, 1H, J=19.3, 10.7, and 3.5 Hz, H-$2^{3\alpha}$), 3.45 (s, 3H, OCH_3-13^4), 3.53 (s, 3H, CH_3-7^1), 3.54 (s, 3H, OCH_3-17^4), 3.74–3.86 (m, 2H, H-17^1), 3.82 (s, 3H, R=OCH_3), 3.92 (ddd, 1H, J=10.7, 7.4 and 4.2 Hz, H-2^2), 4.58 (d, 1H, J=4.2 Hz, H-2^1), 6.13 (d, 1H, J=11.6 Hz, H-$8^{2\alpha}$), 6.33 (d, 1H, J=17.8 Hz, H-$8^{2\beta}$), 7.12 (t, 1H, J=3.5 Hz, H-2^4), 8.10 (dd, 1H, J=17.8 and 11.6 Hz, H-8^1), 8.37 (br s, 1H, H-15), 8.84 (s, 1H, H-20), 9.26 (s, 1H, H-5), 9.32 (br s, 1H, H-10). ^{13}C NMR ($CDCl_3$, 125.77 MHz) δ (ppm): 10.8 (C-12^1), 11.1 (C-18^1), 12.3 (C-7^1), 20.7 (C-13^1), 20.9 (C-17^1), 26.3 (C-2^3), 30.9 (C-2^5), 36.4 (C-17^2), 39.6 (C-2^2), 47.7 (C-2^1), 51.5 (C-13^4), 51.8 (C-17^4), 52.1 (C-2), 52.3 (OMe), 90.3 (C-5), 91.5 (C-20), 97.6 (C-15), 99.0 (C-10), 120.6 (C-2^4), 121.0 (C-8^2), 129.0 (C-7), 129.3 (C-18), 129.8 (C-8^1), 132.0 (C-16), 132.3 (C-9), 133.5 (C-8), 135.4 (C-17), 136.9 (C-12), 137.2 (C-6), 137.9 (C-19), 138.6 (C-13), 145.9 (C-3), 149.2 (C-14), 150.6 (C-11), 155.0 (C-4), 165.6 (C-1), 172.9 (C-2^7), 174.1 (C-17^3), 174.2 (C-2^6 and C-13^3). UV–vis ($CHCl_3$) λ_{max} (log ε) 406 (5.17), 503 (4.06), 539 (3.94), 612 (3.58), 668 (4.56) nm. UV–vis (ethanol) λ_{max} (log ε) 401 (5.15), 500 (3.98), 536 (3.83), 612 (3.53), 668 (4.50) nm. LD-MS m/z 721.3 $(M+H)^+$. HRMS-ESI-TOF m/z calcd for $C_{41}H_{45}N_4O_8^+$ $(M+H)^+$ 721.3232, found 721.3222. Microanalysis calcd for $C_{41}H_{44}N_4O_8.H_2O$: C, 66.65; H, 6.28; N, 7.58. Found C, 66.45; H, 6.22; N, 7.33. Spectroscopic data for **5b**: ^{1}H NMR ($CDCl_3$, 500.13 MHz) δ (ppm): −3.75 and −2.94 (br s, 2H, H-21 and H-23), 1.74 (s, 3H, CH_3-7^5), 2.56 (t, 2H, J=7.9 Hz, H-17^2), 2.59–2.68 (m. 2H, H-13^2), 2.84 (s, 3H, CH_3-18^1), 2.88–2.97 (m, 2H, H-17^1), 2.96 (s, 3H, CH_3-12^1), 3.18 (ddd, 1H, J=18.7, 7.4, and 3.5 Hz, H-$7^{3\beta}$), 3.33–3.39 (m, 2H, H-13^1), 3.47 (s, 3H, OCH_3-17^4), 3.48 (s, 3H, OCH_3-13^4), 3.54 (ddd, 1H, J=18.7, 10.1, and 3.5 Hz, H-$7^{3\alpha}$), 3.59 (s, 3H, CH_3-2^1), 3.88 (s, 3H, OCH_3), 3.93 (ddd, 1H, J=10.1, 7.4, and 4.2 Hz, H-7^2), 4.60 (d, 1H, J=4.2 Hz, H-7^1), 6.15 (dd, 1H, J=11.5 and 1.1 Hz, H-$3^{2\alpha}$), 6.44 (dd, 1H, J=17.8 and 1.1 Hz, H-$3^{2\beta}$), 7.18 (t, 1H, J=3.5 Hz, H-3^1), 7.88 (br s, 1H, H-15), 8.85 (s, 1H, H-10), 9.13 (s, 1H, H-5), 9.24 (s, 1H, H-20). ^{13}C NMR ($CDCl_3$, 125.77 MHz) δ (ppm): 10.7 (C-12^1), 11.0 (C-18^1), 12.4 (C-2^1), 20.3 (C-17^1), 20.6 (C-13^1), 26.5 (C-7^3), 31.0 (C-7^5), 36.2 (C-13^2), 36.5 (C-17^2), 39.5 (C-7^2), 47.5 (C-7^1), 51.7 (C-13^4 and C-17^4), 52.0 (C-7), 52.4 (R=OCH_3), 89.4 (C-10), 92.6 (C-5), 96.7 (C-15), 99.4 (C-20), 120.4 (C-3^2), 121.2 (C-7^4), 129.4 (C-11), 129.8 (C-3^1), 129.9 (C-3), 132.3 (C-14), 132.4 (C-2), 132.5 (C-1), 135.2 (C-13), 136.4 (C-4), 136.7 and 149.7 (C-18 and C-19), 137.6 (C-12), 138.1 (C-17), 145.9 (C-8), 149.3 (C-16), 155.6 (C-9), 165.2 (C-6), 173.0 (C-7^7), 173.8 (C-13^3), 174.3 (C-7^6), 174.8 (C-17^3). UV–vis ($CHCl_3$) λ_{max} (log ε) 406 (5.26), 501 (4.07), 537 (3.93), 612 (3.59), 668 (4.63) nm. UV–vis (ethanol) λ_{max} (log ε) 401 (5.26), 500 (4.03), 536 (3.91), 612 (3.60), 668 (4.62) nm. LD-MS m/z 721.3 $(M+H)^+$. HRMS-ESI-TOF m/z calcd for $C_{41}H_{45}N_4O_8^+$ $(M+H)^+$ 721.3232, found 721.3220. Microanalysis calcd for $C_{41}H_{44}N_4O_8.H_2O$: C, 66.65; H, 6.28; N, 7.58. Found C, 66.68; H, 6.47; N, 7.38.

*4.2.2. 2^1-({2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}carbonyl)-13,17-bis[2-(methoxycarbonyl)ethyl]-2,7,12,18-tetramethyl-8-vinyl-2,2^1,2^2,2^3-tetrahydrobenzo[b]porphyrin-2^2-carboxylic acid (**6a**) and 2^1-({2-[2-(2-methoxyethoxy)ethoxy]ethoxy}carbonyl)-8,12-bis[2-(methoxycarbonyl)ethyl]-2,7,13,17-tetramethyl-18-vinyl-2,2^1,2^2,2^3-tetrahydrobenzo[b]porphyrin-2^2-carboxylic acid (**6b**)*

A crude mixture of **4a** and **4b** prepared from 25.0 mg of protoporphyrin-IX dimethyl ester was cooled to 0 °C. After that, dry CH_2Cl_2 (7 mL), triethyleneglycol monomethyl ether (75 equiv), and dry Et_3N (55 equiv) were added. The reaction mixture was further stirred for 2 h at room temperature. Then, CH_2Cl_2 (50 mL) and H_2O (50 mL) were added and the pH was adjusted to 6–7 with HCl (2 mol L^{-1}). The two phases were separated and the organic layer was washed with brine (50 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The products were pre-purified by column chromatography (silica gel, $CHCl_3$/AcOEt/MeOH 5:3:2 as the eluent) and further purified by preparative TLC (silica, $CHCl_3$/AcOEt/MeOH 5:4:1 as the eluent) giving **6a** (11.1 mg, 13.0 μmol) and **6b** (8.0 mg, 9.4 μmol) in a global 53% yield. Spectroscopic data for **6a**: ^{1}H NMR ($CDCl_3$/CD_3OD 6:4, 500.13 MHz) δ (ppm): 1.82 (s, 3H, CH_3-2^5), 2.97–3.03 (m, 4H, H-$2^{3\beta}$ and H-2^{14}), 3.18–3.27 (m, 1H, H-$2^{3\alpha}$), 3.18 (t, 2H, J=7.9 Hz, H-13^2), 3.21 (t, 2H, J=7.9 Hz, H-17^2), 3.41 (s, 3H, CH_3-12^1), 3.44 (s, 3H, CH_3-18^1), 3.54 (s, 3H, CH_3-7^1), 3.38–3.62 (m, 8H, H-2^{10}, H-2^{11}, H-2^{12} and H-2^{13}), 3.65 (s, 3H, OCH_3-H^4_{17}), 3.67 (s, 3H, OCH_3-H^4_{13}), 3.71–3.80 (m, 2H, H-2^9), 3.87–3.94 (m, 2H, H-2^2), 4.18 (t, 2H, J=7.8 Hz, H^1_{13}), 4.26–4.40 (m, 5H, H-17^1, H-2^8 and H-2^1), 6.18 (d, 1H, J=11.7 Hz, H-$8^{2\alpha}$), 6.37 (d, 1H, J=18.0 Hz, H-$8^{2\beta}$), 7.02 (br s, 1H, H-2^4), 8.18 (dd, 1H, J=18.0 and 11.7 Hz, H-8^1), 8.92 (br s, 1H, H-20), 9.28 (s, 1H, H-5), 9.68 (s, 1H, H-15), 9.82 (s, 1H, H-10). ^{13}C NMR ($CDCl_3$/CD_3OD 6:4, 125.77 MHz) δ (ppm): 11.3 (C-18^1), 11.8 (C-12^1), 12.3 (C-7^1), 21.8 (C-17^1), 22.2 (C-13^1), 26.6 (C-2^3), 31.1 (C-2^5), 37.0 (C-17^2), 37.4 (C-13^2), 40.0 (C-2^2), 49.5 (C-2^1), 52.0 (C-13^4), 52.1 (C-17^4), 52.5 (C-2), 58.8 (C-2^{14}), 64.3 (C-2^8), 69.4 (C-2^9), 70.5, 70.7 and 71.9 (C-2^{10}, C-2^{11}, C-2^{12}, C-2^{13}), 90.8 (C-5), 92.5 (C-20), 98.7 (C-15), 99.8 (C-10), 121.3 (C-2^4), 121.8 (C-8^2), 129.7 (C-7), 130.0 (C-8^1), 130.7 (C-18), 132.8 (C-9), 133.1 (C-16), 134.5 (C-8), 136.4 (C-17), 137.8 (C-6), 138.4 (C-12), 138.7 (C-19), 139.9 (C-13), 146.6 (C-3), 150.5 (C-14), 151.6 (C-11), 156.3 (C-4), 169.2 (C-1), 174.2 (C-17^3), 174.7 (C-13^3), 174.9 and 175.0 (C-2^6 and C-2^7). UV–vis ($CHCl_3$) λ_{max} (log ε) 406 (5.12), 502 (4.01), 539 (3.91), 612 (3.57), 669 (4.51) nm. LD-MS m/z 853.4 $(M+H)^+$. HRMS-ESI-TOF m/z calcd for $C_{47}H_{57}N_4O_{11}^+$ $(M+H)^+$ 853.4018, found 853.3980. Spectroscopic data for **6b**: ^{1}H NMR ($CDCl_3$/CD_3OD 6:4, 500.13 MHz) δ (ppm): 1.75 (s, 3H, CH_3-7^5), 2.96 (ddd, 1H, J=19.2, 6.6 and 3.3 Hz, H-$7^{3\beta}$), 3.14 (s, 3H, CH_3-7^{14}), 3.19 (t, 2H, J=7.7 Hz, H-17^2), 3.23 (t, 2H, J=7.7 Hz) and 3.32 (ddd, 1H, J=19.2, 10.5, and 3.3 Hz, H-13^2 and H-$7^{3\alpha}$), 3.43 (s, 3H, CH_3-18^1), 3.48 (s, 3H, CH_3-12^1), 3.46–3.50 (m, 2H, H-7^{13}), 3.58–3.62 (m, 2H, H-7^{12}), 3.63 (s, 3H, CH_3-2^1), 3.66 (s, 3H, OCH_3-13^4), 3.68 (s, 3H, OCH_3-17^4), 3.65–3.69 (m, 2H, H-7^{11}), 3.71–3.75 (m, 2H, H-7^{10}), 3.85–3.93 (m, 3H, H-7^9 and H-7^2), 4.16–4.21 (m, 2H, H-17^1), 4.28–4.60 (m, 3H, H-13^1 and H-7^1), 4.43–4.50 (m, 2H, H-7^8), 6.07 (d, 1H, J=11.7 Hz, H-$3^{2\alpha}$), 6.33 (d, 1H, J=17.8 Hz, H-$3^{2\beta}$), 7.03 (t, 1H, J=3.3 Hz, H-7^4), 8.20 (dd, 1H, J=17.8 and 11.7 Hz, H-3^1), 9.08 (s, 1H, H-5), 9.26 (s, 1H, H-10), 9.63 (s, 1H, H-15), 9.74 (s, 1H, H-20). ^{13}C NMR ($CDCl_3$/CD_3OD 6:4, 125.77 MHz) δ (ppm): 11.3 (C-12^1), 11.7 (C-18^1), 12.7 (C-2^1), 21.8 (C-13^1), 22.1 (C-17^1), 26.9 (C-7^3), 31.1 (C-7^5), 37.0 (C-13^2), 37.4 (C-17^2), 40.9 (C-7^2), 52.0 and 52.1 (C-13^4 and

C-17^4), 52.4 (C-7), 52.7 (C-7^1), 58.9 (C-7^{14}), 64.2 (C-7^8), 69.8 (C-7^9), 70.2 and 70.3 (C-7^{10} and C-7^{12}), 70.4 (C-7^{11}), 71.6 (C-7^{13}), 90.4 (C-10), 92.6 (C-5), 98.2 (C-15), 99.9 (C-20), 120.6 (C-3^2), 121.1 (C-7^4), 130.0 (C-3^1), 130.6 and 130.7 (C-3 and C-12), 133.2, 133.4 and 133.5 (C-1, C-2, C-14), 136.4 (C-13), 137.8 (C-4), 138.2 (C-18), 138.6 (C-11), 139.5 (C-17), 147.7 (C-8), 150.6 (C-16), 150.8 (C-19), 157.8 (C-9), 170.4 (C-6), 174.0 (C-13^3), 174.3 (C-17^3), 176.6 (C-7^6), 177.8 (C-7^7). UV–vis ($CHCl_3$) λ_{max} (log ε) 406 (5.16), 501 (4.06), 539 (3.93), 614 (3.62), 669 (4.57) nm. LD-MS *m*/*z* 853.4 $(M+H)^+$. HRMS-ESI-TOF *m*/*z* calcd for $C_{47}H_{57}N_4O_{11}^+$ $(M+H)^+$ 853.4018, found 853.3995.

4.2.3. 2^1-({2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy}carbonyl)-13,17-bis[2-(methoxycarbonyl)ethyl]-2,7,12,18-tetramethyl-8-vinyl-2,2^1,2^2,2^3-tetrahydrobenzo[b]porphyrin-2^2-carboxylic acid (**7a**) and 2^1-({2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}carbonyl)-8,12-bis[2-(methoxycarbonyl)ethyl]-2,7,13,17-tetramethyl-18-vinyl-2,2^1,2^2,2^3-tetrahydrobenzo[b]porphyrin-2^2-carboxylic acid (**7b**)

A crude mixture of **4a** and **4b** prepared from 25.0 mg of protoporphyrin-IX dimethyl ester was cooled to 0 °C. After that, dry CH_2Cl_2 (6 mL), triethyleneglycol (75 equiv) and dry Et_3N (55 equiv) were added. The reaction mixture was further stirred for 2 h at room temperature. Then, CH_2Cl_2 (50 mL) and H_2O (50 mL) were added and the pH was adjusted to 6–7 with HCl (2 mol L^{-1}). The two phases were separated and the organic layer was washed with brine (50 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The products were pre-purified by column chromatography (silica gel, $CHCl_3$/AcOEt/MeOH 5:3:2 as the eluent) and further purified by preparative TLC (silica, $CHCl_3$/AcOEt/MeOH 6:2.5:1.5 as the eluent) giving **7a** (9.3 mg, 11.1 μmol) and **7b** (6.7 mg, 8.0 μmol) in a global 45% yield. Spectroscopic data for **7a**: ^{1}H NMR ($CDCl_3$/CD_3OD 6:4, 500.13 MHz) δ (ppm): 1.78 (s, 3H, CH_3-2^5), 2.88–2.96 (m, 1H, H-2$^{3\beta}$), 3.20 (t, 2H, *J*=7.9 Hz, H-13^2), 3.21 (t, 2H, *J*=7.9 Hz, H-17^2), 3.22–3.27 (m, 1H, H-2$^{3\alpha}$), 3.37–3.60 (m, 8H, H-2^{10}, H-2^{11}, H-2^{12} and H-2^{13}), 3.41 (s, 3H, CH_3-12^1), 3.46 (s, 3H, CH_3-18^1), 3.54 (s, 3H, CH_3-7^1), 3.61–3.70 (m, 2H, H-2^9), 3.64 (s, 3H, OCH_3-17^4), 3.67 (s, 3H, OCH_3-13^4), 3.81–3.88 (m. 2H, H-2^2), 4.19 (t, 2H, *J*=7.8 Hz, H$^1_{13}$), 4.24–4.38 (m, 5H, H-17^1, H-2^8 and H-2^1), 6.17 (d, 1H, *J*=11.6 Hz, H-8$^{2\alpha}$), 6.37 (d, 1H, *J*=17.8 Hz, H-8$^{2\beta}$), 7.00 (br s, 1H, H-2^4), 8.20 (dd, 1H, *J*=17.8 and 11.6 Hz, H-8^1), 8.95 (br s, 1H, H-20), 9.30 (s, 1H, H-5), 9.66 (s, 1H, H-15), 9.82 (s, 1H, H-10). ^{13}C NMR ($CDCl_3$/CD_3OD 6:4, 125.77 MHz) δ (ppm): 11.2 (C-18^1), 11.8 (C-12^1), 12.4 (C-7^1), 21.9 (C-17^1), 22.3 (C-13^1), 26.9 (C-2^3), 31.3 (C-2^5), 37.1 (C-17^2), 37.6 (C-13^2), 40.8 (C-2^2), 52.1 (C-13^4 and C-17^4), 52.6 (C-2), 52.7 (C-2^1), 60.8 (H-2^{13}), 63.8 (C-2^8), 69.8, 69.9, 70.0, 70.4 and 71.9 (C-2^9, C-2^{10}, C-2^{11}, C-2^{12}), 90.9 (C-5), 92.7 (C-20), 98.5 (C-15), 99.8 (C-10), 121.2 (C-2^4), 121.8 (C-8^2), 129.5 (C-7), 130.2 (C-8^1), 131.0 (C-18), 132.8 (C-9), 133.3 (C-16), 134.5 (C-8), 136.4 (C-17), 137.8 (C-6), 138.4 (C-12), 139.2 (C-19), 139.8 (C-13), 147.6 (C-3), 150.6 (C-14), 151.4 (C-11), 157.1(C-4), 170.7 (C-1), 174.4 (C-17^3), 175.0 (C-13^3), 176.4 (C-2^6), 178.2 (C-2^7). UV–vis ($CHCl_3$) λ_{max} (log ε) 406 (5.09), 502 (3.97), 539 (3.85), 613 (3.53), 671 (4.48) nm. LD-MS *m*/*z* 839.3 $(M+H)^+$. HRMS-ESI-TOF *m*/*z* calcd for $C_{46}H_{55}N_4O_{11}^+$ $(M+H)^+$ 839.3862, found 839.3844. Spectroscopic data for **7b**: ^{1}H NMR ($CDCl_3$/CD_3OD 6:4, 500.13 MHz) δ (ppm): 1.74 (s, 3H, CH_3-7^5), 2.89–2.97 (m, 1H, H-7$^{3\beta}$), 3.18–3.25 (m, 1H, H-7$^{3\alpha}$), 3.20 (t, 2H, *J*=7.8 Hz, H-17^2), 3.23 (t, 2H, *J*=7.7 Hz, H-13^2), 3.39–3.50 (m, 4H, H-7^{12} and H-7^{13}), 3.43 (s, 3H, CH_3-18^1), 3.47 (s, 3H, CH_3-12^1), 3.50–3.80 (m, 6H, H-7^9, H-7^{10} and H-7^{11}), 3.62 (s, 3H, CH_3-2^1), 3.66 (s, 3H, OCH_3-13^4), 3.68 (s, 3H, OCH_3-17^4), 3.81–3.87 (m, 1H, H-7^2), 4.03–4.24 (br s, 1H, H-7^{14}), 4.12–4.24 (m, 2H, H-17^1), 4.29–4.40 (m, 5H, H-7^1, H-7^8 and H-13^1), 6.03 (d, 1H, *J*=11.6 Hz, H-3$^{2\alpha}$), 6.29 (d, 1H, *J*=17.8 Hz, H-3$^{2\beta}$), 7.00 (br s, 1H, H-7^4), 8.17 (dd, 1H, *J*=17.8 and 11.6 Hz, H-3^1), 9.04 (s, 1H, H-5), 9.24 (s, 1H, H-10), 9.64 (s, 1H, H-15), 9.74 (s, 1H, H-20). ^{13}C NMR ($CDCl_3$/CD_3OD 6:4, 125.77 MHz) δ (ppm): 11.3 (C-12^1), 11.8 (C-18^1), 12.7 (C-2^1), 21.9 (C-13^1), 22.2 (C-17^1), 26.9 (C-7^3), 31.2 (C-7^5), 37.1 (C-13^2), 37.5 (C-17^2), 41.0 (C-7^2), 52.1 (C-13^4 and C-17^4), 52.5 (C-7), 52.7 (C-7^1), 60.7 (C7^{13}), 63.9 (C-7^8), 69.9, 70.0 and 70.3 (C-7^9, C-7^{10}, C7^{11} and C-7^{12}), 90.5 (C-10), 92.7 (C-5), 98.4 (C-15), 100.0 (C-20), 120.6 (C-3^2), 121.3 (C-7^4), 130.1 (C-3^1), 130.7 and 130.8 (C-3 and C-12), 133.3, 133.4 and 133.6 (C-1, C-2, C-14), 136.5 (C-13), 137.9 (C-4), 138.3 (C-18), 138.7 (C-11), 139.7 (C-17), 147.9 (C-8), 150.7 (C-16), 150.9 (C-19), 157.8 (C-9), 170.6 (C-6), 174.4 (C-13^3), 174.9 (C-17^3), 176.4 (C-7^6), 178.1 (C-7^7). UV–vis ($CHCl_3$) λ_{max} (log ε) 406 (5.16), 502 (4.03), 539 (3.94), 613 (3.61), 670 (4.56) nm. LD-MS *m*/*z* 839.3 $(M+H)^+$. HRMS-ESI-TOF *m*/*z* calcd for $C_{46}H_{55}N_4O_{11}^+$ $(M+H)^+$ 839.3862, found 839.3829.

4.2.4. 2^1-[(2-Hydroxyethyl)carbamoyl]-13,17-bis[2-(methoxycarbonyl)ethyl]-2,7,12,18-tetramethyl-8-vinyl-2,2^1,2^2,2^3-tetrahydrobenzo[b]porphyrin-2^2-carboxylic acid (**8a**) and 2^1-[(2-hydroxyethyl)carbamoyl]-8,12-bis[2-(methoxycarbonyl)ethyl]-2,7,13,17-tetramethyl-18-vinyl-2,2^1,2^2,2^3-tetrahydrobenzo-[b]porphyrin-2^2-carboxylic acid (**8b**)

A crude mixture of **4a**/**4b** prepared from 25.0 mg of protoporphyrin-IX dimethyl ester was cooled to 0 °C. After that, dry CH_2Cl_2 (6 mL) and ethanolamine (100 equiv) were added. The reaction mixture was further stirred for 2 h at room temperature. Then, CH_2Cl_2 (50 mL) and H_2O (40 mL) were added and the pH was adjusted to 6–7 with HCl (2 mol L^{-1}). The two phases were separated and the organic layer was washed with brine (50 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The products were pre-purified by column chromatography (silica gel, $CHCl_3$/AcOEt/MeOH 5:3:2 as the eluent) and further purified by preparative TLC (silica, $CHCl_3$/AcOEt/THF/MeOH 4:3:1.5:1.5 as the eluent) giving **8a** (11.6 mg 15.2 μmol) and **8b** (8.2 mg 11.0 μmol) in a global 62% yield. Spectroscopic data for **8a**: ^{1}H NMR ($CDCl_3$/CD_3OD 6:4, 500.13 MHz) δ (ppm): 1.75 (s, 3H, CH_3-2^5), 2.73–2.84 (m, 1H, H-2$^{3\beta}$), 3.10–3.20 (m, 1H, H-2$^{3\alpha}$), 3.18 (t, 2H, *J*=7.8 Hz) and 3.19 (t, 2H, *J*=7.8 Hz, H-17^2 and H-13^2), 3.22–3.29 and 3.51–3.56 (m, 2H, H-2^9), 3.41 (s, 3H, CH_3-12^1), 3.43 (s, 3H, CH_3-18^1), 3.54 (s, 3H, CH_3-7^1), 3.62 (s, 3H, OCH_3-17^4), 3.66 (s, 3H, OCH_3-13^4), 3.65–3.79 (m, 3H, H-2^2 and H-2^{10}), 4.06–4.13 (m, 1H, H-2^1), 4.18 (t, 2H, *J*=7.8 Hz, H-13^1), 4.29 (t, 2H, *J*=7.8 Hz, H-17^1), 4.15–4.31 (br s, 2H, H-2^8 and H-2^{11}), 6.18 (dd, 1H, *J*=11.6 and 1.0 Hz, H-8$^{2\alpha}$), 6.37 (dd, 1H, *J*=17.8 and 1.0 Hz, H-8$^{2\beta}$), 6.92 (br s, 1H, H-2^4), 8.19 (dd, 1H, *J*=17.8 and 11.6 Hz, H-8^1), 8.86 (br s, 1H, H-20), 9.28 (s, 1H, H-5), 9.66 (s, 1H, H-15), 9.81 (s, 1H, H-10). ^{13}C NMR ($CDCl_3$/CD_3OD 6:4, 125.77 MHz) δ (ppm): 11.1 (C-18^1), 11.8 (C-12^1), 12.3 (C-7^1), 21.9 (C-17^1), 22.3 (C-13^1), 27.2 (C-2^3), 31.0 (C-2^5), 37.1 and 37.6 (C-17^2 and C-13^2), 42.0 (C-2^2), 42.9 (C-2^9), 52.1 (C-13^4 and C-17^4), 52.7 (C-2), 53.2 (C-2^1), 61.0 (C-2^{10}), 90.9 (C-5), 92.0 (C-20), 98.9 (C-15), 99.8 (C-10), 121.8 (C-8^2), 121.9 (C-2^4), 129.6 (C-7), 130.2 (C-8^1), 130.6 (C-18), 132.9 (C-9), 133.1 (C-16), 134.6 (C-8), 136.4 (C-17), 138.1 (C-6), 138.3 (C-12), 139.2 (C-19), 139.9 (C-13), 147.3 (C-3), 150.4 (C-14), 151.6 (C-11), 157.7 (C-4), 170.3 (C-1), 174.4 (C-17^3), 174.9 (C-13^3), 176.8 (C-2^6), 179.0 (C-2^7). UV–vis ($CHCl_3$) λ_{max} (log ε) 406 (5.06), 505 (3.95), 539 (3.87), 616 (3.49), 671 (4.41) nm. LD-MS *m*/*z* 750.3 $(M+H)^+$. HRMS-ESI-TOF *m*/*z* calcd for $C_{42}H_{48}N_5O_8^+$ $(M+H)^+$ 750.3497, found 750.3475. Spectroscopic data for **8b**: ^{1}H NMR ($CDCl_3$/CD_3OD 6:4, 500.13 MHz) δ (ppm): 1.71 (s, 3H, H-7^5), 2.76–2.85 (m, 1H, H-7$^{3\beta}$), 3.14–3.21 (m, 1H, H-7$^{3\alpha}$), 3.19 (t, 2H, *J*=7.7 Hz, H-17^2), 3.23 (t, 2H, *J*=7.7 Hz, H-13^2), 3.21–3.30 and 3.55–3.62 (m, 2H, H-7^9), 3.43 (s, 3H, CH_3-18^1), 3.46 (s, 3H, CH_3-12^1), 3.60 (s, 3H, CH_3-2^1), 3.66 (s, 3H, OCH_3-13^4), 3.68 (s, 3H, OCH_3-17^4), 3.65–3.80 (m, 3H, H-7^2 and H-7^{10}), 4.01–4.10 (br s, 2H, H-7^8 and H-7^{11}), 4.10 (d, 1H, *J*=4.2 Hz, H-7^1), 4.14–4.21 (m, 2H, H-17^1), 4.28–4.36 (m, 2H, H-13^1), 6.02 (d, 1H, *J*=11.4 Hz, H-3$^{2\alpha}$), 6.30 (d, 1H, *J*=18.0 Hz, H-3$^{2\beta}$), 6.95 (br s, 1H, H-7^4), 8.14 (dd, 1H, *J*=18.0 and 11.4 Hz, H-3^1), 8.97 (br s, 1H, H-5), 9.21 (s, 1H, H-10), 9.62 (s, 1H, H-15), 9.73 (s, 1H, H-20). ^{13}C NMR ($CDCl_3$/CD_3OD 6:4, 125.77 MHz) δ (ppm): 11.3 (C-12^1), 11.7 (C-18^1), 12.6 (C-8^1), 21.8 (C-13^1), 22.1 (C-17^1), 27.0 (C-7^3), 30.9 (C-7^5), 37.0 (C-13^2), 37.4 (C-17^2), 41.7 (C-7^2), 42.8 (C-7^9), 52.0 and 52.1 (C-13^4 and C-17^4), 52.4 (C-7), 53.2 (C-7^1), 60.8 (C-7^{10}), 90.3 (C-10), 92.0 (C-5), 98.2 (C-15), 100.3 (C-20), 120.4

(C-3^2), 121.7 (C-7^4), 129.9 (C-3^1), 130.4 (C-3), 130.8 (C-12), 133.4 (C-1 and C-2), 133.7 (C-14), 136.5 (C-13), 137.8 (C-4), 138.3 (C-18), 138.8 (C-11), 139.5 (C-17), 147.3 (C-8), 150.7 (C-16), 150.8 (C-19), 158.2 (C-9), 170.0 (C-6), 174.3 (C-13^3), 174.7 (C-17^3), 176.6 (C-7^6), 178.7 (C-7^7). UV–vis ($CHCl_3$) λ_{max} (log ε) 406 (5.09), 502 (4.01), 538 (3.88), 615 (3.54), 670 (4.47) nm. LD-MS m/z 750.3 $(M+H)^+$. HRMS-ESI-TOF m/z calcd for $C_{42}H_{48}N_5O_8^+$ $(M+H)^+$ 750.3497, found 750.3491.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.103.

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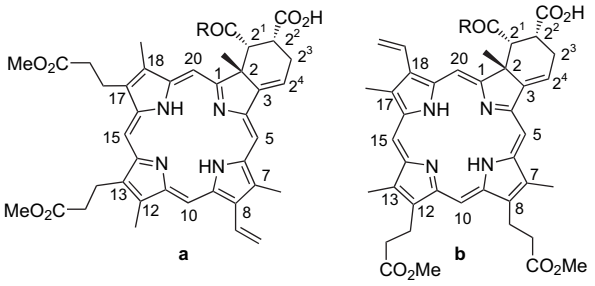

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