Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9083–9090

TETRAHEDRON

Novel peripherally functionalized *seco*-porphyrazines: synthesis, characterization and spectroscopic evaluation

Efstathia G. Sakellariou,[a] Antonio Garrido Montalban,[a] Scott L. Beall,[a] David Henderson,[a] Hubert G. Meunier,[b] David Phillips,[a] Klaus Suhling,[a] Anthony G. M. Barrett[a,*] and Brian M. Hoffman[c,*]

[a]*Department of Chemistry, Imperial College, South Kensington, London SW7 2AZ, UK*
[b]*Department of Chemistry, Assumption College, Worcester, MA 01609, USA*
[c]*Department of Chemistry, Northwestern University, Evanston, IL 60208, USA*

Received 29 July 2003; revised 29 August 2003; accepted 18 September 2003

Abstract—Co-macrocyclizations of 2,3-dipropylmaleonitrile and 2,3-di-(4-(methoxycarbonyl)phenyl)maleonitrile, respectively, with *N*,*N*′-dibenzyl-*N*,*N*′-di-(11-tetrahydropyranyloxy-3,6,9-trioxo-undecyl))maleonitrile and *N*,*N*,*N*′,*N*′-tetramethylmaleonitrile were used to prepare derivatives of the 4,5-diamino-porphyrazine systems including the zinc(II) complexes. Subsequent oxidation of the macrocycles with potassium permanganate gave the corresponding *seco*-porphyrazines. These were shown to be efficient sensitizers for the production of singlet oxygen (Φ_{Δ}=0.15–0.57) by the determination of their photophysical properties.

1. Introduction

Phthalocyanines and related macrocycles, modified by the attachment of peripheral substituents, have found wide applications in diverse areas such as the elaboration of Langmuir Blodgett films,[1] chemical sensors,[2] non-linear optical materials[3] and biomedical agents for diagnosis and therapy.[4] In contrast, the structurally related porphyrazines have been less well studied. However, due to the simple and versatile synthetic route for the preparation of porphyrazines, namely the metal-templated cyclization of the maleonitrile precursors, these macrocyclic compounds are now subject to enhanced interest. Recently, a variety of porphyrazines (pzs) have been obtained showing interesting redox and electronic properties.[5–8] As it has been described previously,[9,10] the preparation of pzs with novel physicochemical properties, including fluorescence and efficient intersystem crossing, is of particular importance since these compounds may find applications as biomedical imaging agents or as novel compounds for photodynamic therapies. In order to be of medical use, any macrocycle of the porphyrazine class must be of sufficient solubility in biological media under standard physiological conditions. In consequence of this need, we sought to prepare novel porphyrazines and the related *seco*-porphyrazines with enhanced solubilities in aqueous media. Two distinct classes of porphyrazines are now reported. The first class contains polyether side chains and the second arenecarboxylate ester functionality. Both classes of porphyrazines and *seco*-porphyrazines were synthesized and their photophysical properties measured including their efficiencies for the sensitized formation of singlet oxygen. The Φ_{Δ} values of the new Zn-*seco* pzs were found to be higher when compared to the Φ_{Δ} values of their free base analogs. However, it should be noted that the most efficient *seco*-pz sensitizer for the production of singlet oxygen reported so far, a *seco*-porphyrazine with an annulated seven-membered ring (Φ_{Δ}=0.74), was recently reported by our group.[12]

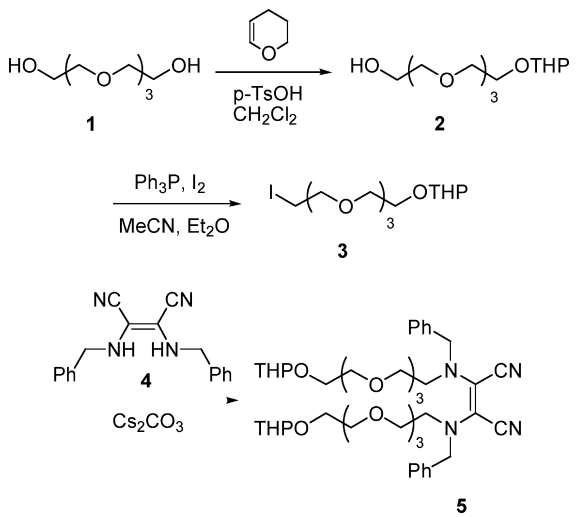
2. Results and discussion

2.1. Synthesis of polyether-appended aminoporphyrazines

Based on previously reported studies,[13] polyether side-chains were successfully attached to the amino groups of diaminomaleonitrile, whereby the macrocycles derived thereof were found to exhibit enhanced solubilities in aqueous media. However, so far only symmetrical polyether-appended aminoporphyrazines have been prepared.[13] Thus, as an extension of this work, the synthesis of the more intriguing unsymmetrical 3:1 pzs bearing a single polyether amino-substituted pyrrole ring was undertaken. Due to the compatible rates of cyclization of dipropylmaleonitrile **6** and various aminomaleonitriles,[5,8] dinitrile **6**[14] was chosen

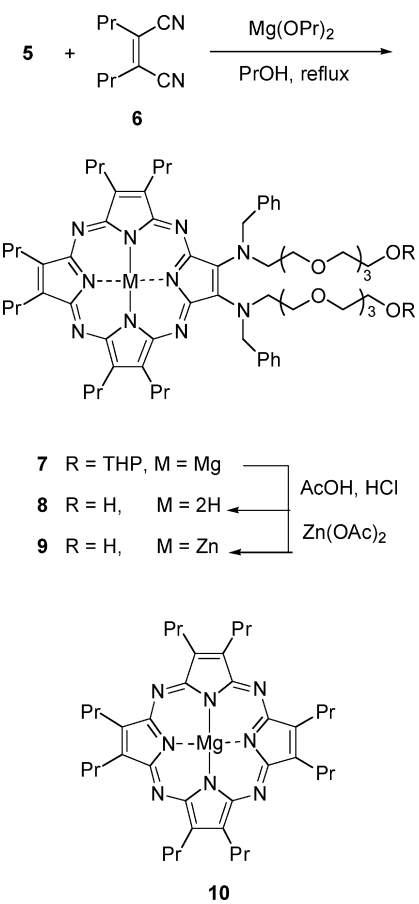
Keywords: porphyrazine; Linstead macrocyclization; sensitization; singlet oxygen.
* Corresponding authors. Tel.: +44-207-594-5766; fax: +44-207-594-5805; e-mail: agmb@ic.ac.uk

0040–4020/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tet.2003.09.060

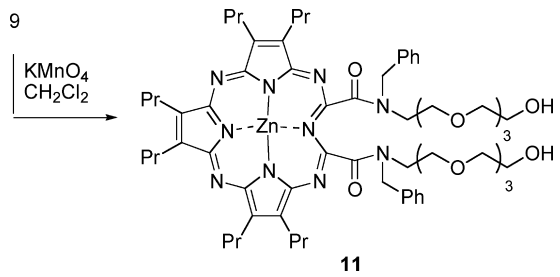


Scheme 1.

as the second agent for the crossed Linstead macrocyclizations. Dinitrile **4** has been previously synthesized,[15] while iodide **3** was obtained from commercially available tetra(ethylene)glycol **1** by mono-protection and conversion to the corresponding iodide **3**. Alkylation of diamine **4** using iodide **3** in the presence of cesium carbonate gave the desired dinitrile **5** in 87% yield (Scheme 1). This was obtained as a mixture of *E* and *Z* isomers as shown by duplication of the low field carbons and *N*-benzyl signals, respectively, in the ^{13}C and ^{1}H NMR spectra. Linstead[16]



Scheme 2.

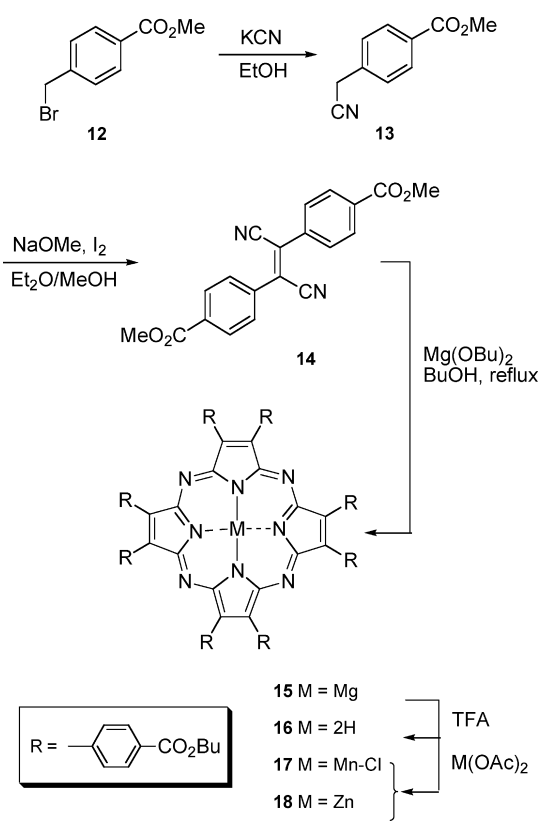


Scheme 3.

co-macrocyclization of dinitriles **5** and **6** in a 1:7 molar ratio resulted in the formation of the Mg-pz **7** along with the Mg-octapropyl pz **10**[5] (Scheme 2). Separation of the two macrocycles was easily achieved by chromatography to give compound **7** in 34% yield. Deprotection of the THP groups and concurrent demetallation of macrocycle **7** using glacial acetic acid followed by concentrated HCl gave diol **8** in 91% yield (Scheme 2). The free base **8** was allowed to react with zinc acetate in DMF to provide the Zn-pz **9** (71%). Subsequent oxidation of pz **9** using an excess of potassium permanganate rapidly afforded the corresponding *seco*-product **11** (92%) (Scheme 3). The incorporation of zinc(II) within the macrocyclic cavity, previously known to enhance the rate of oxidative pyrrole cleavage,[8,11] was also observed in this transformation.

2.2. Synthesis of symmetrical porphyrazines with arenecarboxylate ester substituents

In continuation of our efforts towards the synthesis of hydrophilic *seco*-porphyrazines, but with polar groups not

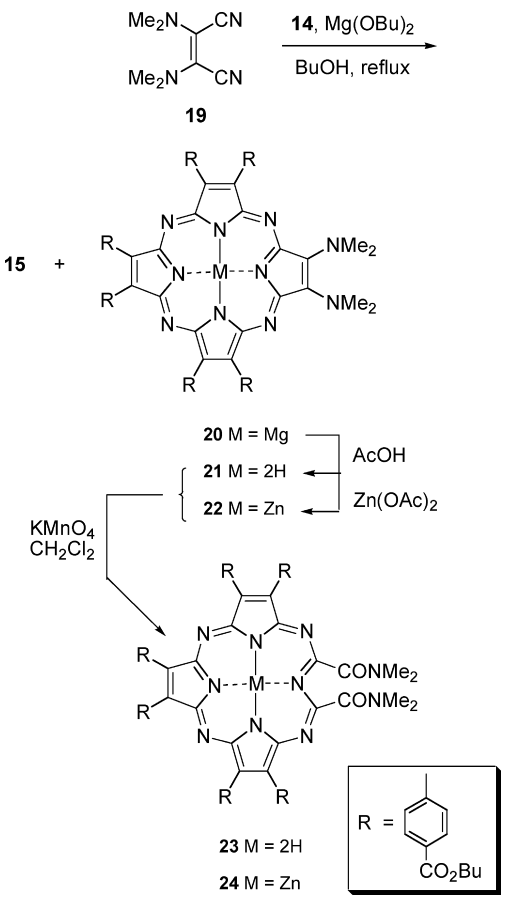


Scheme 4.

directly attached to the amino substituents, the preparation of a second set of macrocycles bearing this time peripheral arenecarboxylate esters was undertaken. Maleodinitrile **14** was prepared via a two-step procedure from the commercially available methyl 4-(bromomethyl)benzoate **12**. Thus, reaction of bromide **12** with potassium cyanide in ethanol at 60°C gave nitrile **13**[17] in 76% yield (Scheme 4). In turn nitrile **13** was oxidatively dimerized, via the enolate and treatment with iodine in methanolic diethyl ether, to provide the maleonitrile **14** (64%). This was isolated as a single isomer, which was tentatively assigned as the *trans* isomer. Both *trans* and *cis* 2,3-diarylmaleonitriles are known to undergo macrocyclization to produce porphyrazines.[18] Having successfully prepared dinitrile **14**, standard Linstead macrocyclization using magnesium as the template was carried out. Thus, reflux of dinitrile **14** and magnesium butoxide in butanol gave, after chromatography, pz **15** in 20% yield (Scheme 4). As expected, concurrent transesterification took place during the reaction. Porphyrazine **15** was, in turn, demetallated to give the free base pz **16** (91%). Remetallation of ligand **16** with manganese(II) acetate in DMF at 100°C followed by an aqueous work-up with brine gave the Mn–Cl-pz **17** (43%). Additionally, heating of the free ligand **16** with zinc acetate in DMF resulted in the formation of the Zn-pz **18** in 74% yield (Scheme 4).

2.3. Synthesis of unsymmetrical porphyrazines with arenecarboxylate ester substituents

In order to obtain the potentially more useful unsymmetrical porphyrazines with ester substituents, the crossover macrocyclization of dinitrile **14** with bis-(dimethylamino)maleonitrile **19** was examined. Thus, when a 7:1 molar ratio of dinitriles **14** and **19** and magnesium butoxide were heated to reflux in butanol, the Mg-pz **20** was obtained along with the Mg-octa-ester-pz **15** (Scheme 5). Although the formation of both dyes was confirmed by mass spectrometry, separation by chromatography proved extremely difficult and time consuming. This problem was overcome by the selective demetallation of pz **20** using glacial acetic acid to yield the requisite unsymmetrical pz **21** (31%), which was separated from the Mg-octa-ester-pz **15** using preparative thin layer chromatography (Scheme 5). Subsequent reaction of ligand **21** with zinc acetate in DMF gave the corresponding Zn-pz **22** (87%). Oxidation of ligand **21** using an excess of potassium permanganate in dichloromethane gave, after 2 h the desired *seco*-pz **23** (Scheme 5) (59%). On the other hand, oxidative cleavage of the Zn-pz **22**, under the same conditions gave, after only 15 min reaction, the desired Zn-*seco*-pz **24** (79%). As observed in previous reports,[8,11] faster oxidative pyrrole cleavage of the Zn-pz to reveal the corresponding *seco*-compound was observed, relative to the free pz ligand. In consequence of this ease of oxidative scission, it was not possible to completely purify and fully characterize the Zn-pz **22**.



Scheme 5.

2.4. Optical properties

2.4.1. Polyether-appended aminoporphyrazines. The electronic absorption spectrum of the free base pz **8** displays a broad Q-band that consists of two absorption features assigned to the non-degenerate Q_x and Q_y transitions centered at 571 and 640 nm, respectively.[19] The electronic absorption spectrum of the Zn-pz **9** displays a broad Q-band at 609 nm. Upon oxidation of **9** to the *seco*-pz **11** the Q-band becomes two sharp peaks with absorptions at 565 and 654 nm. This is in accordance with the model discussed in previous papers in which the broadening of the Q-band is attributed to the overlap of $n\rightarrow\pi^*$ transitions that arise from the nonbonding electrons of the peripheral nitrogens and the macrocyclic π system.[11] On the other hand, decoupling of the nitrogen electron pairs from the macrocyclic core via, for example, *seco*-porphyrazine formation results in sharpening and doubling of the Q-band as a consequence of the C_{2v} symmetry. Both absorption and emission spectra of the *seco*-porphyrazine **11** are given in Figure 1 (λ_{ex}= 570 nm). The photosensitizing ability of the *seco*-pz **11** was also tested. The quantum yields of singlet oxygen formation, Φ_Δ, was calculated relative to the

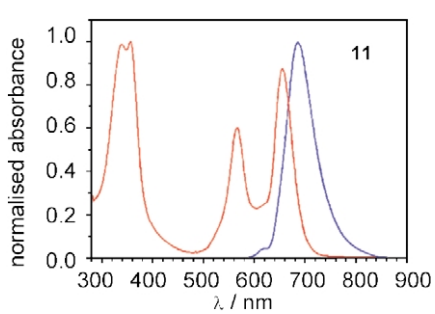
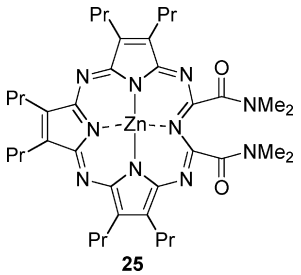


Figure 1. Absorption and emission spectra of porphyrazine **11** in toluene.



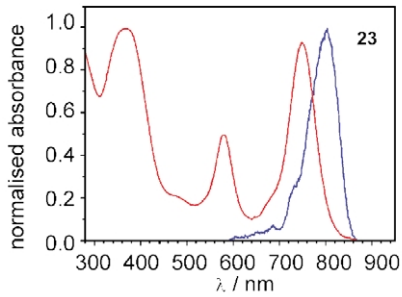
25

Figure 2. Bis-(dimethylamino)-hexapropyl-Zn-*seco*-porphyrazine **25** (Φ_{Δ}=0.54).[11]

bis-(dimethylamino)-hexapropyl-Zn-*seco*-porphyrazine **25** (Fig. 2) (Φ_{Δ}=0.54)[11] as the standard reference and found to be 0.51.

2.4.2. Symmetrical porphyrazines with arenecarboxylate ester substituents. As expected, the Mg-pz **15** has a UV–vis spectrum characteristic of a tetrapyrrolic macrocycle with D_{4h} symmetry exhibiting a single sharp Q-band at 647 nm. Demetallation results in a UV–vis spectrum with a well resolved split Q-band, for the free base, with absorbances at 601 and 668 nm. Remetallation to produce the corresponding Zn-derivative restores the D_{4h} symmetry and thus complex **18** shows again a sharp Q-band at 640 nm. As expected, the UV–vis spectra of the Mg- and Zn-pzs are very similar and thus only the spectrum of porphyrazine **18** is given as a representative example (Fig. 3). On the other hand, incorporation of manganese(III) within the porphyrazine cavity greatly alters the UV–vis spectrum of the derived complex **17**. As previously described for Mn–Cl-pzs,[6] the presence of a high spin electron deficient metal such as manganese(III) results in additional absorptions, which are not readily amenable to interpretation. Thus, apart from the sharp Q-band found at 665 nm, additional peaks at 412 and 473 nm are also present. We tentatively assign these peaks as ligand to metal charge transfer transitions of the type a_{2u} (ring)→e_g (metal) as it has been suggested in analogous porphyrin spectra (Fig. 3).

2.4.3. Unsymmetrical aminoporphyrazines with arenecarboxylate ester substituents. The absorption and emission spectra of the free base and zinc-*seco*-pzs **23** and **24** are



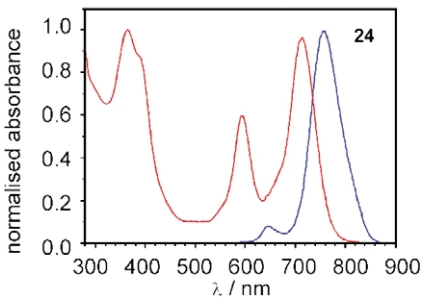


Figure 4. Absorption and emission spectra of porphyrazines **23** and **24** in toluene.

shown in Figure 4 (λ_{ex}=570 nm). Both UV–vis spectra display a well resolved-split Q-band with Q_x and Q_y absorbances at 577 and 743 nm for the free base and 593 and 701 nm for the zinc-*seco*-pz, respectively. In addition, the electronic absorption spectrum of compound **23** is significantly red-shifted and thus of particular interest for biomedical applications due to the deeper penetration of long wavelength light into soft tissue. Both oxidized products are weakly luminescent with fluorescence quantum yields of less than 1×10^{-3}. Similarly to the polyether-appended *seco*-pzs described earlier, the abilities of the two novel *seco*-porphyrazines **23** and **24** to photosensitize the production of singlet oxygen were evaluated. The quantum yield for singlet oxygen production for the free-base and zinc-*seco*-pzs **23** and **24** were found to be Φ_{Δ}=0.15 and 0.57, respectively. Porphyrazine **23** exhibited a much lower singlet oxygen quantum yield than other free base *seco*-analogs, and this can probably be attributed to its red-shifted

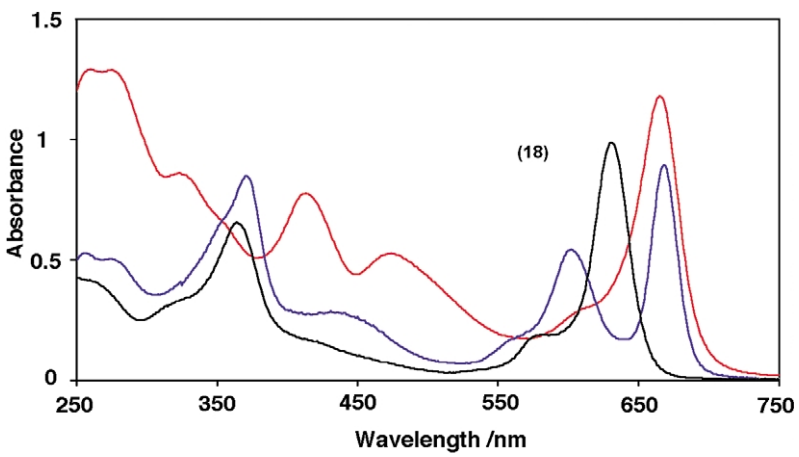


Figure 3. UV–vis absorption spectra of porphyrazines **16**, **17** and **18** in CH_2Cl_2.

Q-band. These results are encouraging, and together with their ease of preparation, these novel ligands are good candidates for further biomedical studies.

3. Conclusions

The successful co-macrocyclization of dinitrile **5** with dipropylmaleonitrile **6** was used to prepare the novel 3:1 porphyrazines **7**–**9**. Oxidation of porphyrazine **9** gave the *seco*-pz **11**, which was an effective sensitizer for the production of singlet oxygen with a quantum yield of 0.51. The synthesis of both symmetrical and unsymmetrical aminoporphyrazines with arenecarboxylate ester substituents is also described herein. Linstead macrocyclization of dinitrile **14** gave the Mg-pz **15**, which on demetallation and remetallation yielded the complexes **17** and **18**. Additionally, macrocycles **20**–**22** were readily obtained by crossover macrocyclizations and converted into the *seco*-pzs **23** and **24**. These were also effective sensitizers with respective quantum yields Φ_Δ of 0.15 (**23**) and Φ_Δ 0.57 (**24**). The biomedical applications of these novel porphyrazines and *seco*-porphyrazines will be reported in due course.

4. Experimental

4.1. General

All reactions were conducted in oven or flame-dried glassware. Reaction temperatures reported refer to external bath temperatures. Hexanes refer to the alkane fraction bp 40–60°C. Butanol was distilled from Mg prior to use, whereas all other reagents were used as commercially supplied. TLC was carried out on E. Merck pre-coated silica gel 60 F_{254} plates. Plates were visualized using UV radiation (254 nm). Chromatography refers to flash chromatography on E. Merck silica gel 60, 40–60 μm (eluants are given in parentheses). HPLC grade solvent (PhMe) was used for all photophysical measurements.

4.2. Steady-state absorption and emission measurements

Electronic absorption spectra were recorded on a dual beam UV–vis spectrometer (Perkin–Elmer Lambda-2) with fixed 2 nm resolution. Fluorescence emission and excitation spectra were recorded on a spectrometer with xenon arc lamp excitation and a photon-counting detection system (Instruments SA Fluoromax). Fluorescence quantum yields were determined by the comparative method using the $Zn[pz(NMe_2)_2(Pr)_6]$ **25** (Φ_f=3.5×10^{-3})[11] in PhMe as the reference standard. To avoid unwanted re-absorption effects, all fluorescence measurements were recorded on solutions with Q-band absorbances of less than 0.1 in 1 cm path length cells.

4.3. Singlet-oxygen measurements

Singlet oxygen quantum yields were measured on a nanosecond, flash photolysis apparatus. Excitation light at 570 nm (for pzs **11**, **23** and **24**) and a repetition rate of 10 Hz was provided by a tunable pulsed dye laser (Lambda Physik) with rhodamine 6G in methanol that was pumped by the frequency doubled output of a Nd/YAG laser (Continuum Surelite I-10). Singlet oxygen phosphorescence decays were detected at 1270 nm using a liquid nitrogen-cooled germanium detector (North Coast EO817-P). The signal from the detector was averaged and recorded by a digital storage oscilloscope (Tektronics TDS 3012). The quantum yields of singlet oxygen formation, ϕ_Δ, were calculated relative to the *seco*-Zn-bis-(dimethylamino)-hexapropyl-porphyrazine **25** (ϕ_Δ=0.54)[11] as the standard reference, with the effect of laser saturation eliminated by measuring the intensity of singlet oxygen phosphorescence as a function of laser power.

4.3.1. 11-Tetrahydropyranyloxy-3,6,9-trioxaundecan-1-ol (2).[20] $TsOH{\cdot}H_2O$ (140 mg, 750 μmol) was added to cooled (0°C) tetraethylene glycol **1** (72.8 g, 375 mmol) and freshly distilled dihydropyran (6.3 g, 75 mmol) in dry CH_2Cl_2 (225 mL). After 10 min at 0°C, the solution was allowed to warm to 20°C and after a further 5 h added to Et_2O (500 mL), brine (125 mL), saturated aqueous $NaHCO_3$ (125 mL), and H_2O (250 mL). The separated organic layer was washed with brine (2×250 mL), dried ($MgSO_4$/K_2CO_3 1:1) and rotary evaporated. Chromatography (EtOAc/hexanes/MeOH 35:60:5) gave alcohol **2** (9.3 g, 45%) as a clear oil: R_f 0.13 (EtOAc/hexanes/MeOH 35:60:5); IR (neat) 3460, 1454, 1350, 1121 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.46–1.83 (m, 6H), 2.63 (br s, 1H), 3.44–3.75 (m, 16H), 3.80–3.88 (m, 2H), 4.61–4.63 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.3, 25.3, 30.4, 61.6, 62.1, 66.5, 70.3, 70.4, 70.5, 72.5, 98.8; MS (CI, NH_3) *m/z* 296 $[M+NH_4]^+$, 212 $[M-THP+NH_4]^+$; HRMS (CI, NH_3) *m/z* calcd for $C_{13}H_{30}NO_6$: $[M+NH_4]^+$, 296.2073; found: $[M+NH_4]^+$, 296.2076. Anal. calcd for $C_{13}H_{26}O_6$: C, 56.10; H, 9.42; Found: C, 55.99; H, 9.59.

4.3.2. 11-Iodo-1-tetrahydropyranyloxy-3,6,9-trioxaundecane (3). I_2 (13.8 g, 54.5 mmol) was slowly added with stirring to alcohol **2** (10.6 g, 38.1 mmol), Ph_3P (13.0 g, 49.6 mmol) and imidazole (3.6 g, 52.2 mmol) in MeCN (38 mL) and Et_2O (63 mL) at 0°C. After 2 h at 0°C, the brown–black slurry was diluted with Et_2O (750 mL), filtered, and sequentially washed with saturated aqueous $CuSO_4$ (3×200 mL), H_2O (3×200 mL), dried ($MgSO_4$/K_2CO_3 1:1), filtered and concentrated to give a white oily solid. Et_2O (50 mL) was added, the resulting suspension was filtered and the filtrate was concentrated to give again a white oily solid. This procedure was repeated with Et_2O (25 mL) to give this time a pale yellow oil. Chromatography (EtOAc/hexanes 1:3 to 1:1) gave iodide **3** (12.0 g, 81%) as a clear oil: R_f 0.3 (EtOAc/hexanes 1:2); IR (neat) 1454, 1351, 1261, 1124 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.47–1.80 (m, 6H), 3.25 (t, 2H, *J*=7 Hz), 3.46–3.89 (m, 14H), 4.60–4.63 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 2.9, 19.4, 25.4, 30.5, 62.2, 66.6, 70.2, 70.5, 70.6, 70.7, 71.9, 98.9; MS (CI, NH_3) *m/z* 406 $[M+NH_4]^+$, 322 $[M-THP+NH_4]^+$; HRMS (CI, NH_3) *m/z* calcd for $C_{13}H_{29}N_1O_5I$: $[M+NH_4]^+$, 406.1091; found: $[M+NH_4]^+$, 406.1095.

4.3.3. 2,3-Di-[benzyl-(11-tetrahydropyranyloxy-3,6,9-trioxo-undecyl)amino]-2-butene-1,4-dinitrile (5). (*E*,*Z*)-Dinitrile **4** (860 mg, 3.0 mmol) and iodide **3** (3.5 g, 9.0 mmol) in DMF (15 mL) was added over 1 h to a rapidly stirring suspension of Cs_2CO_3 (2.15 g, 6.6 mmol) in DMF (15 mL).

The suspension was heated at 50°C for 3 h, allowed to cool to 25°C and left standing for another 16 h. After rotary evaporation, CH_2Cl_2 was added to the residue and the resulting suspension was washed with H_2O (3×15 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (EtOAc/hexanes 3:1) gave dinitrile **5** (2.1 g, 87%), a mixture of *E* and *Z* isomers, as a clear amber oil: R_f 0.25 (EtOAc/hexanes 3:1); IR (neat) 1581, 1562, 1496, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27–1.88 (m, 12H), 3.21–3.28 (m, 4H), 3.46–3.68 (m, 28H), 3.83–3.91 (m, 4H), 4.28 (s, 2H), 4.39 (s, 2H), 4.61–4.64 (m, 2H), 7.16–7.34 (m, 10H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.4, 25.3, 30.5, 50.5, 52.7, 55.8, 58.6, 62.1, 65.9, 66.5, 68.8, 69.2, 70.4, 70.48, 70.53, 70.7, 98.8, 114.0, 115.0, 116.6, 119.3, 127.7, 128.3, 128.5, 128.6, 128.7, 136.2, 136.8; MS (CI, NH_3) *m/z* 808 [$M^{+\cdot}$]; HRMS (CI, NH_3) *m/z* calcd for $C_{44}H_{64}N_4O_{10}$: [$M^{+\cdot}$], 808.4622; found: [$M^{+\cdot}$], 808.4682. Anal. calcd for $C_{44}H_{64}N_4O_{10}$: C, 65.32; H, 7.97; N, 6.93; Found: C, 65.02; H, 7.65; N, 7.21.

4.3.4. 4,5-Di-(benzyl-(11-tetrahydropyranyloxy-3,6,9-trioxaundecyl)amino)-9,10,14,15,19,20-hexapropylporphyrazine (8). Propanol (5 mL), Mg (16.3 mg, 0.7 mmol) and I_2 (two small crystals) were heated to reflux for 24 h under N_2. The suspension was cooled to 20°C and dipropylmaleonitrile **6** (140.7 mg, 0.87 mmol) followed by dinitrile **5** (103.7 mg, 0.13 mmol) were added and the mixture further heated to reflux under N_2 for 60 h. The deep blue suspension was allowed to cool, filtered (Celite), and the solids washed with CH_2Cl_2. Rotary evaporation and chromatography (hexanes/EtOAc 7:3; EtOAc) gave the Mg-pz **7** (56.2 mg, 34%) as a blue solid: R_f 0.7 (EtOAc); UV–vis (CH_2Cl_2) λ_{max} 239, 345, 612 nm; MS (FAB) *m/z* 1320 [$M^{+\cdot}$]; HRMS (FAB) calcd for $C_{74}H_{107}MgN_{10}O_{10}$: [M+H]$^+$, 1319.8022; found: [M+H]$^+$, 1319.7967. This compound was used without further purification. Glacial AcOH (12 drops) was added to pz **7** (22.5 mg, 17 μmol) in $CHCl_3$ (6 mL) and MeOH (1.5 mL) and, after 1 h at 20°C, conc. HCl (four drops) was added. After 2.5 h, the mixture was neutralized with aqueous NaOH (1 M) and the aqueous layer extracted with $CHCl_3$ (2×10 mL). Rotary evaporation and chromatography gave pz **8** (17.4 mg, 91%) as an amorphous purple solid: R_f 0.14 (EtOAc); IR (CH_2Cl_2) 1728, 1567, 1455 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} (log ε) 339 (4.70), 571 (4.37), 640 (4.23) nm; ^1H NMR (270 MHz, pyridine-d_5) δ −1.44 (s, 2H), 1.18–1.43 (m, 18H), 2.26–2.52 (m, 12H), 3.43–3.64 (m, 28H), 3.81–4.13 (m, 16H), 5.91 (s, 4H), 6.16 (br s, 2H), 7.20–7.38 (m, 6H), 7.8 (d, 4H, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 15.1, 25.8, 26.0, 28.5, 52.1, 57.3, 62.0, 70.5, 70.8, 72.6, 127.0, 128.6, 128.8, 136.4, 140.5, 142.4, 143.2, 143.3, 152.4, 155.0; MS (FAB) *m/z* 1129 [$M^{+\cdot}$]; HRMS (FAB) calcd for $C_{64}H_{93}N_{10}O_8$: [M+H]$^+$, 1129.7178; found: [M+H]$^+$, 1129.7158. Anal. calcd for $C_{64}H_{92}N_{10}O_8$: C, 68.06; H, 8.20; N, 12.40; Found: C, 68.01; H, 8.19; N, 12.24.

4.3.5. 4,5-Di-(benzyl-(11-tetrahydropyranyloxy-3,6,9-trioxaundecyl)amino)-9,10,14,15,19,20-hexapropylporphyrazinatozinc(II) (9). Pz **8** (10.1 mg, 9 μmol) and anhydrous zinc acetate (2.4 mg, 13 μmol) in DMF (5 mL) were heated at 100°C for 6 h under N_2. The mixture was allowed to cool to 20°C, rotary evaporated and chromatographed ($CHCl_3$/MeOH 9:1) to give the Zn-pz **9** (7.6 mg, 71%) as an amorphous blue solid: R_f 0.3 ($CHCl_3$/MeOH 9:1); IR (CH_2Cl_2) 1685, 1637, 1463, 1265 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} (log ε) 345 (4.76), 609 (4.47) nm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 15.2, 15.3, 25.9, 26.3, 28.5, 28.6, 28.7, 51.6, 57.3, 60.7, 70.0, 70.2, 70.4, 70.6, 70.7, 71.3, 126.9, 128.6, 128.8, 129.0, 137.6, 141.0, 143.0, 143.3, 144.1, 155.5, 157.2, 157.3; MS (FAB) *m/z* 1191 [M−2H]$^+$; HRMS (FAB) calcd for $C_{64}H_{91}N_{10}O_8Zn$: [M+H]$^+$, 1191.6313; found: [M+H]$^+$, 1191.6279.

4.3.6. 4,5-Di-(benzyl-(11-tetrahydropyranyloxy-3,6,9-trioxaundecyl)amino)-9,10,14,15,19,20-hexapropyl-4,5-dioxo-4,5-*seco*-porphyrazinatozinc(II) (11). $KMnO_4$ (12.6 mg, 80 μmol) was added to pz **9** (5 mg, 8 μmol) in CH_2Cl_2 (10 mL). After 45 min at 20°C, the blue solution was filtered (Celite), and the solids washed with CH_2Cl_2. Rotary evaporation and chromatography (EtOAc/MeOH 19:1) gave the zinc-*seco*-pz **11** (9 mg, 92%) as an intense amorphous blue solid: R_f 0.4 (EtOAc/MeOH 19:1); IR (CH_2Cl_2) 1728, 1638, 1463, 1215 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} 338, 354, 565, 654 nm; ^{13}C NMR (75 MHz, pyridine-d_5) δ 25.4, 25.6, 25.8, 28.1, 28.2, 28.4, 29.4, 29.7, 54.8, 61.3, 70.4, 70.5, 70.6, 73.5, 127.1, 127.7, 128.8, 139.2, 141.3, 142.5, 145.0, 154.9, 156.0, 157.3, 170.2; MS (FAB) *m/z* 1223 [$M^{+\cdot}$], 912 [M−$COCH_2PhNCH_2(CH_2O-CH_2)_3CH_2OH$]$^+$; HRMS (FAB) calc for $C_{64}H_{91}N_{10}O_{10}Zn$: [M+H]$^+$, 1223.6211; found: [M+H]$^+$, 1223.6215.

4.3.7. 2,3-Di-(4-(methoxycarbonyl)phenyl)maleonitrile (14). Ester **12** (1.0 g, 4.4 mmol) and KCN (0.3 g, 4.6 mmol) in EtOH (10 mL) were heated at 60°C for 24 h. The mixture was cooled to 20°C, filtered and rotary evaporated. Chromatography (hexanes/EtOAc 7:3) gave nitrile **13** (0.6 g, 76%) as a white solid mp 57–59°C (lit.[21] 63–64°C): R_f 0.4 (hexanes/EtOAc 7:3); ^1H NMR (270 MHz, $CDCl_3$) δ 3.84 (s, 2H), 3.95 (s, 3H), 7.44 (d, *J*=8.3 Hz, 2H), 8.08 (d, *J*=8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 52.7, 117.5, 130.5, 130.8, 135.2, 166.8; MS (CI) *m/z* 193 [M+NH_4]$^+$. Crude nitrile **13** was used directly without further purification. A slurry of nitrile **13** (0.95 g, 5.42 mmol), and I_2 (1.37 g, 5.42 mmol) in Et_2O and MeOH (1:1; 28 mL) was heated at reflux for 1 h under N_2. The mixture was cooled to 20°C, when methanolic NaOMe (0.27 g of Na in 3.5 mL of MeOH) was added and reflux continued for another 2 h. After rotary evaporation, the crude mixture was redissolved in CH_2Cl_2, washed with H_2O (2×15 mL), and aqueous $Na_2S_2O_3$ (2×15 mL), dried ($MgSO_4$) and rotary evaporated. Recrystallization from $CHCl_3$ and MeOH gave dinitrile **14** (0.6 g, 64%) as a white solid mp 225–227°C: R_f 0.4 (hexanes/EtOAc 7:3); IR (CH_2Cl_2) 1725, 1609, 1437, 1407, 1284 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.94 (s, 6H), 7.91 (d, *J*=8.6 Hz, 4H), 8.20 (d, *J*=8.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.0, 116.3, 126.3, 129.2, 130.8, 133.5, 135.9, 166.1; MS (CI) *m/z* 364 [M+NH_4]$^+$; HRMS (CI) calcd for $C_{20}H_{18}N_3O_4$: [M+NH_4]$^+$, 364.1297; found: [M+NH_4]$^+$, 364.1308. Anal. calcd for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.08; Found: C, 69.34; H, 3.95; N, 7.89.

4.3.8. 4,5,9,10,14,15,19,20-Octa-(4-(butyloxycarbonyl)-phenyl)porphyrazine (16). Butanol (5 mL), Mg (8.8 mg, 0.36 mmol) and I_2 (two small crystals) were heated to reflux

for 24 h under N_2. The suspension was allowed to cool to 20°C when dinitrile **14** (10.4 mg, 30 μmol) was added. The resulting mixture was further heated at reflux for 24 h, filtered (Celite), rotary evaporated and chromatographed ($CHCl_3$/MeOH 9:1) to give the Mg-porphyrazine **15** (10.5 mg, 20%) as an amorphous green solid: R_f 0.9 ($CHCl_3$/MeOH 9:1); IR (CH_2Cl_2) 1714, 1608, 1466, 1279 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} 384, 647 nm; ^1H NMR (270 MHz, pyridine-d_5) δ 0.97 (t, J=7.3 Hz, 24H), 1.40–1.61 (m, 16H), 1.74–1.91 (m, 16H), 4.53 (t, J=6.5 Hz, 16H), 8.57 (d, J=8.5 Hz, 16H), 8.64 (d, J=8.5 Hz, 16H); MS (FAB) m/z 1747 $[M+H]^+$. Crude porphyrazine **15** (10 mg, 6 μmol) was dissolved in TFA (3 mL) and allowed to stand for 30 min under N_2. The solution was added to iced H_2O (10 mL) and neutralized with aqueous NaOH (1 M). The resultant precipitate was filtered off, redissolved in CH_2Cl_2 and the solution dried ($MgSO_4$) and rotary evaporated. Chromatography ($CHCl_3$/MeOH 9:1) gave the free base porphyrazine **16** (9.4 mg, 91%) as an intense green solid: mp >350°C; R_f 0.9 ($CHCl_3$/MeOH 9:1); UV–vis (CH_2Cl_2) λ_{max} (log ε) 370 (4.82), 601 (4.63), 668 (4.84) nm; IR (CH_2Cl_2) 1716, 1610, 1465, 1278 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.05 (t, J=7.3 Hz, 24H), 1.49–1.65 (m, 16H), 1.81–1.96 (m, 16H), 4.46 (t, J=6.7 Hz, 16H), 8.2–8.35 (m, 32H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 19.4, 30.9, 65.2, 129.6, 130.6, 132.7, 136.9, 141.5, 153.7, 166.4; MS (FAB) m/z 1725 $[M+H]^+$. Anal. calcd for $C_{104}H_{106}N_8O_{16}$: C, 72.45; H, 6.20; N, 6.50; Found: C, 72.36; H, 6.17; N, 6.35.

4.3.9. 4,5,9,10,14,15,19,20-Octa-(4-(butyloxycarbonyl)-phenyl)porphyrazinato(chloro)manganese(III) (17). Porphyrazine **16** (17.2 mg, 10 μmol) and anhydrous $Mn(OAc)_2$ (1.76 mg, 10 μmol) in dry DMF (5 mL) were heated at 100°C for 16 h under N_2. The mixture was allowed to cool when brine (4 mL) was added and the mixture was further stirred at 20°C for 30 min. The mixture was extracted with Et_2O and CH_2Cl_2 (4:1; 3×30 mL) and the combined organic layers were washed with H_2O (3×20 mL) and brine (3×20 mL), dried (Na_2SO_4), rotary evaporated and chromatographed (CH_2Cl_2/MeOH 19:1) to give porphyrazine **17** (7.8 mg, 43%) as a dark green solid: mp 214–250°C (dec); R_f 0.5 (CH_2Cl_2/MeOH 19:1); IR (CH_2Cl_2) 1715, 1609, 1466, 1278, 1183 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} (log ε) 258 (4.91), 324 (4.73), 412 (4.66), 473 (4.50), 665 (4.84) nm; MS (FAB) m/z 1777 $[M-Cl]^+$. Anal. calcd for $C_{104}H_{106}ClMnN_8O_{16}$: C, 68.92; H, 5.78; N, 6.18; Found: C, 68.62; H, 5.50; N, 6.01.

4.3.10. 4,5,9,10,14,15,19,20-Octa-(4-(butyloxycarbonyl)-phenyl)porphyrazinatozinc(II) (18). Porphyrazine **16** (20 mg, 11 μmol) and anhydrous $Zn(OAc)_2$ (2.2 mg, 15 μmol) in dry DMF (15 mL) were heated at 90°C for 16 h under N_2. The mixture was allowed to cool, filtered (Celite) and the solids washed with CH_2Cl_2. Rotary evaporation and chromatography (hexanes/EtOAc 7:3; EtOAc) gave the zinc-porphyrazine **18** (14.5 mg, 74%) as an intense green solid: mp >350°C; R_f 0.8 ($CHCl_3$/MeOH 19:1); UV–vis (CH_2Cl_2) λ_{max} (log ε) 374 (4.85), 640 (5.03) nm; IR (CH_2Cl_2) 1712, 1608, 1468, 1279 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 0.98 (t, J=7.3 Hz, 24H), 1.42–1.58 (m, 16H), 1.77–1.92 (m, 16H), 4.54 (t, J=6.7 Hz, 16H), 8.52–8.69 (m, 32H); ^{13}C NMR (67.5 MHz, pyridine-d_5) δ 13.8, 19.5, 31.0, 65.1, 129.8, 130.5, 133.3, 138.7, 142.9, 158.0, 166.4; MS (FAB) m/z 1788 $[M^{+\cdot}]$.

4.3.11. 4,5-Bis-(dimethylamino)-9,10,14,15,19,20-hexa-(4-(butyloxycarbonyl)phenyl)porphyrazine (21). BuOH (55 mL), Mg (363 mg, 14.9 mmol) and I_2 (two small crystals) were heated to reflux for 24 h under N_2. The suspension was allowed to cool to 20°C when dinitrile **14** (369 mg, 1.06 mmol) followed by bis-(dimethylamino)-maleonitrile **19** (40 mg, 240 μmol) were added. The mixture was heated to reflux for 16 h under N_2 and filtered (Celite). Rotary evaporation gave a mixture of the magnesium porphyrazines **20** and **15** (MS (FAB) m/z 1480 $[M^{+\cdot}]$) that was demetallated without further purification. Glacial AcOH (2 mL) was added to the crude mixture of **20** and **15** and, after 30 min under N_2, poured onto iced H_2O (20 mL), neutralized with aqueous NaOH (1 M) and filtered. The solid was redissolved in CH_2Cl_2, the solution dried ($MgSO_4$) and rotary evaporated. Preparative thin layer chromatography ($CHCl_3$/MeOH 9:1) gave porphyrazine **21** as an amorphous blue solid: R_f 0.7 ($CHCl_3$/MeOH 9:1); UV–vis (CH_2Cl_2) λ_{max} (log ε) 359 (4.00), 594 (3.83) nm; IR (CH_2Cl_2) 1713, 1609, 1386, 1278, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, J=7.3 Hz, 18H), 1.44–1.77 (m, 12H), 1.80–1.97 (m, 12H), 3.75 (s, 12H), 4.40–4.57 (m, 12H), 8.08–8.23 (m, 20H), 8.30 (d, J=7.3 Hz, 4H); MS (FAB) m/z 1458 $[M^{+\cdot}]$; HRMS (FAB) calcd for $C_{86}H_{93}N_{10}O_{12}$: $[M+H]^+$, 1457.6974; found: $[M+H]^+$, 1457.6997.

4.3.12. 4,5-Bis-(dimethylamino)-9,10,14,15,19,20-hexa-(4-(butyloxycarbonyl)phenyl)-4,5-dioxo-4,5-secoporphyrazine (23). Porphyrazine **21** (10 mg, 7 μmol) and $KMnO_4$ (158 mg, 1 mmol) in CH_2Cl_2 (10 mL) were stirred at 20°C for 2 h. The resulting mixture was filtered (Celite) and the solids washed with CH_2Cl_2. Rotary evaporation and preparative thin layer chromatography (CH_2Cl_2/MeOH 19:1) gave *seco*-porphyrazine **23** (6.2 mg, 59%) as a dark red–brown amorphous solid: R_f 0.6 (CH_2Cl_2/MeOH 19:1); UV–vis (CH_2Cl_2) λ_{max} (log ε) 256 (4.38), 375 (4.39), 577 (4.02), 743 (4.27) nm; IR (CH_2Cl_2) 1713, 1647, 1608, 1459, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, J=7.4 Hz, 18H), 1.47–1.63 (m, 12H), 1.77–1.91 (m, 12H), 3.29 (s, 6H), 3.80 (s, 6H), 4.38–4.49 (m, 12H), 8.07 (d, J=8.4 Hz, 4H), 8.11–8.24 (m, 16H), 8.26 (d, J=8.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 19.4, 30.9, 35.6, 40.4, 65.0, 65.2, 129.5, 129.6, 129.7, 130.0, 130.6, 130.8, 132.3, 132.5, 132.7, 136.1, 137.0, 137.9, 143.4, 166.6, 167.7; MS (FAB) m/z 1417 $[M-CONMe_2]^+$, 1490 $[M^{+\cdot}]$; HRMS (FAB) calcd for $C_{86}H_{93}N_{10}O_{14}$: $[M+H]^+$, 1489.6873; found: $[M+H]^+$, 1489.6913.

4.3.13. 4,5-Bis-(dimethylamino)-9,10,14,15,19,20-hexa-(4-(butyloxycarbonyl)phenyl)-4,5-dioxo-4,5-secoporphyrazineatozinc(II) (24). Porphyrazine **21** (4.3 mg, 3 μmol) and anhydrous $Zn(OAc)_2$ (0.6 mg, 3 μmol) in dry DMF (6 mL) were heated at 90°C for 16 h under N_2. The mixture was allowed to cool, filtered (Celite) and the solids washed with CH_2Cl_2. Rotary evaporation and chromatography (hexanes/EtOAc 7:3; EtOAc) gave the crude zinc-porphyrazine **22** (4 mg, 87%) as an intense green solid: R_f 0.8 ($CHCl_3$/MeOH 9:1); MS (FAB) m/z 1521 $[M^{+\cdot}]$. Further characterization was not possible due to the rapid oxidation

to the corresponding *seco*-porphyrazine **24** during attempted purification. Thus, a mixture of porphyrazine **22** (2 mg, 1 μmol) and $KMnO_4$ (16 mg, 100 μmol) in CH_2Cl_2 (5 mL) was stirred at 20°C for 15 min. The mixture was filtered (Celite) and the solids washed with CH_2Cl_2. Rotary evaporation and preparative thin layer chromatography (CH_2Cl_2/MeOH 19:1) gave the zinc-*seco*-porphyrazine **24** (1.2 mg, 79%) as a green solid: mp 312–330°C; R_f 0.6 (CH_2Cl_2/MeOH 19:1); UV–vis (CH_2Cl_2) λ_{max} (log ε) 359 (4.65), 387 (4.60), 593 (4.43), 701 (4.63) nm; IR (CH_2Cl_2) 1718, 1645, 1609, 1493, 1274 cm^{-1}; ^1H NMR (270 MHz, pyridine-d_5) δ 0.8–1.09 (m, 18H), 1.19–1.56 (m, 12H), 1.62–1.88 (m, 12H), 3.28 (s, 6H), 4.13 (s, 6H), 4.35–4.58 (m, 12H), 8.30 (d, J=8.2 Hz, 4H), 8.45–8.64 (m, 20H); ^{13}C NMR (75 MHz, pyridine-d_5) δ 13.7, 13.8, 19.4, 19.5, 30.9, 31.0, 34.9, 39.8, 65.0, 129.7, 130.1, 130.4, 130.5, 132.8, 133.1, 138.5, 138.6, 139.3, 140.0, 140.4, 143.4, 154.3, 154.6, 157.8, 158.2, 166.4, 166.5, 168.2; MS (FAB) *m*/*z* 1481 $[M-CONMe_2]^+$, 1554 $[M^{+\cdot}]$; HRMS (FAB) calcd for $C_{83}H_{84}N_9O_{13}Zn$: $[M-CONMe_2]^+$, 1478.5480; found: $[M-CONMe_2]^+$, 1478.5450.

Acknowledgements

We thank GlaxoSmithKline for the generous endowment to A. G. M. B., the EPSRC and NSF for support, and the Royal Society and the Wolfson Foundation for a Royal Society–Wolfson Research Merit Award (to A. G. M. B.) and for establishing the Wolfson center for Organic Chemistry in Medical Sciences at Imperial College London.

References

1. Schultz, H.; Lehmann, H.; Rein, M.; Hanack, M. *Struct. Bond. (Berlin)* **1991**, *74*, 41.
2. Collins, G. E.; Armstrong, N. R.; Pankow, J. W.; Oden, C.; Brina, R.; Arbour, C.; Dodelet, J.-P. *J. Vac. Sci. Technol. A* **1993**, *11*, 1383.
3. Diaz-Garcia, M. A.; Ledoux, I.; Duro, J. A.; Torres, T.; Agulló-López, F.; Zyss, J. *J. Phys. Chem.* **1994**, *98*, 8761.
4. Bonnet, R. *Chem. Soc. Rev.* **1995**, *24*, 19.
5. Lange, S. J.; Nie, H.; Stern, C. L.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **1998**, *37*, 6435.
6. Goldberg, D. P.; Garrido Montalban, A.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **1998**, *37*, 2873.
7. Sibert, J. W.; Baumann, T. F.; Williams, D. J.; White, A. J. P.; Barrett, A. G. M.; Hoffman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 10487.
8. Garrido Montalban, A.; Lange, S. J.; Beall, L. S.; Mani, N. S.; Williams, D. J.; White, A. J. P.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **1997**, *62*, 9284.
9. Sakellariou, E. G.; Garrido Montalban, A.; Meunier, H. G.; Ostler, R. B.; Rumbles, G.; Barrett, A. G. M.; Hoffman, B. M. *J. Photochem. Photobiol. A: Chem.* **2000**, *136*, 185.
10. Sakellariou, E. G.; Garrido Montalban, A.; Meunier, H. G.; Rumbles, G.; Phillips, D.; Ostler, R. B.; Suhling, K.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **2002**, *41*, 2182.
11. Garrido Montalban, A.; Meunier, H. G.; Ostler, R. B.; Barrett, A. G. M.; Hoffman, B. M.; Rumbles, G. *J. Phys. Chem. A* **1999**, *103*, 4352.
12. Baum, S. M.; Trabanco, A. A.; Garrido Montalban, A.; Micallef, A. S.; Zhong, C.; Meunier, H. G.; Suhling, K.; Phillips, D.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **2003**, *68*, 1665.
13. Beall, L. S. Ph.D. Thesis, Imperial College of Science, Technology and Medicine, 1996.
14. Fitzgerald, J.; Taylor, W.; Owen, H. *Synthesis* **1991**, 686.
15. Begland, R. W.; Hartter, D. R.; Jones, F. N.; Sam, D. J.; Sheppard, W. A.; Webster, O. W.; Weigert, F. J. *J. Org. Chem.* **1974**, *39*, 2341.
16. Linstead, R. P.; Whalley, M. *J. Chem. Soc.* **1952**, 4839.
17. Codlington, J. F.; Mosettig, E. *J. Org. Chem.* **1952**, *17*, 1035.
18. Fitzgerald, J.; Taylor, W.; Owen, H. *Synthesis* **1991**, 686. and references therein.
19. Gouterman, M. *The Porphyrins*; Dolphin, D., Ed.; Academic: New York, 1978; Vol. 3, pp 1–165.
20. Jayasuriya, J.; Bosak, S.; Regen, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5851.
21. Codington, J. F.; Mosettig, E. *J. Org. Chem.* **1952**, *17*, 1035.