Reductive Amination – A Convenient Method for Generating Diverse, Mono-Functionalised 5,10,15,20-Tetraphenyl Porphyrins

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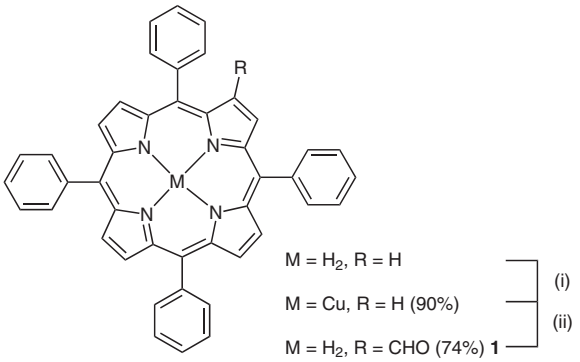
Abstract: Formylation followed by reductive amination of 5,10,15,20-tetraphenyl porphyrin (TPP) is shown to be a versatile synthetic procedure for monosubstitution of the porphyrin core regiospecifically at one β-position. A diverse range of substituents can be introduced in this way in good yields, including cyclen aza-crown macrocycles.

Key words: porphyrin, substitution, cyclen, amination, regioselective

Porphyrins are aromatic tetrapyrrolic macrocycles, which are found widely in nature where they play vital roles in photosynthesis, cellular respiration, oxygen transport and storage, and as components of metalloenzymes.[1] The functions performed by porphyrins in nature have driven research into the use of synthetic porphyrins in many areas including artificial photosynthetic systems,[2] as oxidation catalysts[3] and in photodynamic therapy of cancer.[4] In order to integrate porphyrins into biomimetic systems and fine-tune their optical and redox properties for these applications, efficient methods for functionalising the porphyrin core are constantly under investigation.[5] One area that proves particularly troublesome is the regioselective mono-functionalisation of porphyrins. Synthetic methods leading to porphyrins bearing single functional groups can be roughly divided into two categories: firstly, methods that incorporate a substituent into one of the units used to form the porphyrin, followed by a 'mixed condensation' of this precursor with other unsubstituted units. However, this approach then requires tedious isolation of the monosubstituted product from unsubstituted and higher substituted contaminants, usually by exhaustive chromatography. A second option is to take advantage of the aromatic nature of the porphyrin to perform electrophilic substitution reactions on the core. Several reactions of this type are often used including nitration[6] and halogenation,[7] however, careful control of reaction conditions is often required in order to prevent contamination with di- or higher substituted products. Many electrophilic reactions commonly performed on other aromatic systems also fail on the porphyrins, perhaps the most notable of these being the otherwise ubiquitous Friedel–Crafts alkylation and acylation reactions, thus further limiting the usefulness of electrophilic substitution in porphyrin chemistry. A notable exception to this list of difficulties related to porphyrin substitution is the Vilsmeier–Haack formylation reaction which, due to the formation of a highly electron-withdrawing iminium salt intermediate that must be hydrolysed to give the formyl-substituted product, only results in the introduction of more than one formyl group under extreme forcing conditions. For the reasons described, Vilsmeier–Haack formylation is widely used in porphyrin synthetic chemistry, and the synthesis of monoformyl 5,10,15,20-tetraphenyl porphyrin (**1**; Scheme 1) has been refined and optimised by Crossley and Officer,[8] who also used it as a key intermediate for generating other monosubstituted porphyrins by reduction, halogenation and Wittig-type reactions. In view of the fact that monoformyl TPP can be accessed in excellent yield (>90%) it seemed ideal for generating diversity via a common reaction. Reductive amination using sodium cyanoborohydride is a well-understood reaction,[9] but seemed to us to have been somewhat neglected in porphyrin synthetic chemistry. We therefore undertook a study to investigate the applicability of this method for generating a diverse set of monosubstituted TPPs via the readily accessible formyl derivative.



Scheme 1 *Reagents and conditions*: (i) $Cu(OAc)_2$, MeOH–$CHCl_3$, Δ; (ii) (a) $POCl_3$, DMF–DCE; (b) H_2SO_4; (c) NaOH.

A small set of aliphatic and aromatic amines (Scheme 2) were selected in order to initially test the applicability of the reductive amination reaction. The results suggested that the reaction works well, except for amines which incorporate a free carboxyl group in the structure (both 5-aminopentanoic acid and 4-carboxyaniline failed to give any product); however, the success of the reaction for the 4-carboethoxyaniline, which gave a 74% yield of the expected product **2**, suggested that carboxyl derivatives can be accessed via the ester derivatives. Aniline gave the ex-

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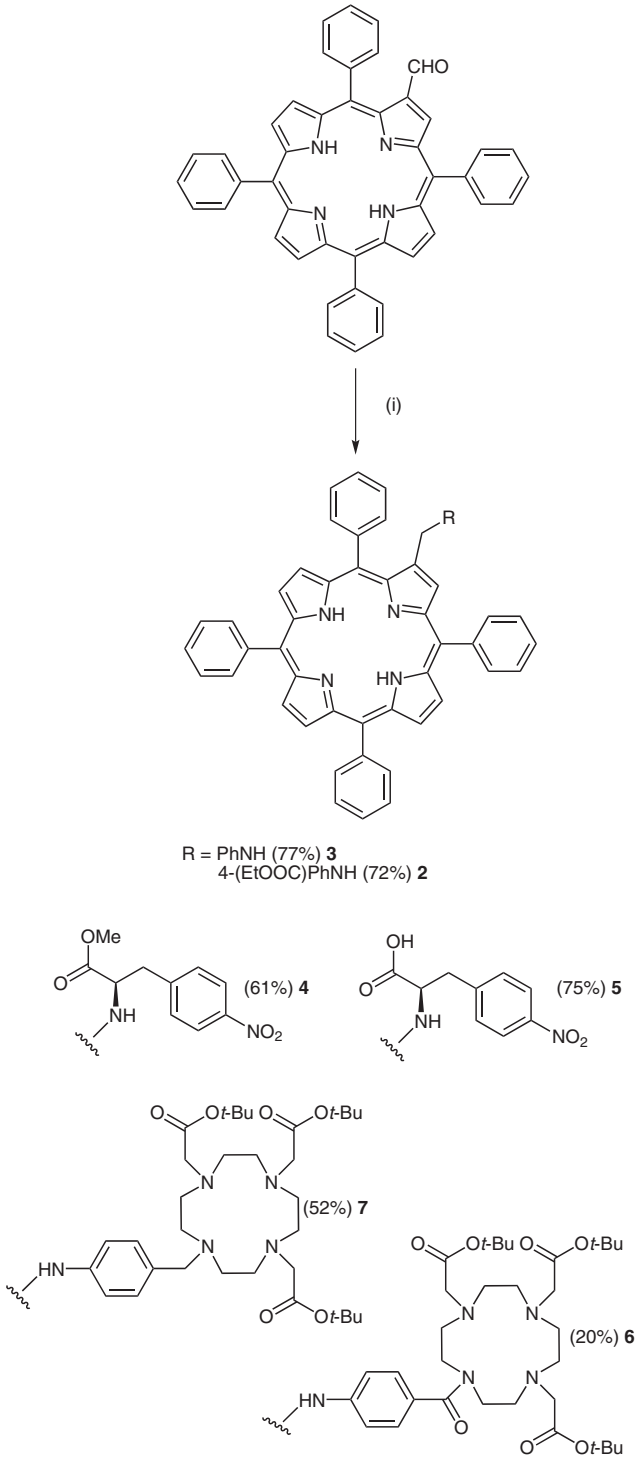
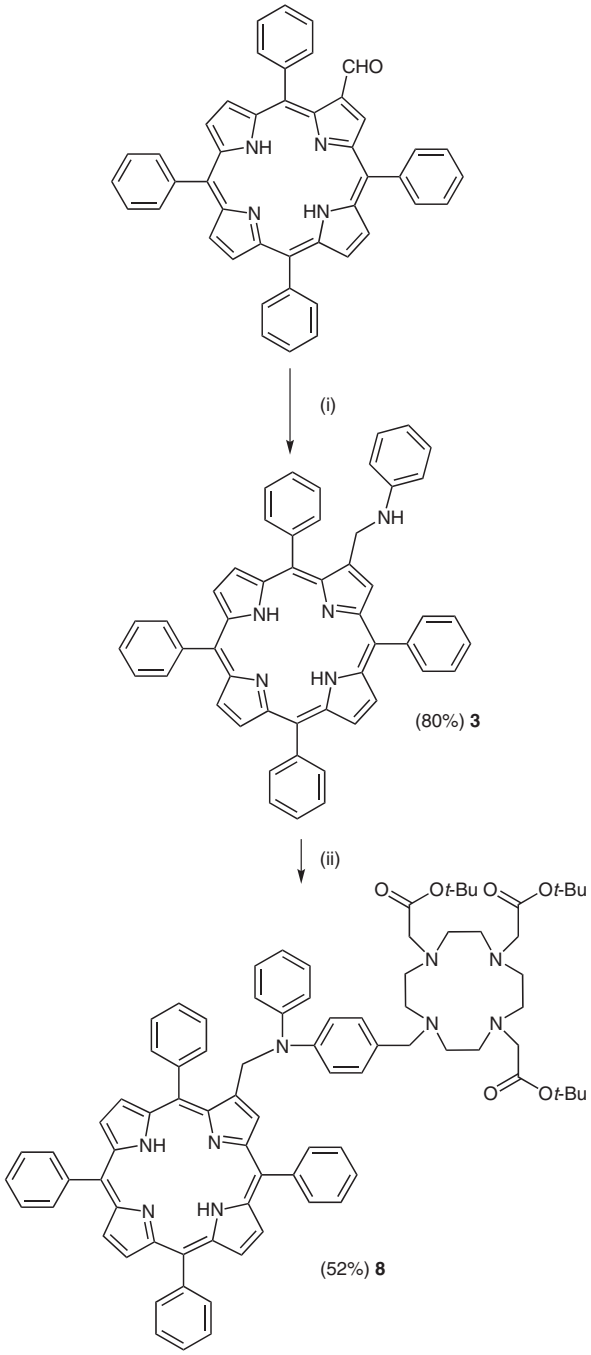


Scheme 2 *Reagents and conditions*: (i) (a) AcOH (cat.), toluene–THF, Δ; (b) $NaBH_3CN$, MeOH.



Scheme 3 *Reagents and conditions*: (i) (a) aniline, AcOH (cat.), toluene; (b) $NaBH_3CN$, MeOH; (ii) (a) 1,4-di(1-bromomethyl)benzene, Et_3N, CH_2Cl_2; (b) 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane, Et_3N.

pected secondary amine **3** in the highest yield (77%) of the four amines tested.

In order to further explore the reaction, two substrates were next selected that bore two different functional groups, nitro and carboxyl or ester-protected carboxyl, in addition to the amine required for attachment to the porphyrin. Such compounds seemed to offer the possibility of introducing two points for further diversification. The methyl ester of 4-(2-amino-2′-carbomethoxy)ethyl nitrobenzene gave the expected product **4** in 61% yield, to our surprise however, the analogous compound bearing a free carboxyl group also underwent reaction to give the desired product **5** in a higher yield of 75%. The latter result suggests that carboxyl groups *per se* do not universally preclude reaction under these conditions.

A number of important metalloenzymes contain two or more complexed metal ions which are integral to the function they perform; notable examples being nitrite reduc-

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tase,[10] and superoxide dismutase.[11] Dinucleating ligands formed with porphyrins and aza-crown macrocycles are of particular relevance to modelling the active site of cytochrome c oxidase.[12,13]

Methods for the construction of linked aza-crown–porphyrin compounds are therefore of great interest in relation to producing biomimetic systems.[14,15] The compounds would also be of interest for use in the construction of agents for detecting tumours using computed tomography or magnetic resonance imaging.[16,17] Bearing this in mind, we chose to next determine whether the reductive amination procedure could be used to conjugate a second macrocyclic ligand system to the porphyrin. Two 1,4,7,10-tetraazacyclodecane (cyclen) based ligands with single amino-presenting side arms were selected for the study, which differed in the linker through which the amino side arm was attached to the cyclen macrocycle. The first of these, in which the linking group was an amide, gave the desired product **6**, but in a rather disappointing yield of 20%. Nevertheless, given the simplicity of the reaction and steric bulk of the porphyrin and cyclen macrocycles, this still represents a convenient method with which to access a relatively complex molecular system. Repeating the reaction with an analogous cyclen, in which the carbonyl of the amide linker was replaced with a saturated carbon, resulted in a dramatic increase in the yield of product **7** to 52%, suggesting that the method is generally useful for the formation of this type of bulky porphyrin–cyclen dimer.

Finally, encouraged by the success of the majority of reactions attempted, we decided to examine the possibility of further diversifying the porphyrin by reaction of the secondary amine generated by the reductive amination reaction. Mono-formyl TPP was therefore reacted with aniline under the optimised conditions to give 80% of the *N*-phenyl-*N*′-methylporphyrinato amine **3**, which was subsequently reacted with 1,4-di(1-bromomethyl)benzene and *N*,*N*′,*N*″-tris(*tert*-butoxycarbonylmethyl)cyclen to yield the expected product **8** in 52% yield (Scheme 3). Given the extreme steric crowding in this system, the success of this reaction was extremely encouraging and suggests the method described here has potential for the construction of relatively complex multifunctional, bis-macrocylic systems.

All reagents were purchased from Lancaster Synthesis or Sigma Aldrich and used without further purification. NMR spectra were obtained on a Jeol JNM-ECP 400 MHz FT-NMR spectrometer, with chemical shifts reported in ppm relative to the residual solvent peak. UV/vis absorption spectra were recorded on an Agilent 8453 spectrometer. Analytical TLC was carried out using aluminium-backed silica gel 60 F_{254} and visualised using UV light (254/365 nm) or iodine vapour. Column chromatography was performed using ICN silica 32-63, 60 Å. Mass spectrometric analyses (ESI) were made using a Waters ZQ-4000 instrument.

Phenyl(5,10,15,20-tetraphenylporphyrin-2-ylmethyl)amine (3)

A mixture of 5,10,15,20-tetraphenylporphyrin-2-carbaldehyde[8] (0.2 g, 0.3 mmol), aniline (0.03 g, 0.3 mmol) and AcOH (2 drops) in anhydrous toluene (50 mL) was heated under reflux conditions, using a Dean–Stark head to remove H_2O from the reaction. The reaction was monitored using TLC (silica; CH_2Cl_2) until no further reaction change was observed (24 h). After cooling, $NaBH_3CN$ (0.02 g, 0.32 mmol) and MeOH (10 mL) were added and the mixture was stirred for 2 h. H_2O (100 mL) was added and the organic layer was separated, washed with brine (100 mL) and dried ($MgSO_4$). After removal of solvent in vacuo, the purple solid residue was adsorbed onto silica and separated using gravity column chromatography (silica; CH_2Cl_2). Relevant fractions were identified by TLC (silica; CH_2Cl_2), collected and concentrated to yield the product.

Yield: 0.17g (77%); purple solid; mp >350 °C (dec.); R_f = 0.28 (silica; CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –2.84 (br s, 2 H, NH), 4.15 (br s, 1 H, PhNH), 4.43 (s, 2 H, C*H*$_2$NH), 6.46 (d, ^3J = 7.8 Hz, 2 H, HN-Ar-2,6-*H*), 6.63 (t, ^3J = 7.8 Hz, 1 H, HN-Ar-4-*H*), 7.05 (t, ^3J = 7.8 Hz, 2 H, HN-Ar-3,5-*H*), 7.57–7.72 (m, 12 H, 5,10,15,20-Ar-3,4,5-H), 8.03–8.07 and 8.11–8.16 (m, 8 H, 5,10,15,20-Ar-2,6-H), 8.57 (d, ^3J = 4.8 Hz, 1 H, β-H), 8.68–8.79 (m, 5 H, β-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.2, 113.3, 117.6, 119.3, 119.4, 120.3, 120.6, 126.6, 126.7, 127.3, 127.6, 127.7, 128.5, 129.0, 133.2, 134.5, 134.6, 134.7, 141.9, 142.0, 142.2, 142.3, 148.1.

UV/Vis (CH_2Cl_2): λ_{max} = 419, 515, 549, 590, 645 nm.

MS (ESI): *m*/*z* = 720 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{51}H_{38}N_5$: 720.3122; found: 720.3109.

Ethyl 4-[(5,10,15,20-Tetraphenylporphyrin-2-ylmethyl)amino]benzoate (2)

A mixture of 5,10,15,20-tetraphenylporphyrin-2-carbaldehyde[8] (0.13 g, 0.2 mmol), ethyl 4-aminobenzoate (0.033 g, 0.2 mmol) and AcOH (2 drops) in toluene (50 mL) was heated under reflux conditions, using a Dean–Stark head to remove H_2O from the reaction. The reaction was monitored using TLC (silica; CH_2Cl_2–MeOH, 249:1) until no further reaction change was observed (30 h). After cooling, $NaBH_3CN$ (0.02 g, 0.32 mmol) and MeOH (10 mL) were added and the mixture was stirred for 2 h. H_2O (100 mL) was added and the organic layer was separated, washed with brine (100 mL) and dried ($MgSO_4$). After removal of solvent in vacuo, the purple solid residue was adsorbed onto silica and separated using gravity column chromatography (silica; CH_2Cl_2–MeOH, 249:1). Relevant fractions were identified by TLC (silica; CH_2Cl_2–MeOH, 249:1), collected and concentrated to yield the product.

Yield: 0.115g (72%); purple solid; mp >350 °C (dec.); R_f = 0.32 (silica; CH_2Cl_2–MeOH, 249:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –2.84 (br s, 2 H, NH), 1.37 (t, ^3J = 7.2 Hz, 3 H, CH_3), 4.33 (q, ^3J = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 4.51 (br d, ^3J = 4.8 Hz, 2 H, C*H*$_2$NH), 4.58 (br t, ^3J = 4.8 Hz, 1 H, PhN*H*), 6.46 (d, ^3J = 8.8 Hz, 2 H, HN-Ar-2,6-*H*), 7.65–7.78 (m, 12 H, 5,10,15,20-Ar-3,4,5-H), 7.83 (d, ^3J = 8.8 Hz, 2 H, Ar-3,5-H), 8.10–8.13 and 8.20–8.23 (m, 8 H, 5,10,15,20-Ar-2,6-H), 8.66 (d, ^3J = 4.8 Hz, 1 H, β-H), 8.74 (s, 1 H, β-H), 8.78–8.87 (m, 5 H, β-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 43.6, 60.3, 111.9, 118.9, 119.3, 119.5, 120.3, 120.7, 126.6, 126.7, 126.8, 127.2, 127.7, 127.8, 128.6, 131.3, 133.2, 134.5, 134.6, 141.8, 141.9, 142.1, 142.2, 151.7, 166.9.

UV/Vis (CH_2Cl_2): λ_{max} = 420, 516, 550, 590, 646 nm.

MS (ESI): *m*/*z* = 792 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{54}H_{42}N_5O_2$: 792.3333; found: 792.3321.

Methyl 3-(4-Nitrophenyl)-2-[(5,10,15,20-tetraphenylporphyrin-2-ylmethyl)amino]propionate (4)

To a stirred solution of 5,10,15,20-tetraphenylporphyrin-2-carbaldehyde[8] (0.16 g, 0.25 mmol) and methyl (*S*)-2-amino-3-(4-ni-

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trophenyl)propanoate[18] (0.056 g, 0.25 mmol) in a mixture of toluene (100 mL) and MeOH (30 mL), was added AcOH (0.25 mL). The dark coloured solution was heated under reflux conditions and, after 1 h, $NaBH_3CN$ (0.2 g, 3 mmol) was added and heating was continued for 48 h. The reaction was monitored by TLC (silica; CH_2Cl_2) and, after complete consumption of starting materials, the solvent was removed in vacuo. The dark solid residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL) and the organic layer was separated and dried over $MgSO_4$. After removal of solvents in vacuo, the product was isolated by column chromatography (silica; CH_2Cl_2).

Yield: 0.13g (61%); purple solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = –2.79 (br s, 2 H, NH), 3.01 (m, 2 H, NHC*H*$_2$), 3.48 (AB*X*, dd, $^3J_{X–A}$ = 7.0 Hz, $^3J_{X–B}$ = 6.7 Hz, 1 H), 3.56 (s, 3 H, $COOCH_3$), 3.84 (ABX, br d, $^2J_{A–B}$ = 16.2 Hz, 1 H), 3.98 (A*B*X, br d, $^2J_{B–A}$ = 16.2 Hz, 1 H), 7.22 (d, ^3J = 8.7 Hz, O_2N-Ar-3,5-H, 2 H), 7.75–7.78 (m, 12 H, 5,10,15,20-Ar-3,4,5-H), 7.99 (m, 4 H, O_2N-Ar-2,6-H, 5-Ar-2,6-H), 8.18–8.20 (m, 6 H, 10,15,20-Ar-2,6-H), 8.57 (d, ^3J = 4.5 Hz, 1 H, β-H), 8.76–8.84 (m, 6 H, β-*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.3, 47.2, 51.8, 61.8, 119.1, 119.2, 120.3, 120.6, 123.4, 126.6, 126.7, 126.9, 127.0, 127.7, 127.8, 128.3, 130.1, 133.2, 133.4, 134.5, 134.6, 141.9, 142.1, 142.2, 142.6, 145.2, 146.8, 174.3.

UV/Vis (CH_2Cl_2): λ_{max} = 420, 517, 549, 583, 646 nm.

MS (ESI): *m*/*z* = 851 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{55}H_{43}N_6O_4$: 851.3340; found: 851.3329.

3-(4-Nitrophenyl)-2-[(5,10,15,20-tetraphenylporphyrin-2-ylmethyl)amino]propionic Acid (5)

To a solution of 5,10,15,20-tetraphenylporphyrin-2-carbaldehyde[8] (0.75 g, 1.2 mmol) and (*S*)-4-nitrophenylalanine (0.2 g, 0.9 mmol) in THF (100 mL) was added a solution of $NaBH_3CN$ (0.11 g, 1.8 mmol) in MeOH (50 mL) and the mixture was heated under reflux conditions. The reaction was monitored by TLC (silica; CH_2Cl_2–MeOH, 95:5) until no further change was discernable (24 h). Solvent was removed in vacuo and the residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, washed with brine (2 × 30 mL) and dried over $MgSO_4$. After removal of solvent, the product was isolated using column chromatography (silica; CH_2Cl_2–MeOH, 97:3).

Yield: 0.55 g (75%); purple solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = –2.79 (br s, 2 H, NH), 3.01 (m, 2 H, NHC*H*$_2$), 3.48 (AB*X*, dd, $^3J_{X–A}$ = 7.0 Hz, $^3J_{X–B}$ = 6.7 Hz, 1 H), 3.56 (s, 3 H, COOC*H*$_3$), 3.84 (*A*BX, br d, $^2J_{A–B}$ = 16.2 Hz, 1 H), 3.98 (A*B*X, br d, $^2J_{B–A}$ = 16.2 Hz, 1 H), 7.22 (d, ^3J = 8.7 Hz, 2 H, O_2N-Ar-3,5-H), 7.75–7.78 (m, 12 H, 5,10,15,20-Ar-3,4,5-H), 7.99 (m, ^3J = 8.7 Hz, 4 H, O_2N-Ar-2,6-H, 5-Ar-2,6-H), 8.18–8.20 (m, 6 H, 10,15,20-Ar-2,6-H), 8.57 (d, ^3J = 4.5 Hz, 1 H, β-H), 8.76–8.84 (m, 6 H, β-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.3, 47.2, 51.8, 61.8, 119.1, 119.2, 120.3, 120.6, 123.4, 126.6, 126.7, 126.9, 127.0, 127.7, 127.8, 128.3, 130.1, 133.2, 133.4, 134.5, 134.6, 141.9, 142.1, 142.2, 142.6, 145.2, 146.8, 174.3.

UV/Vis (CH_2Cl_2): λ_{max} = 420, 517, 549, 583, 646 nm.

MS (ESI): *m*/*z* = 851 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{55}H_{43}N_6O_4$: 851.3340; found: 851.3329.

tert-Butyl [4,7-Bis-*tert*-butoxycarbonylmethyl-10-(4-nitrobenzoyl)-1,4,7,10-tetraazacyclododec-1-yl]acetate

To 4-nitrobenzoic acid (0.07 g, 0.4 mmol) was added $SOCl_2$ (10 mL) and the mixture was stirred at r.t. for 1 h, followed by 5 h heating under reflux conditions. When the evolution of acidic gas had finished, the $SOCl_2$ was removed in vacuo and the residue was triturated with toluene (2 × 10 mL). To the dark solid residue was added a solution of 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane hydrobromide salt[19] (0.2 g, 0.4 mmol) in anhydrous CH_2Cl_2 (25 mL) and Et_3N (0.1 mL). The reaction mixture was stirred at r.t. for 8 h under an argon atmosphere. After removal of solvent in vacuo, the crude residue was taken into CH_2Cl_2 (100 mL) and washed with H_2O (2 × 50 mL). The organic layer was separated, dried over $MgSO_4$, concentrated to a volume of ~10 mL and purified by gravity column chromatography (silica; CH_2Cl_2–MeOH, 97:3). Relevant fractions were identified by TLC (silica; CH_2Cl_2–MeOH, 97:3), collected and concentrated to yield the title compound.

Yield: 0.14 g (54%); yellow oil.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.31 [s, 9 H, $(CH_3)_3$], 1.35 [s, 9 H, $(CH_3)_3$], 1.38 [s, 9 H, $(CH_3)_3$], 2.63 (m, 8 H, 4 × NCH_2), 2.78 (t, ^3J = 6.7 Hz, 2 H, NCH_2), 2.89 (m, 2 H, NCH_2), 2.92 [s, 2 H, $CH_2C(O)$], 3.21 [s, 4 H, 2 × $CH_2C(O)$], 3.52 (t, ^3J = 6.7 Hz, 2 H, NCH_2), 3.67 (t, ^3J = 5.0 Hz, 2 H, NCH_2), 7.51 (d, ^3J = 8.9 Hz, 2 H, O_2N-Ar-2,6-H), 8.15 (d, ^3J = 8.9 Hz, 2 H, O_2N-Ar-3,5-H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 28.2, 28.3, 45.1, 49.3, 52.4, 52.8, 52.9, 53.3, 53.5, 53.5, 54.9, 55.5, 58.6, 81.0, 124.0, 128.0, 144.5, 148.2, 169.7, 170.8, 171.0.

MS (ESI): *m*/*z* = 664 $[M + H]^+$, 686 $[M + Na]^+$.

tert-Butyl [4-(4-Aminobenzoyl)-7,10-bis-*tert*-butoxycarbonylmethyl-1,4,7,10-tetraazacyclododec-1-yl]acetate

To a solution of *tert*-butyl [4,7-bis-*tert*-butoxycarbonylmethyl-10-(4-nitrobenzoyl)-1,4,7,10-tetraazacyclododec-1-yl]acetate (0.5 g, 0.75 mmol) in EtOH (25 mL) was added 5% wt Pd/C (0.1 g) and the mixture was stirred at r.t. under an H_2 atmosphere. After 2 h, TLC (silica; CH_2Cl_2–MeOH, 9:1) showed complete consumption of the starting material, and the catalyst was removed by filtration. After the solvent was concentrated in vacuo to a volume of ~5 mL, the crude mixture was separated by gravity column chromatography (silica; CH_2Cl_2–MeOH, 97:3→93:7). Relevant fractions were identified by TLC (silica; CH_2Cl_2–MeOH, 97:3), collected and concentrated to yield the title compound.

Yield: 0.34 g (71%); yellow solid.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.36 [s, 27 H, $(CH_3)_3$], 2.64 (m, 8 H, 4 × NCH_2), 2.87 (br s, 4 H, 2 × NCH_2), 3.22 (br s, 4 H, 2 × NCH_2), 3.56 [br s, 4 H, 2 × $CH_2C(O)$], 3.91 [br s, 2 H, $CH_2C(O)$], 6.52 (d, ^3J = 8.4 Hz, 2 H, O_2N-Ar-2,6-H), 7.07 (d, ^3J = 8.4 Hz, 2 H, O_2N-Ar-3,5-H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 23.9, 24.0, 52.0 (br), 52.7 (br), 55.2, 57.8 (br), 76.6, 109.9, 122.9, 124.3, 144.0, 166.8, 167.9.

tert-Butyl (4,7-Bis-*tert*-butoxycarbonylmethyl-10-{4-[(5,10,15,20-tetraphenylporphyrin-2-ylmethyl)amino]benzoyl}-1,4,7,10-tetraazacyclododec-1-yl)acetate (6)

To a heated solution of 5,10,15,20-tetraphenylporphyrin-2-carbaldehyde[8] (0.20 g, 0.31 mmol) and *tert*-butyl [4-(4-aminobenzoyl)-7,10-bis-*tert*-butoxycarbonylmethyl-1,4,7,10-tetraazacyclododec-1-yl]acetate (0.17 g, 0.27 mmol) in THF (30 mL), was added AcOH (0.1 mL) followed by a solution of $NaBH_3CN$ (0.1 g, 1.5 mmol) in MeOH (10 mL). The mixture was heated under reflux conditions and monitored by TLC (silica; CH_2Cl_2–MeOH, 9:1) until all the starting material had been consumed (3 d). The solvent was removed in vacuo and CH_2Cl_2 (100 mL) was added to the dark solid residue. After washing with H_2O (100 mL), the organic layer was dried over $MgSO_4$ and the volume reduced to ~10 mL. The crude mixture was separated by gravity column chromatography (silica; CH_2Cl_2–MeOH, 97:3→9:1). Relevant fractions were identified by TLC (silica; CH_2Cl_2–MeOH, 97:3), collected and concentrated to yield the desired product.

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Yield: 0.07 g (20%); purple solid.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = –2.91 (br s, 2 H, NH), 1.35 [s, 27 H, $(CH_3)_3$], 2.61–3.28 [m, 18 H, 8 × NCH_2, $CH_2C(O)$], 3.51 [br s, 4 H, 2 × $CH_2C(O)$], 4.38 (s, 2 H, C*H*$_2$NHPh), 6.38 (d, ^3J = 8.3 Hz, 2 H, O_2N-Ar-3,5-H), 7.06 (d, ^3J = 8.3 Hz, 2 H, O_2N-Ar-2,6-H), 7.61–7.68 (m, 12 H, 5,10,15,20-Ar-3,4,5-H), 8.03 (d, ^3J = 7.9 Hz, 4 H, 5,10-Ar-2,6-H), 8.10 (m, 4 H, 15,20-Ar-2,6-H), 8.56 (d, ^3J = 4.8 Hz, 1 H, β-H), 8.70–8.77 (m, 6 H, β-*H*).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 28.2, 28.3, 43.8, 52.0, 54.1, 55.2, 81.1, 112.5, 119.8, 121.1, 127.1, 127.2, 127.7, 128.1, 128.7, 133.6, 134.9, 134.9, 135.0, 142.2, 142.3, 142.5, 142.7, 171.0.

MS (ESI): *m*/*z* (%) = 1260 $[M + H]^+$, 1282 (100) $[M + Na]^+$.

UV/Vis (CH_2Cl_2): λ_{max} = 419, 515, 549, 592, 646 nm.

tert-Butyl (4,7-Bis-*tert*-butoxycarbonylmethyl-10-{4-[(5,10,15,20-tetraphenylporphyrin-2-ylmethyl)amino]benzyl}-1,4,7,10-tetraazacyclododec-1-yl)acetate (7)

To a heated solution of 5,10,15,20-tetraphenylporphyrin-2-carbaldehyde[8] (0.23 g, 0.36 mmol) and 1,4,7-tris(*tert*-butoxycarbonylmethyl)-10-(4-aminobenzyl)-1,4,7,10-tetraazacyclododecane[20] (0.20 g, 0.32 mmol) in THF (50 mL) under an inert (N_2) atmosphere, was added AcOH (0.1 mL) followed by a solution of $NaBH_3CN$ (0.05 g, 0.8 mmol) in MeOH (20 mL). The mixture was heated under reflux conditions and monitored by TLC (silica; CH_2Cl_2–MeOH, 95:5) until all the starting material had been consumed (5 d). The solvent was removed in vacuo and CH_2Cl_2 (100 mL) added to the dark solid residue. After washing with H_2O (100 mL) the organic layer was separated and dried over $MgSO_4$ and the volume reduced to ~10 mL. The crude mixture was separated by gravity column chromatography (silica; CH_2Cl_2–MeOH, 99:1→95:5). Relevant fractions were identified by TLC (silica; CH_2Cl_2–MeOH, 95:5), collected and concentrated to yield the desired product.

Yield: 0.21 g (52%); purple solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = –2.77 (br s, 2 H, NH), 1.45 [s, 27 H, $(CH_3)_3$], 2.08–2.80 (m, 16 H, 8 × NCH_2), 2.93–3.05 [m, 4 H, 2 × $CH_2C(O)$], 3.18 (s, 2 H, NCH_2Ph), 3.25–3.35 [m, 2 H, $CH_2C(O)$], 4.47 (s, 2 H, C*H*$_2$NHPh), 6.47 (d, ^3J = 8.3 Hz, 2 H, HN-Ar-3,5-*H*), 7.18 (d, ^3J = 8.3 Hz, 2 H, HN-Ar-2,6-*H*), 7.65–7.82 (m, 12 H, 5,10,15,20-Ar-3,4,5-H), 8.10–8.16 (m, 4 H, 5,10-Ar-2,6-H), 8.17–8.27 (m, 4 H, 15,20-Ar-2,6-H), 8.66 (d, ^3J = 4.8 Hz, 1 H, β-H), 8.76–8.88 (m, 6 H, β-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9, 27.9, 44.1, 49.4, 55.7, 55.9, 56.0, 58.9, 82.1, 82.5, 113.3, 119.2, 119.3, 120.4, 120.8, 126.1, 126.6, 126.7, 126.8, 127.2, 127.6, 127.8, 128.4, 130.9, 133.3, 134.5, 134.6, 141.8, 142.1, 142.5, 147.5, 172.6, 173.5.

MS (ESI): *m*/*z* = 1246 $[M + H]^+$.

UV/Vis (CH_2Cl_2): λ_{max} = 419, 516, 549, 593, 646 nm.

tert-Butyl [4,7-Bis-*tert*-butoxycarbonylmethyl-10-(4-{[phenyl(5,10,15,20-tetraphenylporphyrin-2-ylmethyl)amino]methyl}benzyl)-1,4,7,10-tetraazacyclododec-1-yl]acetate (8)

To a solution of compound **3** (0.05 g, 0.07 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (2 drops) and α,α-dibromoxylene (0.018 g, 0.07 mmol), and the mixture was stirred at r.t. Monitoring of the reaction mixture by TLC (silica; CH_2Cl_2) showed consumption of the α,α-dibromoxylene after 4 h. A solution of *tert*-butyl (4,7-bis-*tert*-butoxycarbonylmethyl-1,4,7,10-tetraazacyclododec-1-yl)acetate (0.035 g, 0.07 mmol) in CH_2Cl_2 (5 mL) was added. After heating under reflux conditions for a further 3 d, TLC (silica; CH_2Cl_2–MeOH, 9:1) showed consumption of starting compound **3**. CH_2Cl_2 (100 mL) was added, the solution was washed with H_2O (100 mL) and the organic layer was collected and dried ($MgSO_4$). Following filtration, the solution was concentrated to a small volume (~10 mL) and purified by gravity column chromatography (silica; CH_2Cl_2–MeOH, 9:1). Relevant fractions were identified by TLC (silica; CH_2Cl_2–MeOH, 9:1), collected and concentrated to yield compound **8**.

Yield: 0.044 g (52%); purple solid; mp >350 °C; R_f = 0.44 (silica; CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.05 (br s, 2 H, NH), 1.48 [s, 9 H, $C(CH_3)_3$], 1.49 [s, 18 H, $C(CH_3)_3$], 2.80–2.94 (m, 12 H, NCH_2CH_2N), 3.01–3.10 (m, 4 H, NCH_2CH_2N), 3.29 [s, 2 H, $(CH_2COt\text{-}Bu)$], 3.38 [s, 4 H $(CH_2COt\text{-}Bu)$], 3.42 (s, 2 H, NCH_2-Ph), 4.46 (s, 2 H, NCH_2-Ph), 4.59 (s, 2 H, CH_2NPh), 6.38 (d, ^3J = 7.9 Hz, 2 H, CH_2-Ar-*H*), 6.83–6.89 (m, 1 H, N-Ar-4-H), 6.90–6.99 (m, 4 H, N-Ar-2,6-H and CH_2-Ar-*H*), 7.24–7.31 (m, 2 H, N-Ar-3,5-H), 7.68–7.84 (m, 12 H, 5,10,15,20-Ar-3,4,5-H), 8.00–8.04 and 8.05–8.10 (m, 4 H, Ar-2,6-H), 8.14–8.20 (m, 4 H, Ar-2,6-H), 8.62 (d, ^3J = 4.8 Hz, 1 H, β-H), 8.71 (s, 1 H, β-H), 8.75–8.80 (m, 2 H, β-H), 8.83 (d, ^3J = 4.8 Hz, 1 H, β-H), 8.89–8.91 (m, 2 H, β-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.13, 28.17, 47.4, 48.8 (br), 49.1, 49.7, 51.2, 52.2, 53.4, 55.1, 58.0, 58.4, 81.6, 81.7, 113.5, 117.9, 119.4, 120.3, 120.7, 124.4, 126.7, 126.8, 126.9, 127.4, 128.0, 128.8, 128.9, 129.2, 130.9, 133.1, 134.3, 134.4, 134.5, 141.0, 141.3, 141.6, 141.8, 150.3, 169.6, 170.5.

UV/Vis (CH_2Cl_2): λ_{max} = 420, 516, 551, 589, 646 nm.

MS (ESI): *m*/*z* = 1337 $[M + H]^+$.

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