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Dendritic metalloporphyrins with a *distal* H-bond donor as mimics of haemoglobin †

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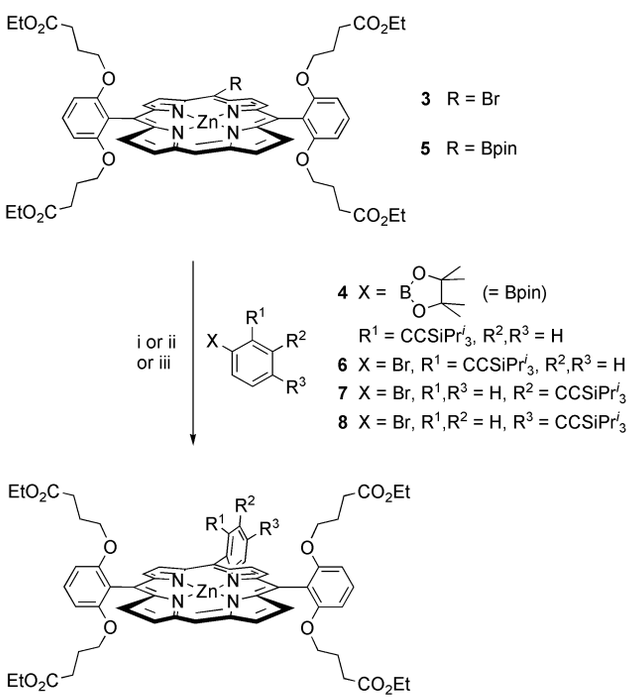
We report the synthesis of iron(II) porphyrins functionalised with first- and second-generation dendrons as mimics of haemoglobin. The porphyrin core bears an ethynyl linker pointing towards the centre of the molecule, in an ideal position for the introduction of a series of *distal* ligands as potential H-bond donors by Pd⁰-catalysed Sonogashira cross-coupling.

Tetrameric haemoglobin (Hb) is an efficient transport protein for O_2 in aerobic organisms; a highly conserved *distal* histidine located near the binding site of the Fe^{II} heme co-factor is thought to play a crucial role in fine-tuning the ligand binding affinities and selectivities critical for aerobic life. Free Fe^{II} heme binds CO *ca*. 20 000 times more strongly than O_2, but in Hb and myoglobin (Mb) this factor is reduced to 200 and 25, respectively. Based on early X-ray crystal structures of HbCO and MbCO,[1] it was assumed[2] that steric hindrance by the *distal* histidine side chain discriminates against the linear CO-binding geometry in favour of the coordination of O_2 which shows an intrinsically bent binding mode. More recent X-ray crystal structure analyses of HbCO[3] and MbCO,[4] however, revealed an approximately linear Fe–C≡O bond geometry with distortions too small to account for the discrimination between O_2 and CO. H-bonding and electrostatic effects are therefore assumed to represent the primary factors influencing gas binding affinities in Fe^{II} heme proteins.[5] Polar pocket effects on O_2 and CO coordination have been analysed in a series of model systems,[6] and support for the formation of an H-bond between a peripheral (*distal*) H-bond donor and bound O_2 was obtained by site-directed mutagenesis of Mb[7] and Hb[8] and studies of synthetic metalloporphyrin–O_2 complexes.[9]

Investigations of dendritic Hb mimics[10,11] provided evidence for influences of the dendritic shell on O_2 complexation.[12,13] A comparison of gas binding data for five-coordinate Fe^{II} porphyrins surrounded by secondary amide- and ester-linked dendrons suggested a stabilising effect of the amide moieties on the formed O_2-adducts. A postulated H-bond between metal-ion-bound O_2 and the secondary amide H–N moieties, however, could not be demonstrated by electron paramagnetic resonance (EPR) studies on the corresponding Co^{II} porphyrin analogues.[14] The question therefore remained open whether micropolarity effects—possibly resulting from different hydrodynamic volumes of the amide- and ester-containing dendrimers—or H-bonding was responsible for the observed increased stability of the Fe^{II}–O_2 complex within the amide-containing system.

For further investigations, it seemed desirable to precisely position—in analogy to Hb and Mb—*distal* H-bond donor groups above the gas binding site of the dendritic metalloporphyrin. Here we describe the synthesis of dendritic models for Hb of first- and second-generation (G1 and G2) with a series of *distal* ligands that could potentially form an H-bond with metal-ion-coordinated O_2. The five-coordinate high-spin ($S = 2$) Fe^{II} porphyrin in the *T*(tense)-state was formed by the addition of an excess of 1,2-dimethylimidazole (dmim),[15] and some preliminary O_2 and CO binding studies are reported.

The synthesis of the targeted dendrimer required the intermediate preparation of *meso*-triphenylporphyrins **1** or **2** (Scheme 1) bearing an *ortho*-(trialkylsilyl)acetylene substituent on the central *meso*-aryl ring and anchors for dendron attachment on the other two *meso*-rings in the *trans*-position. In previous work,[16] this substitution pattern on the porphyrin core had been conveniently obtained by Suzuki cross-coupling



	R^1	R^2	R^3
1	$CCSiMe_3$	H	H
2	$CCSiPr^i_3$	H	H
9	H	$CCSiPr^i_3$	H
10	H	H	$CCSiPr^i_3$
11	Br	H	H

Scheme 1 Suzuki cross-couplings of porphyrins with *meso*-halogen or boronic ester substituents. *Reagents and conditions:* i, **3**, **4**, $[Pd(PPh_3)_4]$, Cs_2CO_3, PhMe–THF 1 : 1, reflux, 14 h, 0% (**2**); ii, **5** and **6**, **7** or **8**, $[Pd(PPh_3)_4]$, Cs_2CO_3, PhMe–THF 1 : 1, reflux, 14–20 h, 0% (**2**), 41% (**9**), 59% (**10**); iii, **5**, 1-bromo-2-iodobenzene, $[Pd(PPh_3)_4]$, Cs_2CO_3, PhMe, reflux, 6 h, 63% (**11**).

† Electronic supplementary information (ESI) available: procedures for the synthesis of **1** and **5** and iron(II) insertion into the dendritic porphyrins including full spectral characterisation and complete EPR characterisation of the complex **22·Co(dmim)** and the corresponding oxygenated complex. See http://www.rsc.org/suppdata/ob/b2/b212468h/

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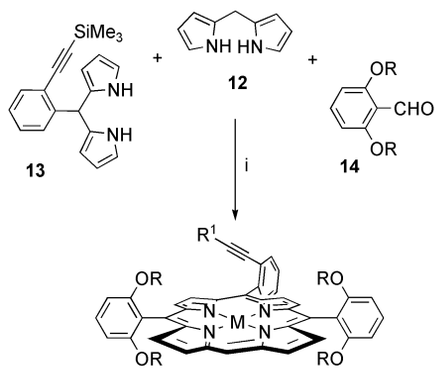
between a *meso*-brominated trans-*meso*-diarylated porphyrin and a phenylboronic ester. Much to our surprise, the Pd°-mediated cross-coupling between bromoporphyrin **3**[16] and 2-phenyl-1,3,2-dioxaborolane **4**, with an *ortho*-(triisopropylsilyl)acetylene substituent afforded a complex product mixture. ‡ In contrast, the control reaction of **4** with bromobenzene yielded almost exclusively the expected biphenyl derivative. Similarly, when the boronic ester-substituted porphyrin **5** was coupled with the *ortho*-alkynylated bromobenzene derivative **6**, traces of **2** were detected by mass spectrometry, but no product could be isolated. On the other hand, coupling of **5** with bromobenzene derivatives **7** and **8**, bearing $Pr^i_3Si–C\equiv C–$ residues in the *meta*- and *para*-position, respectively, afforded the desired coupling products **9** and **10** in good yield.

In a new approach, 1-bromo-2-iodobenzene was first coupled with boronic ester **5** to yield *meso*-triarylated porphyrin **11**. However, all attempts to subsequently introduce $Me_3Si–C\equiv C–$ or $Pr^i_3Si–C\equiv C–$ substituents by Sonogashira cross-coupling under formation of **1** or **2** failed. Indeed, while such reactions of *meta*- and *para*-bromo- and iodoaryl rings in the *meso*-position of porphyrins have found wide application,[17] no such couplings have been reported in the *ortho*-position.

The desired porphyrin **1** was finally prepared in 17% yield by a mixed condensation of the two dipyrromethanes **12** and **13**[18] with aldehyde **14**[19] (ratio 1 : 2 : 3), followed by repeated chromatography (SiO_2-*H*; $CHCl_3$–EtOAc 97 : 3) to separate the multiple porphyrin products[17b,20] formed in the reaction (Scheme 2). Tetracarboxylic acid **15** with a free ethynyl residue, required for anchoring both the dendrons and the *distal* H-bond donor fragment, was subsequently formed in near quantitative yield by basic hydrolysis.



Scheme 2 Synthesis of porphyrins with appended ethynyl groups. *Reagents and conditions:* i, trifluoroacetic acid (TFA), CH_2Cl_2, r.t., 18 h; then *p*-chloranil, reflux, 1 h, 17% (**1**), 5% (**16**); ii, aq. NaOH, dioxane, r.t., 48 h, quant.; iii, $Zn(OAc)_2$ (10 equiv.), $CHCl_3$–MeOH 1 : 1, r.t., 14 h, quant.

By a similar condensation, we also prepared tris-*meso*-arylated porphyrin **16** and converted it into the Zn^{II} complex **17**. Gratifyingly, the latter gave crystals suitable for X-ray analysis upon slow evaporation of a CH_2Cl_2–MeOH mixture. In the crystal, the two enclosed MeOH molecules are involved in short intermolecular contacts. MeOH(1) coordinates to the Zn^{II} centre of **17** with a binding distance Zn(1)–O(56) of 2.16 Å and a Zn(1)–O(56)–C(57) angle of 122°. It is also in contact with its neighboring MeOH(2), the O(56)–O(58) distance being 2.74 Å. MeOH(2) again makes a short contact to **17**, with an O(58)–O(31) distance of 2.93 Å (see Fig. 1). As a result of the 5-fold coordination, the Zn^{II} ion is pulled out of the mean porphyrin plane by *ca*. 0.3 Å. The Zn^{II}–MeOH(1) binding mode resembles the bent geometry of heme Fe^{II}–O_2 complexes, and this

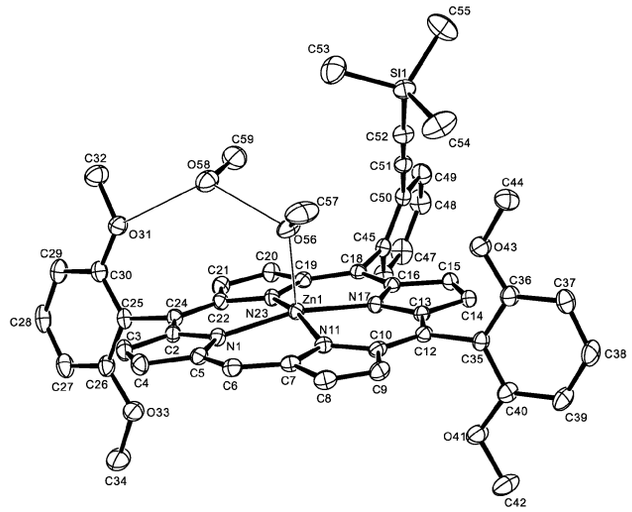


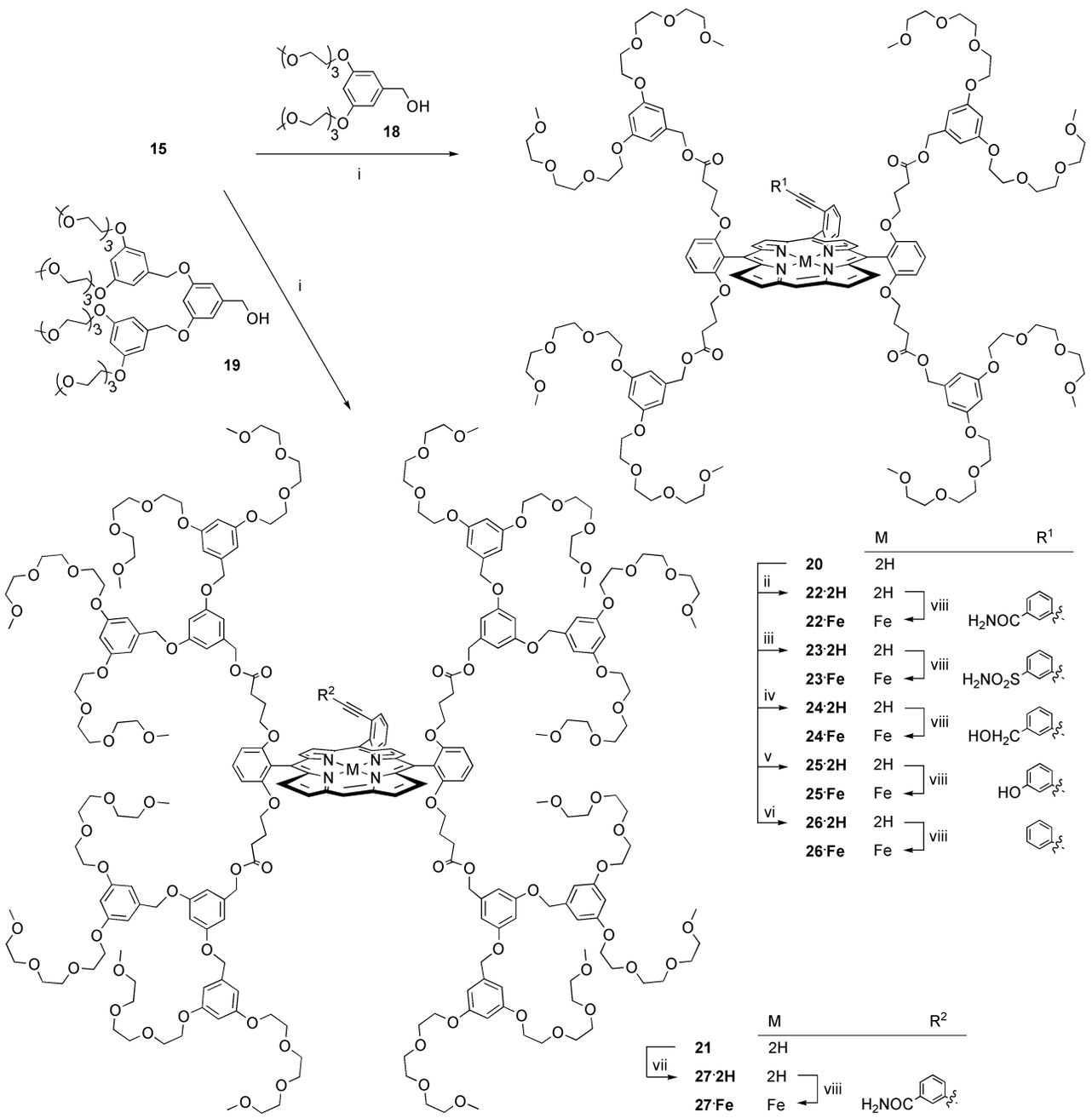
Fig. 1 X-ray crystal structure of the Zn^{II} porphyrin solvate **17**·2 MeOH. Atomic displacement parameters obtained at 203 K are drawn at the 30% probability level. Hydrogen atoms are omitted.

comparison suggests that a distal H-bonding residue, anchored above the Fe^{II} porphyrin by the phenethynyl spacer, would not sterically interfere with O_2-binding, thereby confirming predictions from computer-assisted molecular modeling studies in the early phase of the project.[21] The Si atom of the trimethylsilyl group is located approximately above C(16) of the porphyrin subunit. The shortest distance (neglecting H-atoms) between the trimethylsilyl group and MeOH(1) (C(53)–O(56)) is 4.09 Å. The absolute value of the dihedral angle C(46)–C(45)–C(18)–C(19), which defines the relative orientation of porphyrin and phenethynyl fragments, amounts to *ca.* 66°.

Esterification of **15** with modified Fréchet-type aryl ether dendrons[22,23] of first (G1; **18**) and second (G2; **19**) generation provided dendrimers **20** and **21** as highly viscous oils in 80% and 66% yield, respectively, after purification by preparative gel permeation chromatography (BioRad BioBeads S-X1; CH_2Cl_2) (Scheme 3). The *distal* H-bond donors, consisting of aromatic carboxamide and sulfonamide, benzyl alcohol and phenolic residues, were subsequently introduced by Sonogashira cross-coupling.[17] This reaction required high temperatures of 90 to 160 °C, depending on the nature of the donor fragment introduced, providing the G1 target compounds **22·2H–25·2H**, the corresponding phenyl derivative **26·2H** as a control compound lacking the donor site and the G2 derivative **27·2H**.

Iron(II) insertion into **22·2H–27·2H** was carried out with $FeBr_2$ under N_2 and afforded the corresponding Fe^{II} porphyrins **22·Fe–27·Fe**. In toluene in a glove box, the five-coordinate high-spin complexes with a Soret-band at 435 nm (characteristic absorbance for trisarylated porphyrins[16a]) were immediately formed upon addition of 300 equiv. of dmim in the case of the G1 dendrimers, whereas the coordination proceeded slowly with the G2 derivative, even in the presence of 1000 equiv. of dmim as monitored by UV/Vis spectroscopy. All computer modeling investigations suggested that, for steric reasons, dmim ligation can only occur on the porphyrin face opposite to the one covered by the aromatic H-bond donor.

Upon addition of CO, the Soret band of **22·Fe(dmim)–27·Fe(dmim)** shifted hypsochromically to 421 nm, indicative of quantitative formation of the corresponding six-coordinate complexes. CO gas binding was reversible, and the initial five-coordinate compounds could be quantitatively recovered after 4–7 freeze, pump and thaw cycles. Oxygenation did not result in a defined Fe^{II}–O_2 complex as rapid decomposition to iron(III) species[24] took place immediately, even in the case of the second-generation dendrimer **27·Fe(dmim)**. The mechanism of the



Scheme 3 Synthesis of the dendritic iron(II) porphyrins **22·Fe**–**27·Fe** of first and second generation. *Reagents and conditions:* i, **18** (5 equiv.) or **19** (5 equiv.), *N*,*N*′-dicyclohexylcarbodiimide (DCC, 5 equiv.), 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 1 equiv.), 1-hydroxybenzotriazole (HOBt, cat.), abs. THF, r.t., 3 d, 80% (**20**), 66% (**21**); ii, 3-iodobenzamide (2 equiv.), $[PdCl_2(PPh_3)_2]$, PhMe–NEt_3 2 : 1, 90 °C, 3 h, 57%; iii, 3-iodobenzenesulfonamide (2 equiv.), $[PdCl_2(PPh_3)_2]$, 1,2-dichlorobenzene (DCB)–NEt_3 1 : 1, 160 °C, 1 h, 54%; iv, 3-iodobenzyl alcohol (2 equiv.), $[PdCl_2(PPh_3)_2]$, PhMe–NEt_3 1 : 1, 110 °C, 2 h, 45%; v, 1-bromo-3-[(*tert*-butyldimethylsilyl)oxy]benzene (2 equiv.), $[PdCl_2(PPh_3)_2]$, DCB–NEt_3 1 : 1, 120 °C, 6 h; then Bu_4NF, THF, r.t., 10 min, 21%; vi, bromobenzene (2 equiv.), $[PdCl_2(PPh_3)_2]$, PhMe–NEt_3 2 : 1, 80 °C, 14 h, 63%; vii, 3-iodobenzamide (2 equiv.), $[PdCl_2(PPh_3)_2]$, DCB–NEt_3 1 : 1, 110 °C, 16 h, 16%; viii, $FeBr_2$ (10 equiv.), 2,6-lutidine, abs. THF, r.t., 2–4 d, quant.

oxidative decomposition was not further analysed. Finally, the O_2 complexes of the dendritic porphyrins **22·Co**^{II}–**24·Co**^{II} and **26·Co**^{II} in the presence of dmim as axial base were prepared, as evidenced by their characteristic EPR spectra. The frozen solution EPR spectra are typical of those for oxygenated Co^{II} complexes with magnetic parameters comparable to values reported in the literature (see Electronic Supplementary Information †).[14,25] Multidimensional and multifrequency pulse EPR experiments[14,26] are planned in order to investigate the formed O_2 complexes; by this technique,[27] possible H-bond interactions between Co^{II}-coordinate O_2 and the *distal* H-bond donors could be revealed.

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Notes and references

‡ All new compounds were fully characterised by UV/Vis, IR, ^1H and ^{13}C NMR, and mass spectrometry and for the non-dendritic compounds, microanalysis was performed. Spectroscopic characterisation of **27·2H**: viscous purple oil; λ_{max}(PhMe)/nm 400sh (ε/dm^3 mol^{-1} cm^{-1} 64 400), 417 (313 200), 510 (16 900), 542 (4 200), 586 (5 100) and 640 (1 300); $\nu_{max}(CCl_4)$/cm^{-1} 2877, 1735, 1678, 1597, 1456, 1350, 1296, 1249, 1172, 1147 and 1110; δ_H(500 MHz; $CDCl_3$; Me_4Si) 10.02 (1 H, s), 9.19 (2 H, d, *J* 4.6), 8.90 (2 H, d, *J* 4.6), 8.80 (2 H, d, *J* 4.7), 8.75 (2 H, d, *J* 4.7), 8.19–8.17 (1 H, m), 7.85–7.83 (1 H, m), 7.63 (2 H, t, *J* 8.5), 7.71–7.67 (1 H, m), 7.60–7.56 (1 H, m), 7.02–7.00 (1 H, m), 6.95 (4 H, d, *J* 8.5), 6.55 (8 H, d, *J* 2.1), 6.52 (8 H, d, *J* 2.1), 6.52–6.36 (22 H, m), 4.89–4.85 (16 H, m), 4.76–4.66 (8 H, m), 4.51 (1 H, br s), 4.05–4.00 (32 H, m), 3.89–3.83 (8 H, m), 3.79–3.74 (32 H, m), 3.67–3.59 (96 H, m), 3.51–3.48 (32 H, m), 3.334 (24 H, s), 3.328 (24 H, s), 3.10–3.13 (2 H, br s), 1.52–1.06 (16 H, m) and −2.88 (2 H, br s); δ_C(125 MHz; $CDCl_3$; Me_4Si) 172.4

(2×), 166.4, 160.0 (2×), 159.9 (2×), 159.5, 159.3, 148.3–144.8 (br, 4×), 145.3, 139.0, 138.9, 138.4 (2×), 134.2, 132.9, 132.3, 131.2, 131.4–130.3 (br, 4×), 130.5, 130.4 (2×), 128.4, 128.2, 127.7, 126.9, 122.2, 119.5, 117.4, 111.8, 106.9, 106.8, 106.1, 106.0, 105.4, 105.3, 104.4, 101.6, 101.5, 101.1 (2×), 93.2, 91.0, 71.9 (2×), 70.70, 70.69, 70.54 (2×), 70.47 (2×), 69.9 (2×), 69.6 (2×), 67.4 (2×), 67.1, 67.0, 65.7, 65.5, 59.0 (2×), 29.5, 29.3, 23.7 and 23.4; *m*/*z* (HR-MALDI-MS, 2,5-dihydroxybenzoic acid (DHB)) 4892.3362 (MH^+, $C_{259}H_{352}O_{85}N_5$ requires 4892.3370).

§ *X-ray crystal structure of* **17**. Crystal data at 203 K for $(C_{47}H_{40}N_4O_4Zn)\cdot 2\,(CH_3OH)$ [M_r = 882.37]: orthorhombic, space group $P2_12_12_1$ (no. 19), D_c = 1.339 g cm^{-3}, Z = 4, a = 12.3217(2) Å, b = 15.4829(2) Å, c = 22.9369(2) Å, V = 4375.8(1) Å^3. Bruker–Nonius Kappa-CCD diffractometer, MoKα radiation, λ = 0.7107 Å. A red crystal, obtained by evaporation of a MeOH–CH_2Cl_2 solution (linear dimensions *ca.* 0.3 × 0.15 × 0.13 mm), was mounted at low temperature to prevent evaporation of enclosed solvents. The structure was solved by direct methods (*SIR92*)[28] and refined by full-matrix least-squares analysis (*SHELXL-97*),[29] using an isotropic extinction correction, and $w = 1/[\sigma^2(F_o^2) + (0.027P)^2 + 1.868P]$, where $P = (F_o^2 + 2F_c^2)/3$. All heavy atoms were refined anisotropically (H-atoms isotropically, whereby H-positions are based on stereochemical considerations). Final $R(F)$ = 0.037, $wR(F^2)$ = 0.076 for 602 parameters and 8737 reflections with $I > 2\sigma(I)$ and $2.4 < \theta < 27.5°$ (corresponding *R*-values based on all 9896 reflections are 0.047 and 0.081 respectively). Absolute structure parameter = 0.002(7). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. CCDC reference number 199402. See http://www.rsc.org/suppdata/ob/b2/b212468h/ for crystallographic files in .cif or other electronic format. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge, UK CB2 1EZ (Fax: +44(1223) 336 033; E-mail: deposit@ccdc.cam.ac.uk).

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