Synthesis of dendritic polypyridines with ethoxycarbonyl groups as surface functionality

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The convergent synthesis of dendritic polypyridines having an outer tier of pyridine rings 2,6-difunctionalized with ethoxycarbonyl groups is described. The dendritic fragments were prepared using 4-benzyloxy-2,6-bis(chloromethyl)pyridine and diethyl 4-hydroxypyridine-2,6-dicarboxylate as the building blocks. The final step in the synthesis was the coupling of the dendritic fragments to the trifunctional core 1,3,5-tris(bromomethyl)benzene. The data obtained by spectroscopic techniques correlate well with the structures proposed.

Introduction

Dendritic structures can be constructed by either a divergent or a convergent synthetic strategy.[1-3] In the divergent growth method, the synthesis begins at the core of the macromolecule and proceeds outwards building up branches. In the convergent growth method however, the synthesis proceeds inwards starting from what will become the outer surface of the final macromolecule. The first objective in this approach is the synthesis of large dendritic fragments, which, finally, are attached to a polyfunctional core.

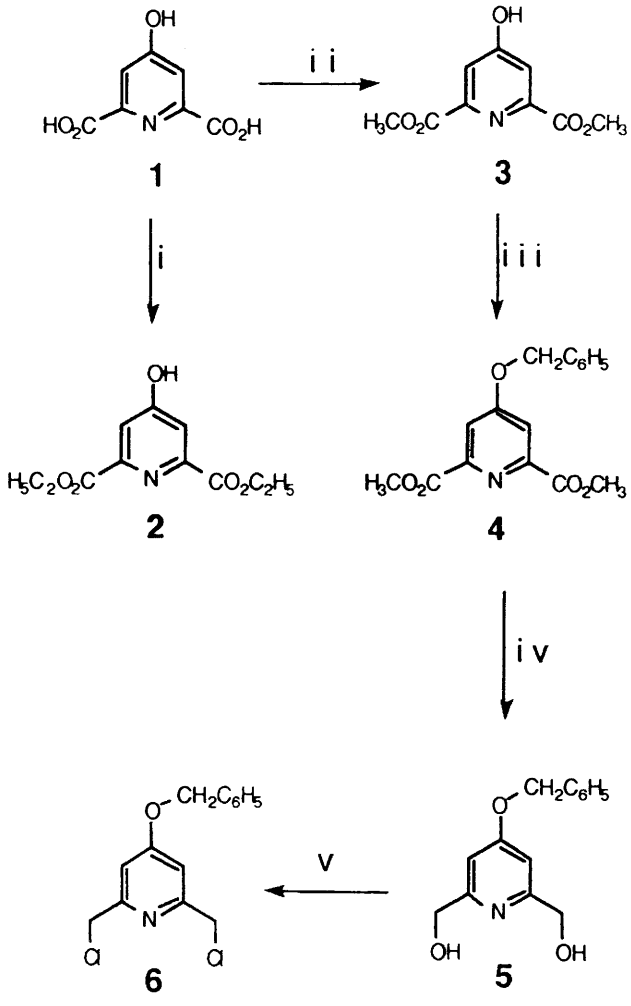
Although both methodologies have been successfully applied to the preparation of a wide variety of dendrimer families, it appears that the convergent strategy allows a better control both of the molecular weights and functional group placements within the macromolecule.[4] In this regard, the preparation of dendrimers with modifiable surface functionalities is particularly attractive because their transformation to other functional groups can modify the compound's material properties. Recent studies on dendritic polyesters have in fact demonstrated that modification of the surface functionality has a significant effect on the solubility and the glass transition temperature of these macromolecules.[5]

Taking into consideration both these factors and the current interest in novel dendritic structures, we report here the synthesis by a convergent route of a dendritic polypyridine, which has its outer tier of pyridine rings 2,6-difunctionalized with ethoxycarbonyl groups. The ester group was chosen as surface functionality because it can be readily transformed into other functional groups, as suggested by previous studies in this field.[6-9] The results of this study include the preparation of dendritic fragments which consist of pyridine nuclei symmetrically attached to one another by ether linkages and preparation of the macromolecule obtained by coupling these dendritic fragments to a trifunctional core.

Results and discussion

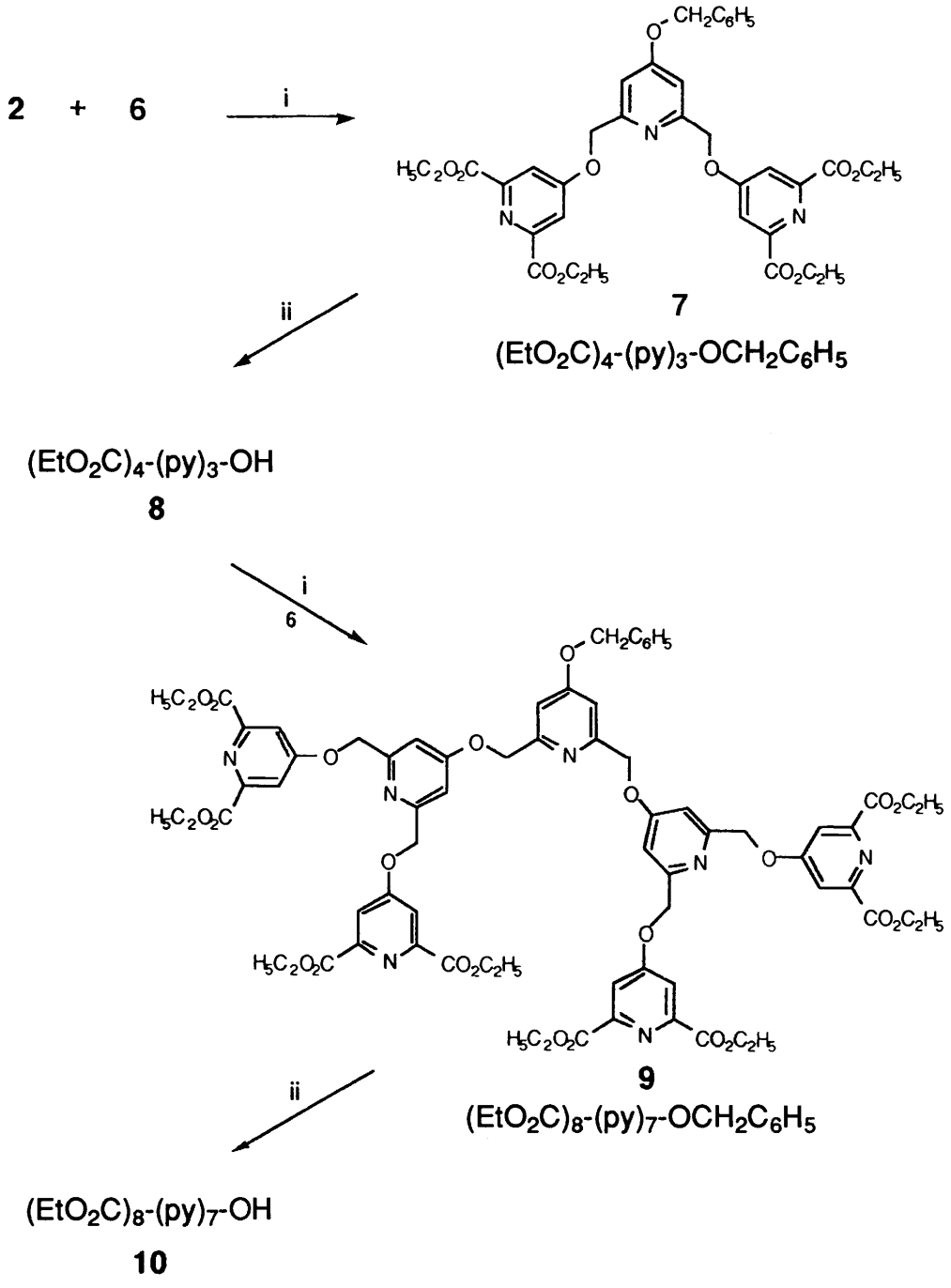
To obtain a dendrimer by a convergent route with ester groups on the outer surface of the macromolecule, diethyl 4-hydroxypyridine-2,6-dicarboxylate **2** was chosen as the starting material. This derivative was preferred to the methyl ester analogue because of its higher solubility in organic solvents. In practice **2** was obtained (91%) from the commercially available 4-hydroxypyridine-2,6-dicarboxylic acid (chelidamic acid) **1** using the esterification chemistry we have previously used for the preparation of the methyl ester analogue.[10]

The other starting material was 4-benzyloxy-2,6-bis(chloromethyl)pyridine **6**, prepared by the four step procedure shown in Scheme 1. Chelidamic acid **1** was esterified in methanol containing $SOCl_2$ to give the dimethyl ester **3**, (75–82%) which was treated with benzyl bromide in the presence of K_2CO_3 in DMF to give **4** (85%). Compound **4** can also be obtained[10] in 82% yield by similar experimental conditions using benzyl chloride and caesium carbonate in DMF. Compound **4** was then converted into the biscarbinol **5** (83%)



Scheme 1 *Reagents:* i, EtOH, $SOCl_2$; ii, MeOH, $SOCl_2$; iii, $C_6H_5CH_2Br$, K_2CO_3; iv, $NaBH_4$; v, $SOCl_2$. Reaction scheme for the synthesis of the monomeric units.

† By IUPAC nomenclature, the BH_4^- ion 'borohydride' is now correctly known as boranuide.

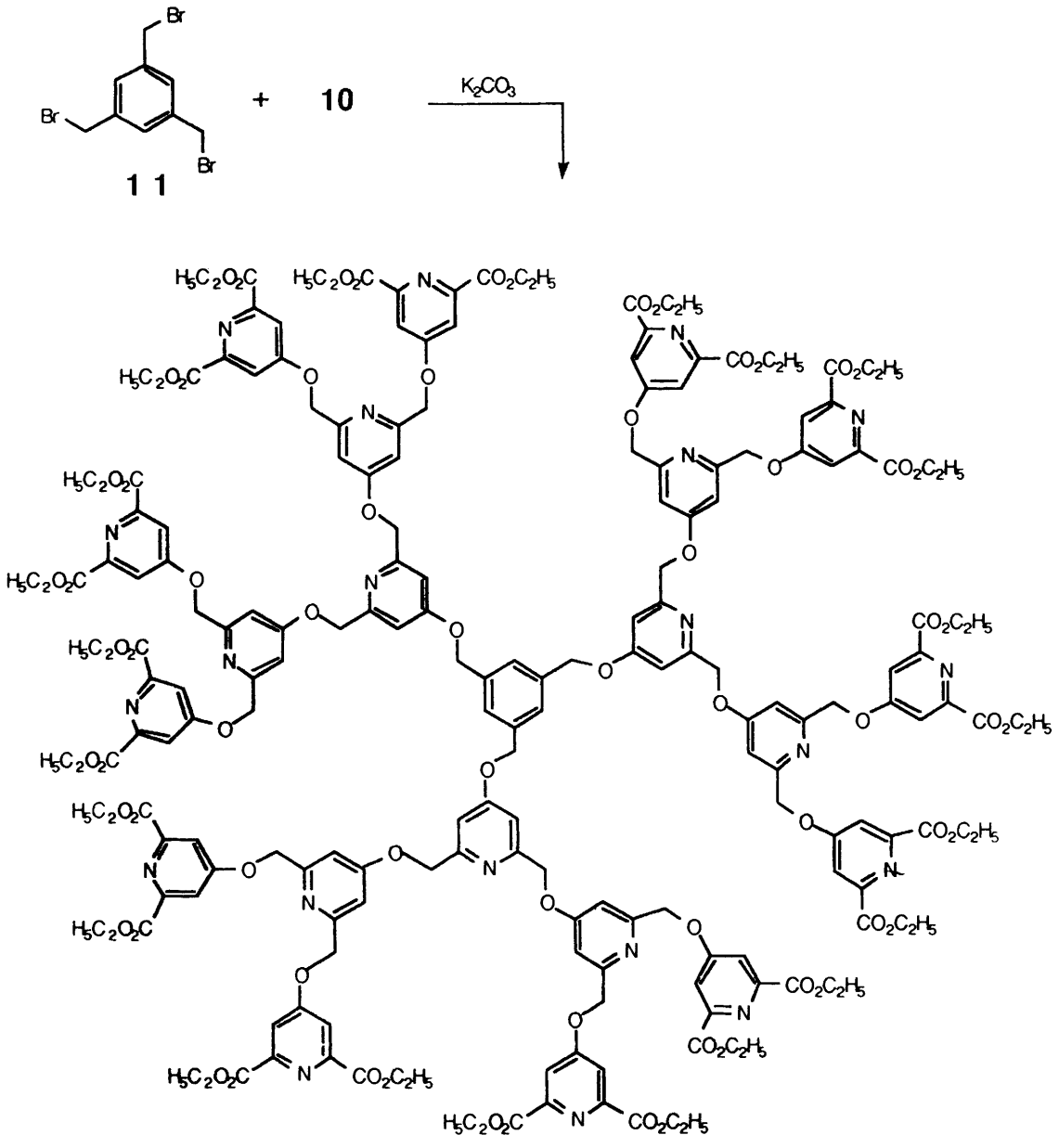


Scheme 2 *Reagents:* i, K_2CO_3; ii, H_2, Pd/C. Reaction scheme for the synthesis of the ethyl ester-terminated dendritic fragments.

by reduction with sodium borohydride.†[10] Treatment of **5** with $SOCl_2$ afforded the desired chloromethyl derivative **6** (93%). Coupling two molecules of **2**, which in our case represents the first generation compound, to the dichloride **6** occurred satisfactorily, as outlined in Scheme 2, in the presence of anhydrous K_2CO_3 in DMF at 70–80 °C. This reaction gave the second generation dendritic fragment **7** (93%) containing four ethoxycarbonyl groups after chromatographic purification and recrystallization.

Tetraester **7** was readily characterized by its ^1H NMR spectrum which shows the ester signals at δ_H 1.44 and 4.47, two sharp singlets for the benzyl methylene at δ_H 5.14 and 5.29 and three singlets at δ_H 7.04, 7.37 and 7.88 corresponding to two, five and four aromatic protons, respectively. The resonances in the ^{13}C spectrum of **7** were also consistent with the proposed structure. The benzyl-blocked fragment **7** was then reduced to the 4-hydroxypyridine derivative **8** (77%) by hydrogenolysis with palladium on carbon. After hydrogenolysis no residual methylene and aromatic protons belonging to the benzyl group were observed in the ^1H NMR spectrum of **8**. This spectrum is worthy of some comments. Apart from the signals due to the ethyl and the methylene groups, the ^1H NMR ($CDCl_3$) spectrum of **8** shows three broad resonances centred at δ_H 6.9 (2 H, 3,5-pyH), 7.7 (4 H, 3′,5′-pyH) and 11.5 (1 H). On lowering the temperature to 253 K (below which value compound **8** precipitates) each resonance split into two, giving rise to three separate couples of signals at δ_H 6.65 (0.7 H) and 6.95 (1.3 H), at 7.53 (1.4 H) and 7.78 (2.6 H) and at 12.12 (0.66 H) and 12.74 (0.34 H). These data are in agreement with a slow room temperature pyridone–hydroxypyridine tautomeric exchange which can be resolved at 253 K.

Reaction of hydroxy compound **8** with the dichloride **6**, as above, gave the third generation octaester **9** (89%). The ^1H NMR spectrum of the dendrimeric fragment **9** is similar to that of **7** except for additional signals at δ_H 5.0–5.3 and 7.0–8.0, respectively. Integration of all the peaks present and comparison with each other confirmed not only the structure of **9** but also the generation number. Removal of the benzyl moiety



Scheme 3 Reaction scheme for the synthesis of the dendrimer **12** containing 24 ethoxycarbonyl groups

from **9** was accomplished by catalytic hydrogenolysis to give **10** (61%) and the debenzylation was confirmed by the disappearance in the ^1H NMR and ^{13}C spectra of **10** of the signals attributed to the benzyl group. However, the catalytic hydrogenolysis of the benzyl protected fragments proved to be a critical step in our synthetic strategy. On the basis of TLC analysis the reactions appeared to be completed in 1 h or less. Longer reaction times gave side products and caused diminished yields of isolated products. This phenomenon is more remarkable for **10** rather than **8** and therefore it could become a limiting factor for the preparation of dendritic fragments of higher generation.

After **10** was obtained, it was coupled to a trifunctional core as shown in Scheme 3. The core was chosen to be 1,3,5-tris(bromomethyl)benzene **11** because this allowed us to employ the same coupling chemistry used to prepare the benzyl protected dendritic fragments. Compound **11** was synthesized by the selective free radical bromination of mesitylene with *N*-bromosuccinimide in CCl_4,[11] and was then coupled with **10** to afford the dendrimer **12** in 56% yield after purification. The structure of **12** was confirmed by its ^1H NMR spectrum (Fig. 1), in which the proton resonances of the core were observed at δ_H 5.15 and 7.53, while before coupling the corresponding peaks were at δ_H 4.45 and 7.35, respectively. The assigned structure of compound **12** was also consistent with its ^{13}C NMR spectrum. In addition to ^1H and ^{13}C NMR spectroscopy, the prepared compounds were also characterized by FT-IR, FAB mass spectroscopy and elemental analysis (see Experimental section). Unfortunately, the nominal molecular weight of the dendritic macromolecule **12** could not be confirmed by FAB mass spectroscopy due to instrument and technique limitations.

The combustion analysis data for compounds **9**, **10** and **12** were outside of acceptable limits, probably due to inclusion of water and/or solvent molecules; for example, the experimental values for $[(EtO_2C)_8\text{-}(py)_7\text{-}O]_3\text{-}[C_6H_3(CH_2)_3]$ **12** (C, 59.6; H, 5.1; N, 7.2%) are consistent with $[(EtO_2C)_8\text{-}(py)_7\text{-}O]_3\text{-}[C_6H_3(CH_2)_3]\cdot 2H_2O$ which requires C, 59.86; H, 5.20; N, 7.19%. On the other hand, the inclusion of impurities and solvent

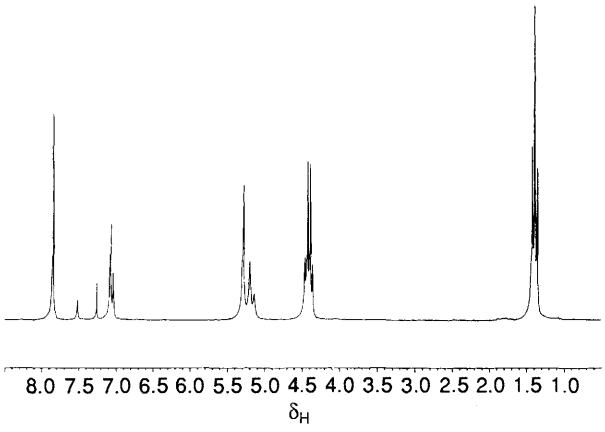


Fig. 1 200 MHz ^{1}H NMR spectrum ($CDCl_3$) of compound $[(EtO_2C)_8\text{-}(py)_7\text{-}O]_3\text{-}[C_6H_3(CH_2)_3]$ **12**

molecules within the dendritic structure is a known phenomenon, which appears to increase with the increase in molecular size.[12]

Conclusions

The present work demonstrates the usefulness of the convergent growth approach to the synthesis up to the third generation of a dendritic polypyridine with modifiable surface funtionality. The synthetic strategy developed to prepare the dendritic wedges employs the benzyl group to protect the hydroxyl functionality located at the focal point. Nevertheless, removal of this functional group by catalytic hydrogenolysis was found to be a critical step, which could prevent the preparation of larger dendritic polypyridines. Work is currently in progress to extend this approach to the preparation of dendritic structures of higher generation and investigate the reactivity of the surface functional groups.

Experimental

Melting points were measured in capillary tubes with a Buchi 535 apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the University of Padua. IR spectra were obtained on a Bio-Rad Digilab FTS-40 spectrophotometer. ^{1}H NMR spectra were obtained in $CDCl_3$ solutions, unless otherwise indicated, on a Bruker AC 200 spectrometer. ^{13}C NMR were obtained at 50 MHz on a Bruker AC 200 spectrometer using $CDCl_3$ solutions, except where noted, and the solvent carbon signal was used as internal standard. *J* Values are given in Hz. Mass spectra were obtained on an Analytical 70–70 EQ mass spectrometer with FAB ionisation in a matrix of acetonitrile–H_2O–bis(2-hydroxyethyl)disulfide–saturated aq. oxalic acid (92:4.5:3:0.5). Analytical TLC was performed on commercial Merck plates with silica gel GF_{254} (0.25 mm thick). *N*,*N*-Dimethylformamide (DMF) was purified by distillation from CaH_2 and stored over 4 Å molecular sieves in a dark bottle.[13] Thionyl chloride was distilled before use. Other solvents and reagents were used without further purification.

Diethyl 4-hydroxypyridine-2,6-dicarboxylate 2
4-Hydroxypyridine-2,6-dicarboxylic acid (chelidamic acid) **1** (45.79 g, 0.25 mol) was added to a solution of thionyl chloride (146 cm^3, 2 mol) in ethanol (500 cm^3) cooled to −10 °C. The mixture was stirred at room temperature for 24 h and then refluxed for an additional 2 h. After cooling, the mixture was concentrated under reduced pressure to give a residue, which was treated with water (400 cm^3). The resultant suspension, cooled to 0 °C, was neutralized with 10% aq. Na_2CO_3 and filtered. The solid material was dried and recrystallized from ethanol–water (1:2) and dried under reduced pressure at 75 °C to give the diester **2** as white crystals (91%), mp 124–125 °C (lit.,[14] 120–121 °C) (Found: C, 55.5; H, 5.5; N, 5.9. Calc. for $C_{11}H_{13}NO_5$: C, 55.22; H, 5.48; N, 5.86%); ν_{max}(KBr)/cm^{-1} 1740, 1728, 1605, 1570, 1459, 1337 and 1243; δ_H([$^2H_6$]acetone) 1.36 (6 H, t, *J* 7.1, CH_2CH_3), 4.38 (4 H, q, *J* 7.1, CH_2CH_3) and 7.64 (2 H, s, 3,5-pyH); δ_C([$^2H_6$]acetone) 14.34, 62.43, 116.47, 149.69, 164.84 and 168.35.

Dimethyl 4-hydroxypyridine-2,6-dicarboxylate 3
This compound was prepared in 75–82% yield from **1** as described previously.[10]

Dimethyl 4-benzyloxypyridine-2,6-dicarboxylate 4
This product was prepared in 85% yield by treatment of **3** (10.56 g, 50 mmol) in DMF (100 cm^3) with benzyl bromide (9.4 g, 55 mmol) and K_2CO_3 (6.9 g, 50 mmol) according to the published procedure.[10]

4-Benzyloxy-2,6-bis(hydroxymethyl)pyridine 5
This compound was prepared in 83% yield from **4** as described previously.[10]

4-Benzyloxy-2,6-bis(chloromethyl)pyridine 6
4-Benzyloxy-2,6-bis(hydroxymethyl)pyridine **5** (12.3 g, 50 mmol) was added to thionyl chloride (100 cm^3) precooled to 0 °C. The solution was heated at 60 °C for 4 h, cooled and the excess of thionyl chloride was removed under reduced pressure. Crushed ice was added to the residue and the resultant suspension (250 cm^3) was neutralized with 10% aq. Na_2CO_3 and filtered. The solid material was dried and recrystallized from ethanol to give **6** as white crystals (93%), mp 101–101.5 °C (Found: C, 59.8; H, 4.7; Cl, 24.9; N, 5.0. Calc. for $C_{14}H_{13}Cl_2NO$: C, 59.59; H, 4.64; Cl, 25.13; N, 4.96%); ν_{max}(KBr)/cm^{-1} 1595, 1452, 1340, 1162 and 1034; δ_H 4.62 (4 H, s, CH_2Cl), 5.16 (2 H, s, $OCH_2C_6H_5$), 7.05 (2 H, s, 3,5-pyH) and 7.43 (5 H, s, C_6H_5); δ_C 46.36, 70.06, 108.69, 127.51, 128.42, 128.66, 135.14, 157.88 and 166.42.

$(EtO_2C)_4$-$(py)_3$-OCH_2Ph 7
A mixture of **2** (5.26 g, 22 mmol) and anhydrous K_2CO_3 (3.04 g, 22 mmol) in dry DMF (50 cm^3) was stirred at room temp. under reduced pressure for 30 min, after which the dichloride **6** (2.82 g, 10 mmol) was added and the reaction mixture was heated at 70–80 °C for 24 h under an atmosphere of argon. The mixture was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 (300 cm^3) and water (200 cm^3). The organic extract was washed with 1% aq. acetic acid (2 × 200 cm^3) and water (2 × 200 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was column chromatographed (SiO_2) eluting with 5% methanol in $CHCl_3$ and recrystallization from ethanol afforded **3** as a white crystalline solid (93%), mp 134.5–135 °C (Found: C, 62.95; H, 5.45; N, 6.1. Calc. for $C_{36}H_{37}N_3O_{11}$: C, 62.88; H, 5.42; N, 6.11%); ν_{max}(KBr)/cm^{-1} 1716, 1597, 1343, 1249, 1120 and 1106; δ_H 1.44 (12 H, t, *J* 7.1, CH_2CH_3), 4.47 (8 H, q, *J* 7.1, CH_2CH_3), 5.14 (2 H, s, $CH_2C_6H_5$), 5.29 (4 H, s, OCH_2py), 7.04 (2 H, s, 3,5-pyH), 7.37 (5 H, s, C_6H_5) and 7.88 (4 H, s, 3′,5′-pyH); δ_C 14.17, 62.41, 70.30, 70.75, 107.71, 114.53, 127.50, 128.55, 128.75, 135.08, 150.37, 156.66, 164.51, 166.18 and 166.70; *m*/*z* (FAB) 688.

$(EtO_2C)_4$-$(py)_3$-OH 8
A stirred solution of the benzyl ether protected tetraester **7** (6.88 g, 10 mmol) in acetic acid (100 cm^3) with 10% Pd/C (1.5 g) was hydrogenated at room temp. for 1 h. The mixture was then filtered through Celite and the filtrate was evaporated under reduced pressure to afford a viscous oil, which was precipitated from ethanol with water. The resultant solid was recrystallized

from ethyl acetate and dried under reduced pressure at 50 °C to give **4** as a crystalline solid (77%), mp 174–175 °C (Found: C, 57.95; H, 5.3; N, 6.9. Calc. for $C_{29}H_{31}N_3O_{11}$: C, 58.29; H, 5.23; N, 7.03%); ν_{max}(KBr)/cm^{-1} 1723, 1600, 1378, 1341, 1255 and 1107; δ_H 1.32 (12 H, t, *J* 7.1, CH_2CH_3), 4.35 (8 H, q, *J* 7.1, CH_2CH_3), 5.20 (4 H, s, OCH_2py), 6.89 (2 H, broad s, 3,5-pyH), 7.74 (4 H, broad s, 3′,5′-pyH) and 11.1–12.1 (1 H, broad s); *m*/*z* (FAB) 598.

$(EtO_2C)_8$-(py)$_7$-OCH_2Ph 9

Compound **9** was synthesized from **6** (1.41 g, 5 mmol) and **8** (6.57 g, 11 mmol) in DMF (100 cm^3) containing K_2CO_3 (1.52 g, 11 mmol) by the procedure and work-up described above for the preparation of **7**. The crude product was recrystallized twice from $CHCl_3$–ethanol (1:2, 150 cm^3) and finally dried under reduced pressure at 50 °C to give **9** as an amorphous white solid (89%) (Found: C, 60.2; H, 5.1; N, 6.9. Calc. for $C_{72}H_{73}N_7O_{23}$: C, 61.58; H, 5.24; N, 6.98%); ν_{max}(KBr)/cm^{-1} 1718, 1597, 1342, 1249, 1157 and 1107; δ_H 1.43 (24 H, t, *J* 7.1, CH_2CH_3), 4.45 (16 H, q, *J* 7.1, CH_2CH_3), 5.12 (2 H, s, $CH_2C_6H_5$), 5.20 (4 H, s, OCH_2py), 5.31 (8 H, s, OCH_2py), 7.01 (2 H, s, 3,5-pyH), 7.09 (4 H, s, 3′,5′-pyH), 7.36 (5 H, s, C_6H_5) and 7.89 (8 H, s, 3″,5″-pyH); δ_C 14.12, 62.39, 70.21, 70.35, 70.64, 107.41, 107.54, 114.48, 127.59, 128.47, 128.66, 135.05, 150.31, 156.83, 156.93, 164.43, 166.10, 166.25 and 166.61; *m*/*z* (FAB) 1404.

$(EtO_2C)_8$-(py)$_7$-OH 10

Compound **9** (5.62 g, 4 mmol) was hydrogenated in acetic acid (250 cm^3) with 10% Pd/C (600 mg) for 1 h. The catalyst was filtered off and the filtrate was evaporated to give a residue which was precipitated from $CHCl_3$ with ethanol. The product was then purified by chromatography (SiO_2) eluting with 5% methanol in $CHCl_3$ and recrystallized from ethyl acetate to give **10** as an amorphous white solid (61%) (Found: C, 58.6; H, 5.05; N, 7.4. Calc. for $C_{65}H_{67}N_7O_{23}$: C, 59.4; H, 5.14; N, 7.46%); ν_{max}(KBr)/cm^{-1} 1725, 1596, 1342, 1252, 1160 and 1108; δ_H 1.41 (24 H, t, *J* 7.1, CH_2CH_3), 4.43 (16 H, q, *J* 7.1, CH_2CH_3), 5.15 (4 H, s, OCH_2py), 5.29 (8 H, s, OCH_2py), 6.71 (2 H, s, 3,5-pyH), 6.98 (4 H, s, 3′,5′-pyH) and 7.85 (8 H, s, 3″,5″-pyH); δ_C 14.05, 62.39, 70.30, 70.63, 107.51, 108.66, 114.50, 150.17, 156.51, 156.67, 164.30, 165.86, 166.12 and 166.30; *m*/*z* (FAB) 1314.

[$(EtO_2C)_8$-(py)$_7$-O]$_3$[$C_6H_3(CH_2)_3$] 12

1,3,5-Tris(bromomethyl)benzene **11** (178.5 mg, 0.5 mmol) was treated with the hydroxy derivative **10** (2.17 g, 1.65 mmol) and K_2CO_3 (228 mg, 1.65 mmol) in DMF (50 cm^3) as described above for **7**. After the usual work-up, the crude product was treated twice with $CHCl_3$–ethanol (1:3, 120 cm^3) and then cooled. The product precipitated as a thick viscous material, which was chromatographed on silica gel eluting with 5% methanol in $CHCl_3$ and dissolved in CH_2Cl_2. Addition of this solution to diethyl ether gave **12** as an amorphous white solid (56%) (Found: C, 59.6; H, 5.1; N, 7.2. Calc. for $C_{204}H_{207}N_{21}O_{69}$: C, 60.4; H, 5.14, N, 7.25%); ν_{max}(KBr)/cm^{-1} 1718, 1596, 1341, 1248, 1157 and 1106; δ_H 1.40 (72 H, t, *J* 7.1, CH_2CH_3), 4.42 (48 H, q, *J* 7.1, CH_2CH_3), 5.15 (6 H, s, CH_2 of core), 5.21 (12 H, s, OCH_2py), 5.29 (24 H, s, OCH_2py), 7.04 (6 H, s, 3,5-pyH), 7.08 (12 H, s, 3′,5′-pyH), 7.53 (3 H, s, ArH of core) and 7.85 (24 H, s, 3″,5″-pyH); δ_C 14.08, 62.34, 69.68, 70.45, 70.64, 107.31, 107.52, 114.43, 127.34, 136.38, 150.26, 156.85, 157.09, 164.38, 166.04, 166.20 and 166.35.

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