New enantiomerically pure oligomeric macrocycles based on a 3,4-dihydroxypyrrolidine nucleus

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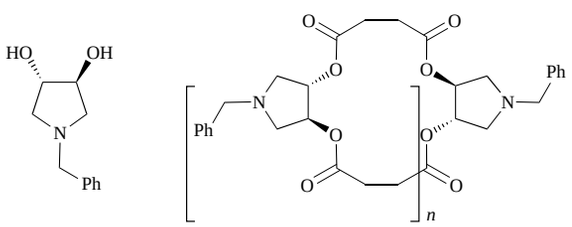
(3*S*,4*S*)-*N*-Benzyl-3,4-dihydroxypyrrolidine 1 has been used as a building block for new enantiopure macrocyclic polyesters. Two different synthetic approaches are presented leading to complementary results. The structure of the macrocycles synthesized has been confirmed by NMR spectroscopy and FAB mass spectrometry, and that for dimer 8 has been confirmed by X-ray analysis.

Introduction

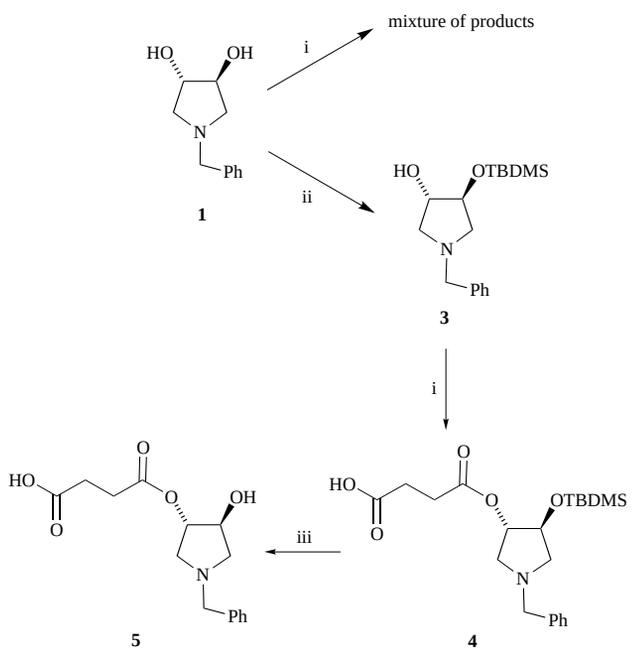
Many natural compounds active as ionophores, like enniatin, valinomycin[1] and enterobactin,[2] consist of optically pure macrocyclic polyesters constructed by symmetrical repetition of identical subunits. In the light of our interest in designing new chiral materials for molecular recognition we referred strictly to what can be learned from Nature and we focused on the synthesis of new macrocyclic polyesters incorporating the chiral *trans*-3,4-dihydroxypyrrolidine **1** unit. The choice of this building block resides in the easy availability, in multigram scale, of compound **1** in both enantiomeric forms from D- or L-tartaric acid.[3] The C_2 symmetry of diol **1** is able to confer interesting stereochemical properties to the intermediate and final products. The presence of a basic nitrogen atom could cooperatively work in molecular recognition of organic and inorganic compounds, or serve as a reacting site for derivatization (attachment of other molecules or a solid phase). As a first example of our approach we report here the successful synthesis of two new chiral macrocyclic polyesters of general structure **2** with their complete characterization including the X-ray analysis of one of them.



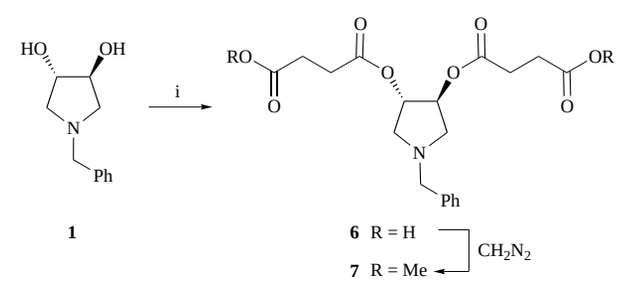
1 **2**

Results and discussion

The succinic acid subunit was chosen as the linker between the pyrrolidine subunits for its flexibility and size compatibility with the macrocyclic rings. Our initial approach suggested the homopolymerization of compound **5** (Scheme 1), whose synthesis was, however, troublesome. The simple reaction of diol **1** with 1 mol equiv. of succinic anhydride afforded a complex mixture of compounds. Alternatively, the reaction of diol **1** with *tert*-butyldimethylsilyl chloride (TBDMSCl) afforded the monoprotected derivative **3** in low yield (21%), besides the starting material and the *O*-diprotected pyrrolidine, which could be recycled. The monoprotected diol **3** reacted with succinic anhydride to afford compound **4**. Desilylation of compound **4** with KF gave compound **5** in modest yield (21%) and low purity, making the overall process useless for synthetic purposes.



Scheme 1 *Reagents and conditions*: (i) succinic anhydride, CH_2Cl_2, 40 °C, 3 h; (ii) TBDMSCl, imidazole, DMF, room temp., 12 h; (iii) KF, 18-crown-6, CH_3CN, 81 °C, 7 h



Scheme 2 *Reagents and conditions*: (i) succinic anhydride, CH_2Cl_2, 40 °C, 2 h

We then turned our attention to the diacid **6**, which was produced quantitatively from reaction of diol **1** with 2 mol equiv. of succinic anhydride (Scheme 2). The diacid **6** was fully characterized after conversion into the corresponding dimethyl ester **7**.

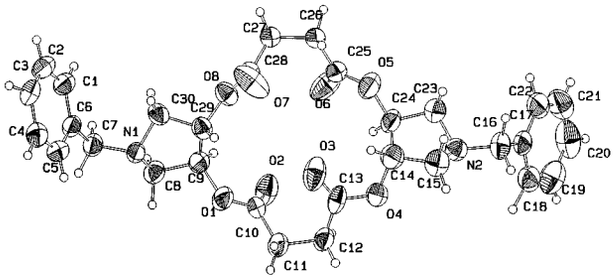
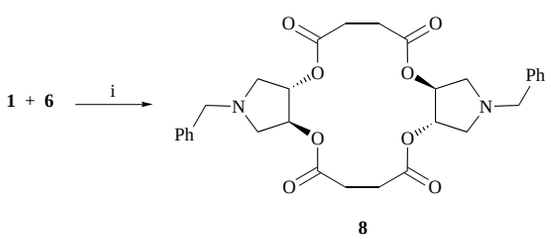


Fig. 1 X-Ray crystal structure of compound **8**, with crystallographic numbering scheme

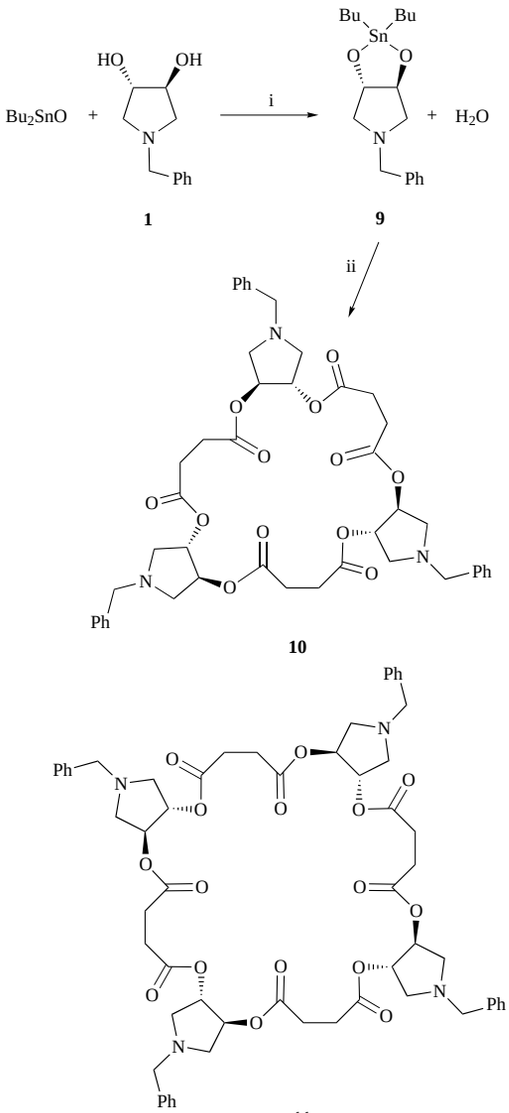
Reaction of diacid **6** with diol **1** in presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) as activating agent in refluxing 1,4-dioxane afforded a mixture of polymeric compounds from which only one cyclic oligomeric compound with structure **8** could be isolated, in 11% yield (Scheme 3). The structural assignment of product **8** was



Scheme 3 *Reagents and conditions*: (i) EDC, 1,4-dioxane, 100 °C, 18 h

easily made with the help of a fast-atom bombardment (FAB) mass spectrum, which showed a peak at *m*/*z* 551 corresponding to the mass of a dimeric compound. The low number of peaks in the ^{1}H and ^{13}C NMR spectra testified to the high symmetry of the product and confirmed the cyclic nature of compound **8**. The diagnostic signal in the ^{1}H NMR spectrum was the broad singlet at δ 5.32, corresponding to the hydrogen atoms at positions 3 and 4 on the pyrrolidine rings, which were deshielded by ~1 ppm with respect to the corresponding signal of the pyrrolidine **1**. Integration of signals gave a 1:2 ratio for the methine protons with the methylenic protons of the succinic groups, according to the theoretical ratio for a cyclic oligomer. The ^{13}C NMR spectrum confirmed the structure assignment, showing two sharp signals, one for the four methylenic carbons of succinic acid (δ_C 29.3) and one for the four ester groups.

A single-crystal X-ray analysis of compound **8** was the conclusive structural proof, and gave an insight into the arrangement of groups in the macrocyclic ring. The C_2 symmetry of the pyrrolidine nuclei is transferred to the whole molecule, with the carbonyl groups arranged alternatively on opposite sides of the main plane as well as the two pyrrolidine rings (Fig. 1). The C_2 axis lies on the main plane of the molecule and passes through the succinic fragments. Carboxylic oxygen atoms 2, 3, 6 and 7 (crystallographic numbering scheme) experience large thermal motion, which is a pre-requisite to favour host–guest interactions. Compound **8** is, anyway, a 16-membered tetralactone and probably still too small and rigid to work efficiently as a ligand. We then turned our attention to alternative synthetic methods which might afford larger rings. Another synthetic approach towards macrocyclic esters is the one introduced by Schanzer and co-workers.[4] This method requires the formation of a dioxastannolane from dibutyltin oxide and a diol, followed by reaction with the acyl dichloride of a dicarboxylic acid. It has been widely used for the synthesis of polyesters,[5] and it is reported to afford mixtures of cyclic derivatives from dimer up to higher oligomers with very good yields. The use of this methodology on our substrate, a cyclic diol with a basic nitrogen, afforded, *via* the postulated dioxastannolane **9**, a polymeric mixture from which trimer **10** and tetramer **11** were



Scheme 4 *Reagents and conditions*: (i) Bu_2SnO, Dean–Stark apparatus, toluene, 110 °C, 12 h; (ii) succinoyl dichloride, $CHCl_3$, room temp., 2 h

isolated in 26% overall yield (Scheme 4). Trimer **10** was obtained pure after flash chromatography, whereas tetramer **11** could be only enriched.

The structural assignment of compounds **10** and **11** was again based on FAB spectra, which showed peaks relative to the molecular ion mass, and NMR spectroscopy which showed the high symmetry of the molecules. ^{13}C NMR spectroscopy revealed useful data for the determination of the trimer–tetramer ratio in mixtures of the two oligomers, since the carbonyl resonance was the only one with two distinct signals for trimer **10** (δ_C 171.2) with respect to tetramer **11** (δ_C 171.0). No evidence for the formation of dimer **8** (δ_C 171.4) in this reaction was found. The addition of a 10% excess of Bu_2SnO in the reaction mixture and prolonged reflux favoured the thermodynamic equilibrium of the products leading to a trimer–tetramer ratio of 10:1 but again no dimer was isolated. It is worth noting that in our hands the stannolane methodology failed to produce a dimeric polyester, and in general gave only low yields of oligomeric materials. The role of the rigid, cyclic pyrrolidinediol appears to be crucial in determining the obtained results. On the other hand, a nice complementarity of methods of macrocyclization has been brought into evidence in this work.

A preliminary test of the complexing ability of dimer **8** and

trimer **10** showed, for the second, a higher affinity for potassium picrate. Further work, in progress in our laboratory, is necessary to evaluate the ability for molecular recognition of these chiral polyesters.

Experimental

Mps were determined with a Kofler hot-plate apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 881 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian GEMINI spectrometer at 200 MHz and 50 MHz respectively with coupling constants (*J*) given in Hz. Mass spectra were recorded on a QMD 1000 Carlo Erba instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyser. Dry solvents and reagents were obtained using standard procedures. Optical rotations were measured on a JASCO DIP-370 instrument; $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Light petroleum refers to the fraction with distillation range 40–70 °C.

Synthesis of (3*S*,4*S*)-1-benzyl-4-(*tert*-butyldimethylsiloxy)-3-hydroxypyrrolidine 3

A solution of the pyrrolidine **1** (4.14 g, 21.5 mmol) and imidazole (2.95 g, 43 mmol, 2 mol equiv.) in dry dimethylformamide (DMF) (20 cm^3) was cooled at 0 °C and TBDMSCl (3.23 g, 21.5 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and at room temp. for 12 h. Water (100 cm^3) was then added and the mixture was extracted with diethyl ether (2 × 70 cm^3). The organic phase, washed twice with water, was dried with Na_2SO_4 and concentrated to afford 3.21 g of crude material. Purification of the reaction mixture by flash column chromatography (eluent ethyl acetate–light petroleum 1:1) afforded 1.8 g of diprotected pyrrolidine (R_f 0.83) and 1.4 g of *monoprotected compound* **3** (R_f 0.23; 21%) (Found: C, 66.75; H, 9.8; N, 4.3. $C_{17}H_{29}NO_2Si$ requires C, 66.4; H, 9.5; N, 4.5%); mp 55 °C; $[a]_D^{20}$ 14.3 (*c* 1.01, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3619 (OH), 2956 (CH), 1436 (CH) and 1103 (C–O); δ_H(200 MHz; $CDCl_3$) 0.02 (3 H, s, Me), 0.04 (3 H, s, Me), 0.85 (9 H, s, Bu^t), 2.15 (1 H, dd, *J* 9.9 and 4.8, *H*CHN), 2.65 (2 H, m, CH_2N), 3.16 (1 H, dd, *J* 9.8 and 6.2, *H*CHN), 3.60 (2 H, J_{AB} 12.8, NCH_2Ph), 3.92 (1 H, m, *H*COH), 4.09 (1 H, m, HCOSi) and 7.30 (5 H, m, Ph); δ_C −4.8 (2 q, $SiMe_2$), 17.6 (s, SiC), 25.8 (3 q, Bu^t), 60.0 (t, CH_2N), 60.1 (t, CH_2N), 61.3 (t, N*C*H_2Ph), 78.9 (d, CHOH), 79.2 (d, CHOSi), 127.0 (d, Ar), 128.3 (2 d, Ar), 128.8 (2 d, Ar) and 138.8 (s, Ar); *m*/*z* 307 (M^+), 250, 171, 133, 91, 75 and 42.

Synthesis of (3*S*,4*S*)-1-benzyl-4-(*tert*-butyldimethylsiloxy)-3-(3-carboxypropionyloxy)pyrrolidine 4

A solution of monoprotected pyrrolidine **3** (100 mg, 0.33 mmol) and succinic anhydride (32 mg, 0.33 mmol, 1 mol equiv.) in 2 cm^3 of CH_2Cl_2 was refluxed for 3 h. The solution was then concentrated and the crude material was purified by flash column chromatography (eluent ethyl acetate–methanol 10:1) to afford *compound* **4** (R_f 0.32; 81 mg, 61%) (Found: C, 62.0; H, 7.9; N, 3.1. $C_{21}H_{33}NO_5Si$ requires C, 62.3; H, 8.2; N, 2.8%); $[a]_D^{20}$ −35.3 (*c* 0.67, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2955 (CH), 1786 (C=O), 1735 (C=O), 1360 (CH), 1155 (C–O) and 1112 (C–O); δ_H(200 MHz; $CDCl_3$) 0.09 (3 H, s, Me), 0.12 (3 H, s, Me), 0.90 (9 H, s, Bu^t), 2.66 (5 H, m, CH_2CH_2, *H*CHN), 3.13 (2 H, m, 2 × *H*CHN), 3.58 (1 H, dd, *J* 12.1 and 5.2, *H*CHN), 4.03 (2 H, J_{AB} 12.6, NCH_2Ph), 4.34 (1 H, br s, SiOCH), 4.97 (1 H, br s, O=COCH), 7.33 (5 H, m, Ph), 9.57 (1 H, br s, CO_2H); δ_C −4.8 (2 q, $SiMe_2$), 17.8 (s, SiC), 25.6 (3 q, Bu^t), 30.2 (2 t, CH_2CH_2), 56.0 (t, CH_2N), 59.0 (t, CH_2N), 60.2 (t, N*C*H_2Ph), 74.7 (d, SiOCH), 78.6 (d, O=CO*C*H), 128.3 (d, Ar), 128.6 (2 d, Ar), 129.9 (2 d, Ar), 133.9 (s, Ar) and 171.9 (2 s, C=O); *m*/*z* 407 (M^+), 350, 289, 171, 158, 91 and 73.

Synthesis of (3*S*,4*S*)-1-benzyl-4-(3-carboxypropionyloxy)-3-hydroxypyrrolidine 5

A solution of siloxane **4** (100 mg, 0.25 mmol) and KF (30 mg, 0.5 mmol, 2 mol equiv.) and 15 mg of 18-crown-6 in 3 cm^3 of CH_3CN was refluxed for 7 h. The crude reaction mixture was purified by flash column chromatography (eluent ethyl acetate–methanol 10:1) to afford compound **5** (R_f 0.27; 16 mg, 21%), δ_H(200 MHz; $CDCl_3$) 2.50 (4 H, br s, CH_2CH_2), 2.88 (2 H, m, CH_2N), 3.14 (1 H, m, *H*CNH), 3.30 (1 H, m, *H*CHN), 3.89 (2 H, J_{AB} 12.8, NCH_2Ph), 4.23 (1 H, br s, SiOC*H*), 4.97 (1 H, br s, O=COCH) and 7.33 (5 H, m, Ph).

Synthesis of (3*S*,4*S*)-1-benzyl-3,4-bis(3-carboxypropionyloxy)-pyrrolidine 6

A solution of the pyrrolidine **1** (193 mg, 1 mmol) and succinic anhydride (200 mg, 2 mmol, 2 mol equiv.) in 6 cm^3 of dry CH_2Cl_2 was refluxed under nitrogen for 2 h. The solution was then concentrated to afford compound **6** (390 mg, 100%) which was sufficiently pure for use, δ_H(200 MHz; D_2O) 2.56 (8 H, m, 2 × CH_2CH_2), 3.58 (2 H, d, *J* 13.6, 2 × *H*CHN), 3.85 (2 H, dd, *J* 13.5 and 4.4, 2 × *H*CHN), 4.46 (2 H, m, NCH_2Ph), 5.35 (2 H, d, *J* 4, OCH) and 7.49 (5 H, m, Ph); δ_C 32.3 (2 t, 2 × *C*H_2CH_2), 33.0 (t, 2 × CH_2*C*H_2), 59.2 (2 t, CH_2N), 62.8 (t, N*C*H_2Ph), 77.3 (2 d, OCH), 132.2 (d, Ar), 132.3 (2 d, Ar), 133.2 (s, Ar), 133.6 (2 d, Ar) and 176.1 (4 s, C=O).

Synthesis of (3*S*,4*S*)-1-benzyl-3,4-bis[3-(methoxycarbonyl)-propionyloxy]pyrrolidine 7

A solution of compound **6** (390 mg, 1 mmol) in 10 cm^3 of diethyl ether–ethyl alcohol (10:1) was cooled to 0 °C and treated with a saturated ethereal solution of CH_2N_2 until the resulting solution remained yellow. The reaction mixture was stirred at room temp. for 18 h. The crude mixture was purified by passage through a short pad of silica gel (eluent ethyl acetate–light petroleum 1:1 + 1% triethylamine) to afford *compound* **7** (R_f 0.42; 320 mg, 76%) (Found: C, 60.0; H, 6.7; N, 3.0. $C_{21}H_{27}NO_8$ requires C, 59.85; H, 6.4; N, 3.3%); $[a]_D^{20}$ 33.6 (*c* 1.04, CH_2Cl_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3045 (CH), 2953 (CH), 1733 (C=O), 1422 (CH), 1360 (CH) and 1156 (C–O); δ_H(200 MHz; $CDCl_3$) 2.59 (10 H, m, 2 × CH_2CH_2, 2 × *H*CHN), 3.08 (2 H, dd, *J* 10.6 and 6.2, 2 × *H*CHN), 3.61 (2 H, m, NCH_2Ph), 3.68 (6 H, s, 2 × OMe), 5.16 (2 H, t, *J* 4.8, 2 × OCH) and 7.30 (5 H, m, Ph); δ_C 28.8 (2 t, 2 × *C*H_2CH_2), 29.0 (2 t, 2 × CH_2*C*H_2), 51.8 (2 q, 2 × Me), 57.9 (2 t, 2 × CH_2N), 59.6 (t, N*C*H_2Ph), 77.8 (2 d, 2 × OCH), 127.3 (d, Ar), 128.3 (4 d, Ar), 128.8 (s, Ar) and 171.6 (4 s, C=O); *m*/*z* 421 (M^+), 290, 158 and 91.

Synthesis of dimer 8

A solution of the pyrrolidine **1** (340 mg, 1.76 mmol) and diacid **6** (690 mg, 1.76 mmol, 1 mol equiv.) in 300 cm^3 of dry 1,4-dioxane was treated with 45 mg of 4-(dimethylamino)pyridine (DMAP) and EDC (675 mg, 2 mol equiv.) and refluxed for 18 h. The solution was concentrated, the crude material was dissolved in CH_2Cl_2, and the solution was washed with water. The organic phase was dried over Na_2SO_4 and concentrated to obtain 1.12 g of crude material. The crude reaction mixture was purified by flash column chromatography (eluent ethyl acetate–light petroleum 1:1 + 1% triethylamine) to give compound **8** (R_f 0.32; 110 mg, 11%) as yellowish crystals. Further elution afforded 900 mg of polymeric material.

Dimer **8** (Found: C, 65.4; H, 6.2; N, 4.9. $C_{30}H_{34}N_2O_8$ requires C, 65.4; H, 6.2; N, 5.1%); $[a]_D^{20}$ 8.8 (*c* 0.95, $CHCl_3$); mp 165 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 2803 (CH), 1737 (C=O), 1355 (CH) and 1151 (C–O); δ_H(200 MHz; $CDCl_3$) 2.60 (12 H, m, 2 × CH_2CH_2, 2 × NCH_2Ph), 3.01 (4 H, br s, 4 × *H*CHN), 3.63 (4 H, br s, 4 × *H*CHN), 5.32 (4 H, br s, 4 × OCH) and 7.29 (10 H, m, Ph); δ_C 29.3 (4 t, 2 × CH_2CH_2), 57.6 (4 t, 4 × CH_2N), 59.7 (2 t, 2 × N*C*H_2Ph), 77.9 (4 d, 4 × OCH), 127.2 (2 d, Ar), 128.4 (4 d, Ar), 128.8 (4 d, Ar), 137.4 (2 d, Ar) and 171.4 (4 s, C=O); *m*/*z* 275, 158, 91, 74, 71 and 58; *m*/*z* (FAB) 551 ($M^+ + 1$).

Synthesis of trimer 10 and tetramer 11

Method A. A 500 cm^3 two-necked flask equipped with a

Dean–Stark apparatus was charged with the pyrrolidine **1** (2.2 g, 11.4 mmol), Bu_2SnO (2.7 g, 11.4 mmol, 1 mol equiv.) and 100 cm^3 of toluene and the mixture was refluxed for 12 h. The solution was concentrated under vacuum and the waxy residue was dissolved in 100 cm^3 of dry $CHCl_3$. The Dean–Stark apparatus was substituted with a dropping funnel and a solution of succinoyl dichloride (1.3 cm^3, 11 mmol) in 100 cm^3 of dry $CHCl_3$ was added over a period of 3 h at room temp. The resulting solution was refluxed for 1 h and concentrated to afford 6 g of a crude reaction mixture, which was purified by passage through a short pad of silica gel (eluent ethyl acetate–light petroleum 2:1 + 1% triethylamine) to afford compound **10** (R_f 0.36; 667 mg, 22%) and compound **11** (121 mg, 4%). Further elution afforded 2 g of polymeric material.

Method B. To the final chloroform solution was added Bu_2SnO (0.27 g, 10% of the initial amount) and the mixture was refluxed for 18 h. Work-up and purification of the reaction mixture was the same as above and afforded compound **10** (836 mg, 28%) and compound **11** (75 mg, 3%).

Trimer **10** (Found: C, 65.2; H, 6.2; N, 4.8. $C_{45}H_{51}N_3O_{12}$ requires C, 65.4; H, 6.2; N, 5.1%); $[\alpha]_D^{20}$ 55.4 (*c* 0.98, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3010 (CH), 2974 (CH), 1739 (C=O) and 1155 (C–O); δ_H(200 MHz; $CDCl_3$) 2.58 (18 H, m, 3 × CH_2CH_2, 3 × NCH_2Ph), 3.08 (6 H, m, 6 × *H*CHN), 3.64 (6 H, m, 6 × *H*CHN), 5.15 (6 H, m, 6 × OCH) and 7.32 (15 H, m, Ph); δ_C 28.9 (6 t, 3 × CH_2CH_2), 57.9 (6 t, 6 × CH_2N), 59.6 (3 t, 3 × N*C*H_2Ph), 77.9 (6 d, 6 × OCH), 127.3 (3 d, Ar), 128.4 (6 d, Ar), 128.8 (6 d, Ar), 137.5 (3 s, Ar) and 171.2 (6 s, C=O); *m*/*z* (FAB) 826 (M^+ + 1).

Tetramer **11** (Found: C, 65.2; H, 6.2; N, 4.8. $C_{45}H_{51}N_3O_{12}$ requires C, 65.4; H, 6.2; N, 5.1%); δ_C 29.1 (8 t, 4 × CH_2CH_2), 57.8 (8 t, 8 × CH_2N), 59.7 (4 t, 4 × N*C*H_2Ph), 77.9 (8 d, 8 × OCH), 127.3 (4 d, Ar), 128.4 (8 d, Ar), 128.9 (8 d, Ar), 137.5 (4 s, Ar) and 171.0 (8 s, C=O); *m*/*z* (FAB) 1102 (M^+ + 2).

X-Ray analysis of dimer 8

A crystal of approximate dimensions 0.2 × 0.2 × 0.3 mm was used for the data collection.

Crystal data. $C_{30}H_{34}N_2O_8$, M = 550.59, monoclinic, a = 11.261(5), b = 8.655(2), c = 14.971(3) Å, β = 105.05(3)°, V = 1401.1(8) $Å^3$, space group $P2_1$, Z = 4, D_c = 1.300 g cm^{-3}, μ(CuKα) = 0.782 mm^{-1}, F(000) = 584. Data were collected at room temperature on a CAD4 four-circle diffractometer in the range $3 \leqslant \theta \leqslant 60°$. 2284 Reflections were collected, of which 1616 were unique with $I \geqslant 2\sigma(I)$. Data were corrected for Lorentz and polarization effect but not for absorption. The structure was solved by direct methods using SIR92[6] and refined with SHELXL93.[7] All non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were located in the difference Fourier map and refined isotropically. Residuals after the last least-squares cycles were R = 0.0522, R_w = 0.1537 for a weighting scheme $w = 1.000/[\sigma^2(F_o^2) + (0.0725\ P)^2 + 0.0688\ P]$ where $P = [\mathrm{Max}(F_o^2,0) + 2\ F_c^2]/3$. The max. and min. residual densities were 0.246 and −0.219 e $Å^{-3}$.†

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† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web pages (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/159.

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