Lithium selective ionophores based on pendant arm substituted crown ethers

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Ligands have been synthesised which offer good selectivity for lithium ions over sodium based on substituted 14-crown-4 derivatives which bear diamide groups on the ethylene chain or, less effectively, on the central carbon of the propylene chain. The behaviour of potentiometric membrane electrodes based on these ionophores is compared.

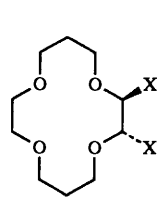
Introduction

Lithium plays an important therapeutic role in the treatment of manic depressive behaviour. Manic psychosis is commonly treated by administering daily doses of about 1 gram of lithium carbonate,[1] equivalent to an *in vivo* serum concentration of 1 mmol dm^{-3}. However, an excessive dose of lithium can cause adverse physiological effects such as nausea and vomiting. Clearly, the monitoring of lithium levels in blood is desirable, and a variety of lithium-sensitive electrodes has been developed to this end.

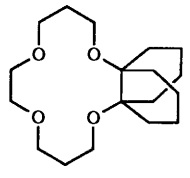
Ligands for use as ionophores in such ion-selective electrodes should ideally fulfil certain conditions: they should be selective for lithium over other metal ions (especially sodium as it has a concentration of over 140 mmol dm^{-3} in blood), they should exhibit rapid exchange kinetics, and should be sufficiently lipophilic to prevent leaching of the ligand into the solution surrounding a typical membrane electrode. In addition, the ligand should be non-basic to maximise the pH range over which the ionophore can be used.

Certain ionophores based on *acyclic* systems have been developed, but the best of these reported so far offers a lithium to sodium selectivity (log $K^{pot}_{Li,Na} = -2.5$),[2] that is less than that required for measurement *in vivo* with less than 1% interference, for which a figure of log $K^{pot} = -4.3$ is sought. Studies have shown that *macrocyclic* crown ethers based on 14-membered rings offer better selectivity for lithium over sodium and potassium. It is generally accepted that the 'cavity' of the 14-membered crown ether ring matches most closely the dimensions of the lithium ion, favouring formation of 1:1 complexes.[3] Initial work by Shono showed that substitution on the central methylene carbon of the C_3 unit enhanced Li/Na selectivity and values of the order of log $K^{pot} = -2.3$ were obtained for a variety of mono and *gem*-dialkyl substituted compounds.[4] Similar selectivities were obtained when the alkyl group was replaced with a variety of potentially ligating substituents, including CH_2OMe, CH_2CONEt_2, $CH_2OPO(OEt)_2$ and $(CH_2)_2OMe$. This suggested that the substituent was not playing an important role in Li binding, although the amide-substituted derivative did show the highest Li/Na selectivity, by a factor of nearly two.

There have been two related approaches to improving the lithium selectivity of such macrocyclic ligands. The first, reported by us in 1990, involved the use of *trans*-disposed pendant substituents on the ethylene chain of the 14-crown-4 ring.[5] In this approach, NMR and IR studies were used to demonstrate that pendant CH_2CONR_2 substituents could *cooperatively* ligate to the Li ion bound in the plane of the ring. The amide substituents were chosen to enhance discrimination in favour of the more charge dense lithium ion, and they were sufficiently lipophilic to restrict the approach of water molecules. In addition the steric bulk of these ligands disfavoured competitive 2:1 complexation of the larger sodium ion. The best of these ligands, the dibutylamide derivative, **1a** (log $K^{pot}_{Li,Na} = -2.92$), gave high selectivity for lithium over sodium, and this di-*n*-butyl ionophore was shown to be effective in serum measurements of lithium concentration.[6]



1a X = $CONBu_2$
b X = $CONBu^i_2$
c X = $CON(CH_2Ph)_2$
d X = $CONEt_2$
e X = $CON(C_8H_{17}{}^n)_2$
f X = CO_2Bu
g X = CN
h X = CO_2Me
j X = CO_2H



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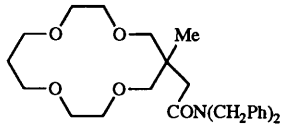

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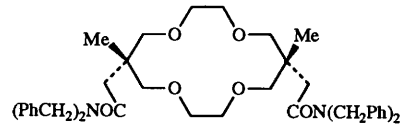
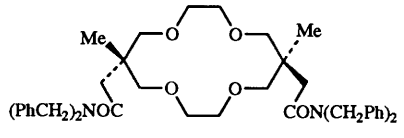


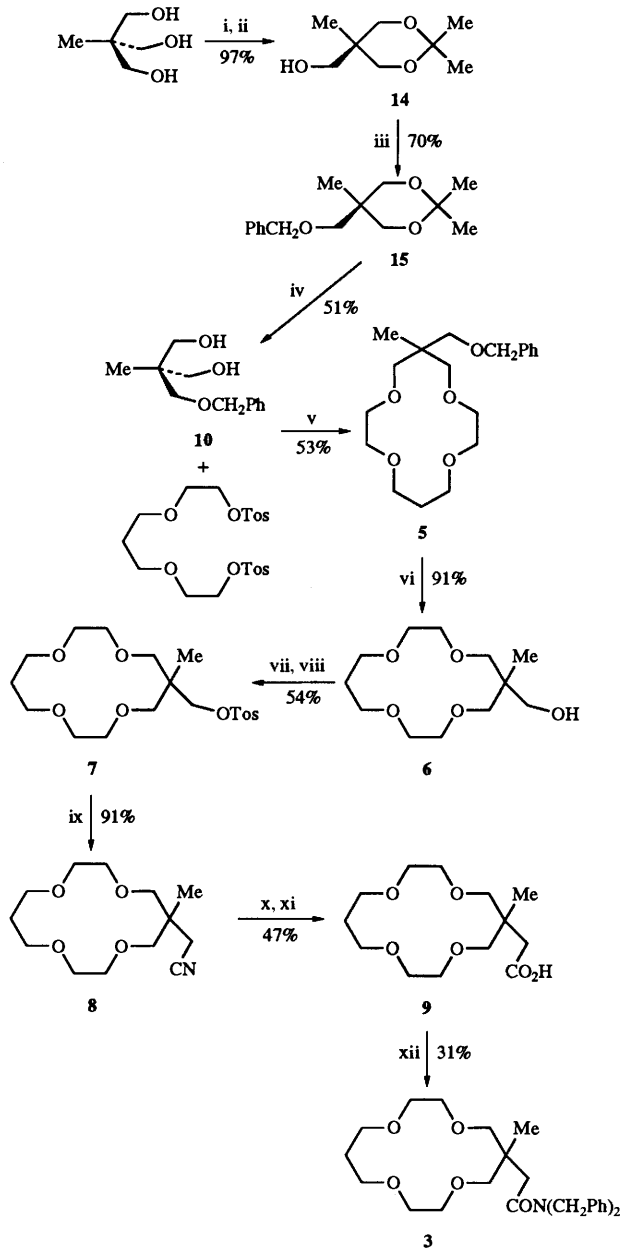
4a



4b

An alternative, more recent approach,[7] has relied upon increasing the steric bulk around the 14-crown-4 macrocycle in order to favour 1:1 Li binding and disfavour 2:1 binding to the competing sodium ion. By introducing decalin groups into the ligand, *e.g.*, **2**, good selectivity for Li over Na was observed (log $K^{pot}_{Li,Na} = -3.1$).

In the studies reported here, a modification of the first approach was sought by synthesising ligands where *two* pendant amide groups were located in the middle of the trimethylene chain of a 14-crown-4 macrocycle. Inspection of



Scheme 1 *Reagents and conditions:* i, toluene-*p*-sulfonic acid, Me_2CO, $CHCl_3$; ii, moist Na_2CO_3; iii, $Bu_4N^+HSO_4^-$, NaOH, BnCl, THF; iv, c HCl, MeOH; v, Li, LiBr, Bu^{t}OH; vi, $Pd(OH)_2$–C, toluene-*p*-sulfonic acid, EtOH, H_2 (3 atm); vii, toluene-*p*-sulfonyl chloride, py, −10 °C; viii, H_2O; ix, KCN, DMSO, 18-crown-6; x, NaOH, 2:1 H_2O–methoxyethanol; xi, HCl (6 mol dm^{-3}); xii, DCC, DMAP, CH_2Cl_2, $(PhCH_2)_2NH$

molecular models suggested that the amide substituents could bind cooperatively to a lithium ion that was sitting in the plane of the 14-O-4 ring. The original report of Shono involved examples where there was only one amide group that could bind.

Results and discussion

The synthesis of ligands, *e.g.*, **3** and **4**, which incorporate amide functionality into the C-3 chain may be traced back to some simple neopentyl fragments (**3**, **4a** and **4b**). Mono-substituted neopentyl derivatives were synthesised from 2-hydroxymethyl-2-methylpropane as shown in Scheme 1. The procedure relies on acetonide protection of the terminal primary hydroxy groups allowing selective benzylation of the C-2 position. Deprotection followed by a lithium templated reaction with 3,6-dioxanonane-1,9-diyl ditoluene-*p*-sulfonate yielded the benzylated macrocycle **5** in good overall yield. It should be noted that these cyclisation yields (typically in the range 50–70%), compare to values of the order of 2–7% for the syntheses of the ligands reported by Suzuki recently.[7]

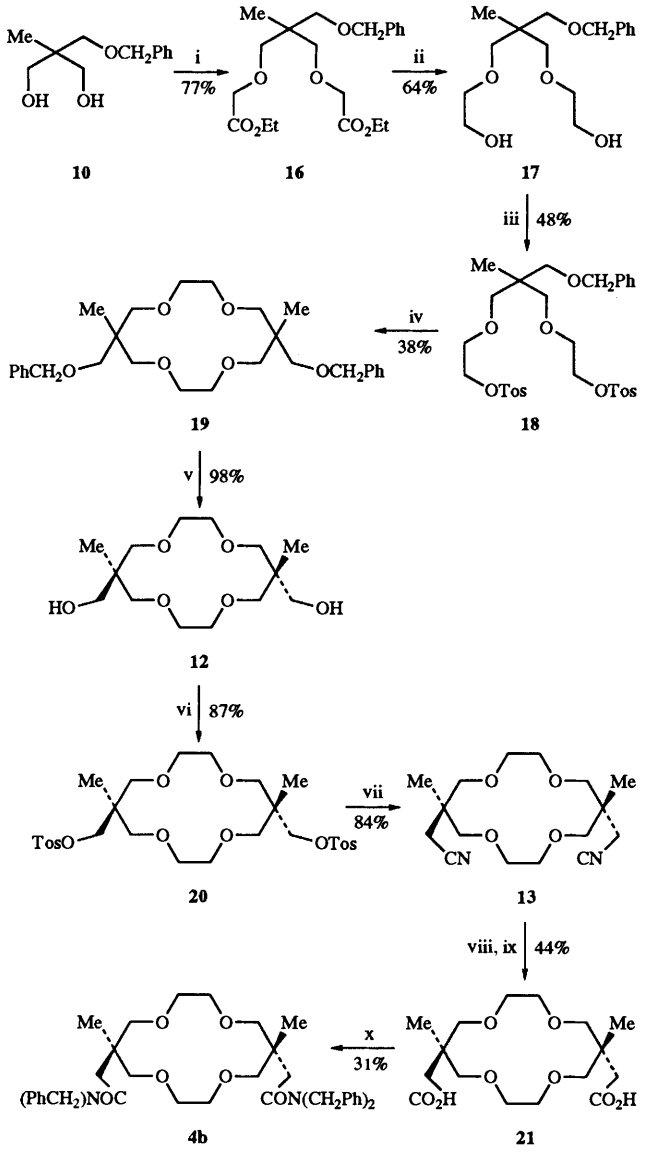
Debenzylation was carried out by hydrogenolysis of the benzyl group using Pearlman's catalyst in the presence of toluene-*p*-sulfonic acid. The alcohol thus produced, **6**, was converted into the tosylate **7** and thence to the cyanide **8** by reaction of the tosylate with KCN in dimethyl sulfoxide (DMSO) in the presence of 18-crown-6. Alcoholysis of this cyanide proved difficult under a variety of acidic conditions, presumably because the neopentyl site is sterically hindered. However, basic hydrolysis in a mixed aqueous–2-methoxyethanol solvent gave the carboxylate **9** successfully. Some difficulties were also experienced in converting the acid into the dibenzylamide **3** and the coupling was eventually achieved using dicyclohexylcarbodiimide in the presence of the acyl transfer catalyst 4-dimethylaminopyridine, but in only a 31% yield.

The synthesis of the 3,10-substituted derivative was broadly analogous to that of the mono-substituted ligand and is shown in Scheme 2. Reaction of the monobenzylated diol, **10**, with ethyl diazoacetate followed by reduction with $LiAlH_4$ afforded the extended diol **17**. Tosylation of **17** followed by co-condensation with **10** in the presence of LiOBu^t in *tert*-butyl alcohol yielded a mixture of the *cis*- and *trans*-substituted macrocycles. Initially this mixture of dibenzyl ethers proved difficult to separate, and the mixture was carried through the further steps of the synthesis to yield a *cis*/*trans* mixture of the bis(dibenzylamides) (**4a** and **4b**). These diastereoisomeric lipophilic diamides were incorporated into a conventional plasticised PVC membrane,[8] to facilitate a study of its electrode response and hence determine the potentiometrically derived selectivity coefficients, using the fixed interference method of analysis.

Separation of the diastereoisomeric diols **11** and **12** was eventually achieved by careful column chromatography on neutral alumina using an unusual acetonitrile–dichloromethane eluent system. The *cis*-diol **11**, eluted first (R_f = 0.8 in MeCN–CH_2Cl_2, 1:2), while the *trans* isomer **12** was considerably more polar (R_f = 0.4). The *trans* configuration of this more polar isomer was assigned retrospectively by analysis of the related dinitrile **13** which was obtained subsequently from this diol. The crystal structure (Fig. 1) of the dinitrile clearly shows the relative disposition of the cyanomethyl groups in the molecule. The observed relative polarity of the two diastereoisomeric diols may be related to the fact that the *trans* isomer can adopt a much 'flatter' conformation while the *cis* isomer may be inhibited from interacting with the surface hydroxy groups on the alumina because of intramolecular hydrogen bonding, which was evident in a concentration-dependent infrared spectral study carried out in dichloromethane. A sharp band at 3540 cm^{-1} was evident over the concentration range 10^{-2}–10^{-4} mol dm^{-3}, while the broad intermolecularly hydrogen-bonded band at 3300 cm^{-1} diminished in intensity with increasing dilution in CH_2Cl_2.

Both the *cis* and *trans* diols were then taken through the synthesis shown in Scheme 2. The *trans*-bis (dibenzylamide) **4a** was formed without difficulty. However, attempts to synthesise the *cis* analogue separately proved unsuccessful as ditosylation of the isolated *cis* diol, **11**, proved to be irritatingly capricious. Attempts at mesylation of this *cis*-diol at low temperature (CH_2Cl_2, TsCl, Et_3N, −30 °C) were equally unsuccessful.

The diamide ligands **4b** and **4a**/**4b** (mixture) were used to prepare conventional PVC-based membranes plasticised with *o*-nitrophenyl octyl ether, using standard methods[8] and with an



Scheme 2 *Reagents and conditions:* i, BF_3·Et_2O, $N_2CH_2CO_2Et$; ii, $LiAlH_4$, Et_2O; iii, toluene-*p*-sulfonyl chloride, py, −10 °C; iv, Li, LiBr, **10**, Bu^{t}OH; v, $Pd(OH)_2$–C, toluene-*p*-sulfonic acid, EtOH, H_2 (3 atm); vi, toluene-*p*-sulfonyl chloride, py, −10 °C; vii, KCN, DMSO, 18-crown-6; viii, NaOH, 2:1 H_2O–methoxyethanol; ix, HCl (6 mol dm^{-3}); x, DCC, DMAP, CH_2Cl_2, $(PhCH_2)_2NH$

ionophore composition (1.2% ligand, 65.6% plasticiser, 32.8% PVC and 0.4% of a lipophilic anion, see the experimental section for details) that was the same as that used in prior work.[6] For purposes of comparison, electrode response studies for an extended series of the chiral 2,3-disubstituted derivatives were also made. The di-*n*-butyl amide **1a** has been reported previously and it showed an excellent selectivity for lithium over sodium ($-\log K^{pot} = 2.92$), as well as showing minimal protein interference in serum studies.[6] The amide ligands **1b**, **1c**, **1d**, **1e**, bearing two diisobutyl, dibenzyl, diethyl and dioctyl groups respectively were prepared from the corresponding diacid.[5] The dibutyl ester **1f** was also made, for purposes of comparison.

It has previously been established that with the di-*n*-butylamide ligand **1a**, lithium forms a 1:1 complex and the amide carbonyls bind cooperatively to the lithium ion. A ^{13}C NMR titration examining the shift in the ^{13}C resonances of the dibenzylamide derivative **1c**, as a function of added LiCl was carried out in deuteriomethanol (Fig. 2). The form of the

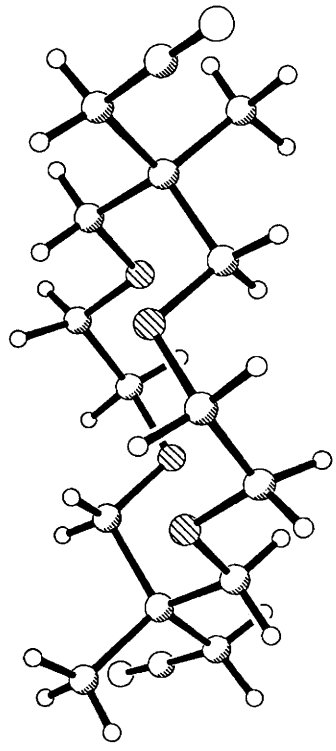


Fig. 1 Molecular structure in the crystal of the *trans*-dinitrile **13**

variation of $\Delta\delta_C$ *vs.* [Li] is consistent with a complex in which there is fast exchange between free and bound ligand and in which there is selective formation of a 1:1 complex.

Electrode response studies

Electrode response studies of membrane electrodes incorporating the monoamide **3**, the *trans* diamides, **4a**, **1b**, **1c**, **1d**, **1e**, the diester **1f**, and the *cis*/*trans* mixture of the diamides **4a** and **4b** were determined. The selectivity coefficients of plasticised PVC-based membrane electrodes were measured using a fixed interference method.[8] Membranes were fabricated using the following mixture: 1.2% sensor, 65.6% plasticizer (*o*-nitrophenyl octyl ether), 32.8% PVC, and 0.4% of a lipophilic anion [potassium tetrakis(*p*-chlorophenyl)borate]. The detection limit and electrode slope were determined using a background concentration of 150 mmol dm^{-3} NaCl, 4.3 mmol dm^{-3} KCl, 0.9 mmol dm^{-3} $MgCl_2$ and 1.26 mmol dm^{-3} $CaCl_2$, to simulate a clinical background. For the evaluation of Li/Na selectivities a fixed interference background of 100 mmol dm^{-3} NaCl solution was used.

The selectivity coefficient $K^{pot}_{Li,B}$ is defined for a system containing Li^+ and an interferent ion B by the semiempirical Nicolsky–Eisenmann equation [eqn. (1)].

$$E = E^\circ + \frac{2.303RT}{z_{Li}F} \log \{[Li^+] + K^{pot}_{Li,B}[B]z_{Li}/z_B\} \quad (1)$$

The results of the studies are shown in Table 1. For the 2,3-disubstituted 14-crown-4 series **1b**–**1f** there were some dramatic and somewhat unexpected differences in electrode response between the amide derivatives. For example the diisobutyl derivative **1b** showed an excellent Li/Na selectivity (Table 1) of 1500:1, while the diethylamide-based electrode, although behaving quite well in pure LiCl solution, showed severe interference in either a simulated clinical or sodium background. The dibenzylamide ionophore also exhibited a good lithium selectivity, and although it showed a sub-

Table 1 Electrode response of plasticised PVC-based membrane electrodes incorporating 14-crown-4 derivatives **1**, **3** and **4** (310 K)

Ionophore	Slope[a]/mV decade^{-1} (clinical background)	Limit of detection (LiCl only) $-(\log[Li^+])$	Limit of detection[b] (clinical background) $-(\log[Li])$	$-\log K^{pot}_{Li,Na}$[c]
1a	61 (60)	5.1	3.8	2.92
1b[d]	61 (50)	5.2	4.1	3.25
1c	54 (61)	5.5	3.75	2.93
1d	(52)	4.5	Severe interference	
1e	Too slow to respond	—	—	—
1f	61 (60)	4.4	3.25	2.25
3	60 (61)	5.0	3.1	2.30
4a + **4b** (mixture)	59 (61)	4.9	3.1	2.30
4b	58 (60)	4.9	3.1	2.30

[a] Values in parentheses refer to slope in a background of pure LiCl only. [b] In a simulated background of clinical ions: [NaCl] = 150 mmol dm^{-3}; [KCl] = 4.3 mmol dm^{-3}; $CaCl_2$ = 1.26 mmol dm^{-3}; $MgCl_2$ = 0.9 mmol dm^{-3}. [c] In a fixed background of 100 mmol dm^{-3} NaCl solution. [d] Did not behave well in serum: significant protein interference.

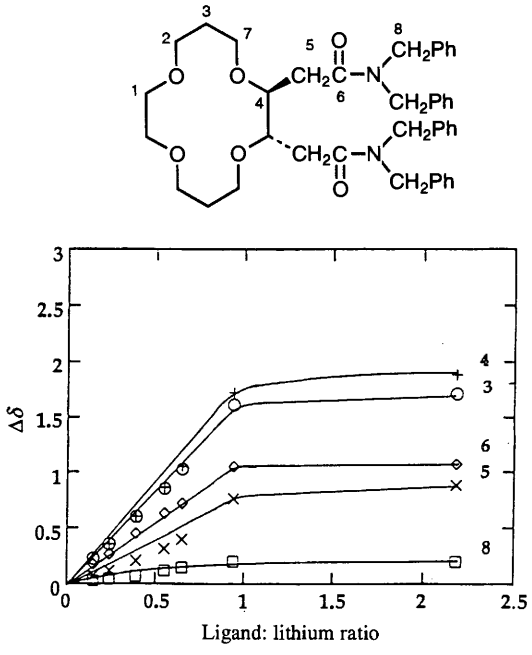


Fig. 2 ^{13}C chemical shift displacements for the given carbon atoms of ligand **1c** following addition of LiCl (298 K, CD_3OD)

Nernstian slope in pure LiCl solution, in a simulated clinical background it had good response characteristics. It also behaved well in a fixed background of sodium ions (log $K^{pot}_{Li,Na}$ = −2.93). The dioctyl derivative, **1e**, which was prepared as an example of a very lipophilic ionophore, was too slow to respond to changes in lithium activity in solution to allow any reliable measurements to be taken. Care was taken to ensure that the membrane used was homogeneous and in a separate experiment a similar effect was noted with bis(butylpentyl) adipate as the plasticiser, in place of *o*-nitrophenyl octyl ether. Although no further detailed studies were taken to define why such a poor response was found, it is tempting to speculate that the ionophore may have aggregated in the rather fluid membrane phase and charge transport may have been too slow to allow an equilibrium emf to be established at the aqueous interface. Slowness of electrode response associated with high ionophore lipophilicity has been observed previously in other ionophores.[9]

The results obtained with the amide derivatives **3** and **4** do not compare favourably with those reported for ligands **1** and **2** (Table 1). The Li/Na selectivities found for **3**, **4a**/**4b** (mixture) and **4b** (pure *trans* isomer) were all very similar (log K^{pot} = −2.30). These results are consistent with a lack of participation of the amide moieties in metal ion binding. The Li/Na selectivities obtained are also similar to that found for the dibutyl ester **1f** (Table 1), suggesting that in this diester the carbonyl oxygens play no significant role in Li binding. Indeed for these compounds the measured Li/Na selectivities are very similar to the values found for the series of 3,3-dialkyl substituted 14-crown derivatives reported by Shono (typically log $K^{pot}_{Li,Na}$ = −2.3).[4] The obvious implication of this correlation is that only the ring oxygens are involved in lithium binding. It is possible that with **3** and **4**, the *C*-linked amide substituent at the quaternary carbon strongly prefers to adopt a pseudo-equatorial conformation and cannot therefore take part in lithium binding.[10] Such problems could be overcome by use of an ether linkage to the macrocycle ring (instead of a methylene link) in order to impose a pseudoaxial conformation. This sort of a conformational preference has been shown to be adopted recently in related benzo-14-crown-4 systems.[10]

Experimental

For all the reactions performed, temperatures are quoted in degrees centrigrade. Alumina refers to Merck alumina (activity II–III) and silica refers to Merck Silica gel F^{60} (230–400 mesh).

Proton and carbon-13 NMR spectra were recorded using either a Bruker AC250 or a Varian VXR 400 spectrometer. The Bruker AC250 was operated at 250.134 MHz (^1H) and 62.896 MHz (^{13}C), whilst the Varian VXR 400 was operated at 399.952 MHz (^1H) and 100.577 MHz (^{13}C). All chemical shifts are given in ppm [referenced to Me_4Si (TMS) at 0 ppm].

Mass spectra were recorded on a VG 7070E mass spectrometer, operating in CI, EI or FAB modes as stated. Gas chromatography was performed on a Hewlett-Packard HP5890 using an SE30 capillary column. Infrared spectra were recorded on a Perkin-Elmer 577 spectrometer as thin films, KBr discs or Nujol mulls as stated.

Potentiometric studies: membrane preparation

The membranes were made up by dissolving 1.2% of the lithium ionophore, 65.6% of a suitable plasticizer [*o*-nitrophenyloctyl ether or bis(butylpentyl) adipate], 32.8% of PVC (high molecular weight Fluka) and 0.4% of a lipophilic anion [potassium tetrakis(*p*-chlorophenyl)borate] in 6 cm^{-3} of spectroscopic grade tetrahydrofuran (THF) which was poured into a 33 mm id glass ring resting on a sheet of plate glass. A pad of filter papers was placed on top of the ring and kept in place by a heavy weight. The assembly was left for 48 h to allow slow solvent evaporation. A small disc was cut from the membrane and affixed to a Philips Pye electrode body to form the ion-selective electrode.

Solutions were made up using anhydrous lithium chloride (BDH), sodium chloride (BDH), potassium chloride (BDH)

and calcium chloride solution 1 mol dm^{-3} (BDH) and deionised water (MilliQ).

Flow system

A constant-volume cell was used for the ion-selective electrodes. It was made from a water-jacketed glass tube with B19 ground glass joints. Drilled glass stoppers were used with a wax seal in order to fit the electrodes.

The ion-selective and reference electrodes were connected to a digital multimeter (Keithley 197 Autoranging Microvolt DMM) *via* a buffer amplifier. The reference electrode was a porous plug, saturated calomel electrode (RE1 Petiacourt). A flat bed Linseis *y–t* chart recorder, provided with back-off facilities, was used for monitoring potential difference changes. A suitable capacitor was connected across the input of the chart recorder to smooth out residual noise. The peristaltic pump used was an RS330-812. The temperature of the system was maintained at 37 °C using a Techne Tempette junior TE-85 Thermostat bath.

The synthesis of the diamides **1a**, **1b**, and their homologues was carried out using the methods discussed in ref. 4. Some minor improvements to the original transformations from the dinitrile **1g** have been made and are reported.

(2*S*,3*S*)-(−)-2,3-Bis(methoxycarbonylmethyl)-1,4,8,11-tetraoxacyclotetradecane (1h)

Through a solution of the dinitrile **1g** (350 mg, 1.24 mmol), in dry methanol was bubbled dry HCl(g) for 1 h. The mixture was then refluxed for 5 h, cooled and the solvent removed to yield a residue. This was treated with H_2O (10 cm^3) and extracted with dichloromethane (3 × 30 cm^3), dried (MgO_4) and the solvent removed to yield a residue which was chromatographed on alumina eluting with hexane–ethyl acetate (1:1) (R_f = 0.57) to yield a pale yellow oil, 302 mg (70%). $[\alpha]_D^{20}$ = −39.5 (*c* 1.0, CH_2Cl_2); $\delta_H(CDCl_3)$ 1.74 (4 H, m, CH_2C), 2.48 (4 H, m, CH_2CO) and 3.43–4.00 (20 H, m, CH_3O, CH_2O + CHO); $\delta_C(CDCl_3)$ 30.8 (CH_2C), 35.9 (CH_2CO), 51.7 (CH_3O), 66.4, 66.6, 70.1 (CH_2O), 76.5 (CHO) and 171.5 (C=O); ν_{max}(thin film)/cm^{-1} 1742 (C=O); *m/z* (CI, isobutane) 349 (M^+ + 1, 100%) and 171 (80) (Found: C, 67.3; H, 10.0. $C_{16}H_{28}O_4$ requires: C, 67.6; H, 9.86%).

(2*S*,3*S*)-(−)-2,3-Bis(carboxymethyl)-1,4,8,11-tetraoxacyclotetradecane (1j) [5]

To a solution of the diester **1h** (300 mg, 0.86 mmol) in aqueous methanol (10 cm^3; 1:1 H_2O–MeOH) was added tetrabutylammonium hydroxide (1 g) and the mixture was refluxed for 2 h. After the removal of the solvent under reduced pressure, the residue was treated with HCl (5 cm^3, 6 mol dm^{-3}) and extracted with diethyl ether (6 × 20 cm^3). The combined extracts were dried (MgO_4), filtered and the solvent evaporated off to yield an off-white waxy solid, 210 mg (77%). $\delta_H(D_2O)$ 1.83 (4 H, m, CH_2C), 2.61 (4 H, dd, CH_2CO) and 3.69–4.00 (14 H, m, CH_2O + CHO); $\delta_C(D_2O)$ 29.9 (CH_2C), 35.6 (CH_2CO), 66.1, 67.0, 69.4 (CH_2O), 78.0 (CHO) and 174.8 (CO_2H); ν_{max}(Nujol)/cm^{-1} 3600–3100 (OH, br) and 1710 (C=O).

(2*S*,3*S*)-(−)-2,3-Bis(dibutylcarbamoylmethyl)-1,4,8,11-tetraoxacyclotetradecane (1a) [5]

To a solution of the diacid **1j** (500 mg, 1.55 mmol) in dichloromethane (10 cm^3) was added phosphorus pentachloride (675 mg, 3.24 mmol) and the mixture was stirred at room temperature under nitrogen for 12 h. After removal of the solvent under reduced pressure an IR spectrum was recorded to confirm that the conversion into the acid chloride was complete. The residue was redissolved in dichloromethane (20 cm^3) and this solution was slowly added to a solution of dibutylamine (805 mg, 6.2 mmol) and triethylamine (630 mg, 6.2 mmol) in dichloromethane (15 cm^3) at 0 °C. The reaction was stirred for 2 h after which the solvent was removed under reduced pressure and the residue partitioned between hexane and water. The organic phase was washed with HCl (0.1 mol dm^{-3}) (2 × 5 cm^3), dried ($MgSO_4$) and the solvent evaporated off to yield a residue which was purified by chromatography on neutral alumina eluting with hexane–ethyl acetate (1:1) (R_f = 0.45) to yield a colourless oil, 512 mg (61%). $[\alpha]_D^{20}$ = −33.7 (*c* 1.0 in CH_2Cl_2); $\delta_H(CDCl_3)$ 0.85 (12 H, m, CH_3), 1.30–1.45 (16 H, m, CH_2C), 1.75 (4 H, m, CH_2C ring), 2.31 (4 H, dd, CH_2CO), 3.12 (8 H, m, CH_2N) and 3.50–3.89 (14 H, m, CH_2O + CHO); $\delta_C(CDCl_3)$ 13.8 (CH_3C), 20.1 (CH_2C), 29.7, 31.1, (NCH_2CH_2), 45.9, 47.9 (NCH_2), 35.3 (CH_2CO), 66.7, 67.6, 70.2 (CH_2O), 80.1 (CHO) and 170.6 (CO); ν_{max}(thin film)/cm^{-1} 1638 (C=O); *m/z* (CI, isobutane) 543 (M^+ + 1, 55%) and 231 (M^+ − 2CONBu) (Found: C, 80.3; H, 12.2. $C_{30}H_{56}O_2$ requires: C, 80.3; H, 12.5%).

(2*S*,3*S*)-(−)-2,3-Bis(diisobutylcarbamoylmethyl)-1,4,8,11-tetraoxacyclotetradecane (1b)

This was prepared as described for **1a** [5] from the corresponding diacid **1h** (100 mg, 0.29 mmol), dichloromethane (2 cm^3), phosphorus pentachloride (130 mg, 0.60 mmol), isobutylamine (180 mg, 1.4 mmol dm^{-3}) and triethylamine (120 mg, 1.2 mmol dm^{-3}). Purification by column chromatography on alumina, eluting with hexane–ethyl acetate (1:1) (R_f = 0.45) yielded a pale yellow oil (98 mg, 62%). $\delta_H(CDCl_3)$ 0.89 (24 H, m, CH_3C), 1.71 (4 H, m, CH_2C), 1.95 [4 H, m, $CH(CH_3)_2$], 2.23–2.67 (4 H, m, CH_2C=O) and 3.04–3.98 (22 H, m, CH_2O, CHO, CH_2N); $\delta_C(CDCl_3)$ 20.14 (CH_3C), 26.66 and 28.33 (CHC), 31.04 (CH_2C), 35.79 (CH_2C=O), 54.09 and 56.09 (CH_2N), 66.89, 67.80 and 70.38 (CH_2O); ν_{max}(thin film)/cm^{-1} 1643 (C=O) and 1087 (C–O); *m/z* (CI, isobutane) 543 (M^+ + 1, 100%) (Found: C, 80.1; H, 12.0. $C_{30}H_{56}O_2$ requires: C, 80.3; H, 12.5%).

(2*S*,3*S*)-(−)-2,3-Bis(dioctylcarbamoylmethyl)-1,4,8,11-tetraoxacyclotetradecane (1e)

This was prepared as described for **1b** using the diacid **1h** (100 mg, 0.29 mmol), dichloromethane (2 cm^3), phosphorus pentachloride (130 mg, 0.60 mmol), dioctylamine (290 mg, 1.2 mmol) and triethylamine (120 mg, 1.2 mmol). Purification by column chromatography on alumina with ethyl acetate–hexane (1:1) (R_f = 0.75) to yield a pale yellow oil, 189 mg (77.1%). $\delta_H(CDCl_3)$ 0.85 (12 H, q, CH_3), 1.28 (40 H, br s, CH_2C), 1.52 (8 H, m, CH_2CH_2N), 1.72 (4 H, m, CH_2CN), 2.32–2.60 (4 H, m, CH_2CO), 3.15 (4 H, m, CH_2CN), 3.49–3.73 (12 H, m, CH_2O) and 3.93 (2 H, m, CHO); $\delta_C(CDCl_3)$ 14.05 (CH_3), 26.60, 27.05, 26.91, 27.76, 29.35, 31.1, 31.78 (CH_2C), 35.51 (CH_2CO), 46.43, 48.39 (CH_2CO), 66.92, 67.81, 70.41 (CH_2O), 80.36 (CHO) and 170.78 (C=O); ν_{max}/cm^{-1} 1640 (C=O stretch) [Found: (M^+ + 1) 768.231 08. $C_{46}H_{90}N_2O_6$ requires (*M* + 1) 768.2310].

(2*S*,3*S*)-(−)-2,3-Bis(dibenzylcarbamoylmethyl)-1,4,8,11-tetraoxacyclotetradecane (1c)

This was prepared as described for **1b** using the diacid **1h** (100 mg, 0.29 mmol), dichloromethane (2 cm^3), phosphorus pentachloride (130 mg, 0.60 mmol), dibenzylamine (230 mg, 1.2 mmol) and triethylamine (120 mg, 1.2 mmol). Purification by column chromatography on alumina with ethyl acetate–hexane (1:1) (R_f = 0.44) yielded a colourless glassy solid (157 mg, 80%). $\delta_H(CDCl_3)$ 1.64 (4 H, m, CH_2C), 2.37–2.66 (4 H, m, CH_2CO), 3.49–3.66 (10 H, m, CH_2O), 3.92 (2 H, m, CHO), 4.04 (2 H, dd, CH_2O), 4.33–4.83 (8 H, m, CH_2N) and 7.13–7.34 (20 H, m, ArH); $\delta_C(CDCl_3)$ 30.98 (CH_2C), 35.47 (CH_2CO), 48.43 and 50.19 (CH_2N), 66.73, 67.89 and 70.27 (CH_2O), 80.06 (CHO),

126.42, 127.43, 127.54, 128.31, 128.47, 128.87, 136.55 and 137.30 (ArC); ν_{max}(thin film)/cm^{-1} 1638 (C=O stretch), 1430 (C–N stretch), 730 and 697 (C–H bend); *m/z* (DCI, chloroform) 678 (M^+, 11%), 593 (6), 503 (13), 196 (NBz_2, 11), 179 (37), and 106 (9) [Found: (M^+ + 1) 679.8711. $C_{42}H_{50}N_2O_6$ + H requires *M*, 679.8712].

(2*S*,3*S*-(−)-2,3-Bis(diethylcarbamoylmethyl)-1,4,8,11-tetraoxacyclotetradecane (1d)

This was prepared as described for **1b** using the diacid **1h** (70 mg, 0.20 mmol), dichloromethane (2 cm^3), phosphorus pentachloride (85 mg, 0.40 mmol), and diethylamine (2 cm^3, excess). Purification by column chromatography on alumina with ethyl acetate–hexane (1:1) (R_f = 0.31) yielded a colourless oil (75 mg, 85%). δ_H($CDCl_3$) 1.13 (12 H, m, CH_3C), 1.72 (4 H, m, CH_2C), 2.21–2.65 (4 H, m, CH_2CO) and 2.95–4.00 (22 H, m, CH_2O, CH_2N and CHO); δ_C($CDCl_3$) 13.05 and 14.40 (CH_3C), 31.11 (CH_2C), 35.51 (CH_2CO), 40.46 and 42.37 (CH_2N), 66.92, 67.86 and 70.43 (CH_2O), 80.44 (CHO) and 170.49 (C=O); ν_{max}(thin film)/cm^{-1} 1644 (C=O stretch) and 1433 (C–N stretch); *m/z* (DCI chloroform) 431 (M^+ + 1, 100%) [Found: (M^+ + 1): 431.5089, $C_{22}H_{42}N_2O_6$ + H requires *M*, 431.5088].

(2*S*,3*S*)-(−)-2,3-Bis(butoxycarbonylmethyl)-1,4,8,11-tetraoxacyclotetradecane (1f)

A solution of the diacid **1h** (160 mg, 0.56 mmol) in butanolic HCl (50 cm^3) (produced by bubbling dry HCl gas through dry *n*-butanol for 1 h) was refluxed for 5 h. After cooling, the solvent was removed *in vacuo* to yield a residue which was partitioned between H_2O (5 cm^3) and dichloromethane (50 cm^3). The organic portion was then concentrated *in vacuo* to yield a residue which was chromatographed on neutral alumina eluting with 4:1 hexane–ethyl acetate (R_f = 0.62) to yield a colourless oil (110 mg, 45%). δ_H($CDCl_3$) 0.93 (6 H, t, CH_3C), 1.37–1.76 (12 H, m, CH_2C), 2.50 (4 H, m, CH_2C=O), 3.57–3.94 (14 H, m, CH_2O and CHO), 4.10 (4 H, t, CH_2O); δ_C($CDCl_3$) 13.60 (CH_3C), 19.03, 30.56 and 30.86 (CH_2C), 35.33 (CH_2C=O), 64.38, 66.70 and 70.13 (CH_2O), 78.21 (CHO) and 171.61 (C=O); ν_{max}(thin film)/cm^{-1} 1736 (C=O stretch) and 1120 (C–O); *m/z* (DCI, chloroform) 450 (M^+ + 18, 24%), 433 (M^+ + 1, 100%), 359 (M^+ − OBu, 25%), 255 (100%) and 179 (35%) (Found: C, 71.4; H, 11.2. $C_{22}H_{40}O_4$ requires: C, 71.8; H, 10.9%).

2,2-Dimethyl-5-hydroxymethyl-5-methyl-1,3-dioxane (14)[11]

1,1,1-Tris (hydroxymethyl)ethane (60 g, 0.5 mol), 2,2-dimethoxypropane (57.2 g, 0.55 mol), toluene-*p*-sulfonic acid (460 mg) were dissolved in dry chloroform (250 cm^3) and placed in a 1 dm^3 flask which was fitted with a Soxhlet extraction apparatus containing 4 Å molecular sieves. The mixture was refluxed for 17 h with one change of sieves and then cooled and stirred with moist sodium carbonate and filtered. The filtrate was then concentrated *in vacuo* to yield a colourless oil identical with an authentic sample[11] (77 g, 96%). δ_H($CDCl_3$) 0.83 (3 H, s, CH_3C), 1.39 (3 H, s, CH_3C), 1.44 (3 H, s, CH_3C), 2.83 (1 H, s, br, OH), 3.62 (2 H, d, 11.6 Hz, CH_2O), 3.67 (2 H, s, CH_2OH) and 3.70 (2 H, d, *J* 11.7 Hz, CH_2C); δ_C($CDCl_3$) 17.38 (CH_3C), 20.13 and 26.82 (CH_3C), 34.52 (CH_3–*C*–CH_2), 65.00 (CH_2OH), 65.97 (CH_2O) and 97.72 ([CH_3]$_2$–*C*–[OCH_2]$_2$); ν_{max}(thin film)/cm^{-1} 3500–3100 (O–H stretch) and 1115 (C–O stretch); *m/z* (dci, chloroform) 161 (M^+ + 1, 100%) and 145 (15).

2,2-Dimethyl-5-benzyloxymethyl-5-methyl-1,3-dioxane (15)[11]

To a solution of (**14**) (77 g, 0.48 mol) in dry THF (250 cm^3) was added fused ground sodium hydroxide (30 g, 0.75 mol) and tetrabutylammonium hydrogen sulfate (6.22 g, 0.018 mol) and the mixture stirred mechanically under nitrogen while a solution of benzyl chloride (64 cm^3, 70.4 g, 0.55 mol) in THF (250 cm^3) was added. The mixture was then refluxed for 48 h, cooled and filtered to remove the precipitated salt. The filtrate was then concentrated *in vacuo* to give a yellow oil. This was distilled under vacuum through a 20 mm Vigreux column to yield a colourless oil which was identical in properties with an authentic sample[11] (84.78 g, 70%), bp 87–91 °C (0.002 mmHg); δ_H($CDCl_3$) 0.89 (3 H, s, CH_3C), 1.37–1.42 (6 H, d, CH_3C), 3.46 (2 H, s, CH_2OBz), 3.50 (2 H, d, *J* = 11.6 Hz, CH_2O), 3.72 (2 H, d, *J* = 11.6 Hz, CH_2O), 4.53 (2 H, s, CH_2Ph), 7.31 (5 H, m, ArH); δ_C($CDCl_3$) 18.17 (CH_3C), 20.98 (CH_3C), 26.23 (CH_3C) and 34.22 (CH_2–*C*–CH_3), 66.39 (CH_2O), 72.91 (CH_2O), 73.13 ($ArCH_2O$), 97.66 ([CH_3]$_2$–*C*–[OCH_2]$_2$), 127.21, 127.61, 128.11 and 138.51 (Ar); ν_{max}(thin film)/cm^{-1} 1611 (arom C=C), 1088 (C–O stretch), 735 and 698 (=CH Ar *o,o,p*); *m/z* (DCI, chloroform) 251 (M^+ + 1, 100%), 193 (43), 158 (46) and 91 (Bz, 43).

2-Benzyloxymethyl-2-methylpropane-1,3-diol (10)

The isopropylidene derivative **15** was refluxed with concentrated HCl (45 cm^3) in methanol (450 cm^3) for 72 h. The solvent was then removed *in vacuo* to yield a yellow oil which was then recrystallised from toluene–hexane (35.53 g, 51%), mp 44–45 °C; δ_H($CDCl_3$) 0.83 (3 H, s, CH_3C), 2.45 (2 H, br s, OH), 3.47 (2 H, s, CH_2OBz), 3.60 (2 H, d, *J* = 10.8, CHHOH), 3.69 (2 H, d, *J* = 10.8, CHHOH), 4.52 (2 H, s, CH_2Ar) and 7.25–7.45 (5 H, m, ArH); δ_C($CDCl_3$) 17.33 (CH_3C), 40.78 (CH_2–*C*–CH_3), 67.83, 73.60 and 75.60 (CH_2O), 127.51, 127.47, 127.78 and 137.85 (Ar); ν_{max}(KBr)/cm^{-1} 3300 (O–H stretch), 1041 (C–O stretch), 738 and 697 (C–H bend); *m/z* (DCI, MeOH), 228 (M^+ + 18, 36%), 211 (M^+ + 1, 100), 108 (33), 91 (CH_2Ar, 20) and 86 (63) (Found: C, 68.3; H, 8.51%. $C_{12}H_{10}O_3$ requires C, 68.6; H, 8.61%).

Diethyl 5-benzyloxymethyl-5-methyl-3,7-dioxanonanedioate (16)

To a solution of (**10**) (10.0 g, 48 mmol) and BF_3–diethyl ether (20 cm^3) in dry dichloromethane (120 cm^3) was carefully added a solution of ethyl diazoacetate (10.86 g, 96 mmol) in dry dichloromethane (50 cm^3), under nitrogen. The solution was then stirred at 40 °C for 6 h. After cooling, the solvent was removed *in vacuo* to yield a yellow oil. This was purified by short-path distillation (115 °C, 0.05 mmHg), to yield a pale yellow oil (14.1 g, 77%). GC analysis indicated that the compound was ≥99.5% chemically homogeneous. δ_H($CDCl_3$) 1.05 (3 H, s, CH_3C), 1.27 (6 H, t, CH_3C), 3.42 (2 H, s, CH_2O) 3.42 (2 H, s, CH_2O), 3.48 (4 H, s, CH_2O), 4.06 (4 H, s, CH_2O), 4.18 (4 H, q, OCH_2–CH_3), 4.51 (2 H, s, OCH_2Ar) and 7.32 (5 H, m, Ar); δ_C($CDCl_3$) 14.11 (CH_3C), 17.17 (CH_3CH_2), 40.95 (CH_3–*C*–CH_2), 60.54, 68.88, 72.46, 73.18 and 74.44 (CH_2O), 127.26, 128.14 and 138.75 (ArC) and 170.58 (C=O); ν_{max}/cm^{-1} 1749 (C=O stretch), 1136 (C–O stretch), 740 and 700 (C–H *o,o,p* bend); *m/z* (DCI, methanol) 400 (M^+ + 18, 59%), 383 (M^+ + 1, 100), 308 (M^+ − CO_2Et, 21), 291 (M^+ − Bz, 16), 157 (23), 108 (OBz + 1, 43%) and 91 (Bz, 26).

5-Benzyloxymethyl-5-methyl-3,7-dioxanonane-1,9-diol (17)

To a suspension of lithium aluminium hydride (7 g, 184 mmol) in dry ether (150 cm^3) at 0 °C was added dropwise a solution of (**16**) (23.49 g, 61.3 mmol) in dry ether (300 cm^3). The mixture was then heated under reflux, under nitrogen, for 7 h with vigorous stirring and then stirred for a further 7 h at room temperature. The reaction mixture was then cooled to 0 °C and H_2O (24 cm^3), NaOH (15%, 48 cm^3) and H_2O (24 cm^3) were carefully added in turn. The aluminium salts were filtered off and the solvent removed under reduced pressure to yield a small amount of crude product. The aluminium salts were then boiled under reflux with chloroform–methanol (90:10) (250 cm^3) for 3 h to extract the product. The resultant suspension was then cooled to room temperature, filtered to remove the aluminium

salts and the solvent removed under reduced pressure to yield a residue. The product was purified by short path distillation (145 °C, 0.05 mmHg) to yield a colourless oil (11.7 g, 64%). GC analysis indicated that the compound was ≥97% chemically homogeneous. $\delta_H(CDCl_3)$ 0.97 (3 H, s, CH_3C), 2.61 (2 H, s, OH), 3.35 (2 H, s, CH_2O), 3.40 (4 H, d, CH_2O), 3.51–3.70 (8 H, dt, CH_2O), 4.50 (2 H, s, $ArCH_2O$) and 7.32 (5 H, m, Ar); $\delta_C(CDCl_3)$ 17.82 (CH_3C), 40.89 (CH_3–*C*–CH_2), 61.57, 72.41, 73.19, 73.36 and 73.88 (CH_2O), 127.44, 127.50, 128.29 and 138.48 (arom C); ν_{max}(thin film)/cm^{-1} 3380 (O–H stretch) and 1107 (C–O stretch); *m*/*z* (DCI) 299 (M^+ + 1, 100%).

5-Benzyloxymethyl-5-methyl-1,9-ditoluene-*p*-sulfonato-3,7-dioxanonane (18)

To a solution of **17** (10.0 g, 0.33 mmol) in dry pyridine (100 cm^3) at −10 °C was slowly added toluene-*p*-sulfonyl chloride (19.2 g, 0.136 mol). The mixture was then held at −20 °C for 72 h, then poured onto 300–400 g of crushed ice and stirred for 30 min. The product was purified by chromatography on silica eluting with a gradient of dichloromethane–methanol (100:0 to 97:3) to yield a viscous colourless oil (9.78 g, 48%). $\delta_H(CDCl_3)$ 0.84 (3 H, s, CH_3C), 2.43 (6 H, s, CH_3–Ar), 3.21 (2 H, s, CH_2O), 3.23 (4 H, s, CH_2O), 3.55 (4 H, t, CH_2O), 4.10 (4 H, t, CH_2O), 4.44 (2 H, s, CH_2Ar), 7.29–7.80 (13 H, m, Ar); $\delta_C(CDCl_3)$ 17.22 (CH_3C), 21.62 (CH_3–Ar), 40.98 (CH_3–*C*–CH_2), 68.76, 69.26, 72.71, 73.26, 73.64 (CH_2O), 127.34, 127.41, 127.93, 128.29, 129.84, 133.16, 138.83 and 144.75 (Ar); ν_{max}(thin film)/cm^{-1} 1601 (arom C=C stretch); *m*/*z* (DCI, chloroform) 624 (M^+ + 18, 100%), 607 (M^+ + 1, 10) and 437 (100) (Found: C, 59.27; H, 5.22. $C_{30}H_{38}S_2O_9$ requires C, 59.39; H, 6.31%).

6-Benzyloxymethyl-6-methyl-1,4,8,11-tetraoxacyclotetradecane (5)

This was prepared using the same procedure as for the preparation of **19**, using Li (870 mg, 125 mmol), LiBr (3.65 g, 42 mmol), **18** (8.72 g, 42 mmol), 1,9-ditoluene-*p*-sulfonato-3,7-dioxanonane[4] (19.87 g, 42 mmol), and *tert*-butyl alcohol (500 cm^3). The residue was purified by chromatography on neutral alumina eluting with hexane–ethyl acetate (3:1; R_f = 0.44) to yield a pale yellow oil (7.21 g, 53%). $\delta_H(CDCl_3)$ 0.98 (3 H, s, CH_3C), 1.77 (2 H, m, CH_2C), 3.32–3.66 (14 H, m, CH_2O), 4.49 (2 H, s, OCH_2Ar) and 7.31 (5 H, m, Ar); $\delta_C(CDCl_3)$ 16.67 (CH_3C), 29.57 (CH_2C), 39.63 (CH_2–*C*–CH_3), 65.42, 66.63, 69.27, 71.64 and 72.24 (CH_2O), 127.27, 127.19 and 137.44 (arom C); ν_{max}(thin film)/cm^{-1} 1132 (C–O stretch), 740 and 700 (CH, *o*,*o*,*p* bend); *m*/*z* (DCI, chloroform) 339 (M^+ + 1, 100%) (Found: C, 67.2; H, 8.60. $C_{19}H_{30}O_5$ requires C, 67.5; H, 8.87%).

6,13-Bis(benzyloxymethyl)-6,13-dimethyl-1,4,8,11-tetraoxacyclotetradecane (19)

Lithium metal (1.04 g, 150 mmol) was added to dry Bu^{t}OH (700 cm^3) and the mixture was stirred until the lithium had dissolved. To this solution was added **10** (10.3 g, 0.0495 mol), **18** (30.0 g, 0.0495 mol) and LiBr (4.34 g, 50 mmol) and the mixture was stirred at 60 °C (under nitrogen) for 36 h. Further **10** (7.30 g, 0.015 mol) was added and again the mixture was stirred at 60 °C (under nitrogen) for 72 h. After cooling, the solvent was removed under reduced pressure and the residue treated with HCl (6 mol dm^{-3}) until the pH = 2. The solution was then extracted with dichloromethane (2 × 75 cm^3) and chloroform (1 × 75 cm^3), washed with H_2O (50 cm^3), dried (K_2CO_3), filtered and the solvent removed. The residue was chromatographed on neutral alumina eluting with hexane–ethyl acetate (4:1, R_f = 0.4) to yield a pale yellow oil (8.92 g, 38%). $\delta_H(CDCl_3)$ 0.98 (6 H, s, CH_3C), 3.23–3.57 (16 H, m, CH_2O), 4.50 ($ArCH_2O$) and 7.32 (Ar); $\delta_C(CDCl_3)$ 17.72, 17.84 (CH_3C), 40.56 (CH_2–*C*–CH_2), 70.27, 72.35, 73.25 (CH_2O), 73.95 ($ArCH_2O$), 127.22, 127.27, 128.24 and 138.93 (Ar); ν_{max}(thin film)/cm^{-1} 1128 (C–O stretch), 738 and 699 (CH, *o*,*o*,*p* bend); *m*/*z* (DCI, chloroform) 490 (M^+ + 18, 42%), 473 (M^+ + 1, 44), 425 (70), 423 (39) and 383 (M^+ − Bz, 100) (Found: C, 71.0; H, 8.21. $C_{28}H_{40}O_6$ requires: C, 71.2; H, 8.53%).

6-Hydroxymethyl-6-methyl-1,4,8,11-tetraoxacyclotetradecane (6)

A suspension of **5** (7.0 g, 20.7 mmol), Pearlman's catalyst [*i.e.*, $Pd(OH)_2$ on C] (500 mg) and toluene-*p*-sulfonic acid (20 mg) in ethanol (50 cm^3) was shaken under H_2 (3 atm, 25 °C) for 48 h. After filtration and concentration *in vacuo*, a pale yellow oil (4.74 g, 91%) was isolated. This was not purified further. $\delta_H(CDCl_3)$ 0.76 (3 H, s, CH_3C), 1.77 (2 H, m, CH_2C), 3.26 (1 H, s, OH) and 3.41–3.77 (18 H, m, CH_2O); $\delta_C(CDCl_3)$ 17.55, 17.66, (CH_3C), 29.81 (CH_2C), 40.14 (CH_2–*C*–CH_3), 66.55, 70.24, 70.62, 70.65 and 74.49 (CH_2O); ν_{max}(thin film)/cm^{-1} 3440 (O–H stretch) and 1130 (C–O stretch); *m*/*z* (DCI, chloroform) 249 (M^+ + 1, 100%).

***trans*-6,13-Bis(hydroxymethyl)-6,13-dimethyl-1,4,8,11-tetraoxacyclotetradecane (12)**

This was prepared using the same procedure as for the preparation of **6**, using **19** (8.5 g, 18 mmol dm^{-3}), Pearlman's catalyst (750 mg), toluene-*p*-sulfonic acid (30 mg) and ethanol (100 cm^3). After filtration and concentration *in vacuo* a white solid was isolated (5.21 g, 98%). The two diastereoisomers were separated by chromatography on neutral alumina with a gradient elution system, CH_2Cl_2–MeCN (1:0 to 2:1). The *trans* diastereoisomer eluted with an R_f of 0.4 (2% MeOH–CH_2Cl_2). $\delta_H(CD_3CN)$ 0.79 (6 H, s, CH_3C), 2.76 (2 H, s, OH), 3.32–3.55 (20 H, m, CH_2O); $\delta_C(CDCl_3)$ 17.78 (CH_3C), 41.46 (CH_2–*C*–CH_3), 67.89, 71.14 and 73.74 (CH_2O); ν_{max}(KBr)/cm^{-1} 3315 (O–H stretch) and 1116 (C–O stretch); *m*/*z* (DCI, acetonitrile) 293 (M^+ + 1, 100%) (Found: C, 56.7; H, 9.45. $C_{14}H_{28}O_6$ requires C, 56.72; H, 9.64%).

6-Toluene-*p*-sulfonyloxymethyl-6-methyl-1,4,8,11-tetraoxacyclotetradecane (7)

To a solution of (**6**) (2.1 g, 8.47 mmol) in dry pyridine (30 cm^3) at −10 °C was added slowly, toluene-*p*-sulfonyl chloride (2.25 g, 12.0 mmol) and the mixture was held at −20 °C for 96 h. It was then poured onto crushed ice (50 g) and stirred for 30 min. The aqueous layer was decanted off and the residue purified by chromatography on silica eluting with dichloromethane–methanol (98:2) (R_f = 0.28) to yield a white solid (1.85 g, 54%), mp 64–66 °C. $\delta_H(CDCl_3)$ 0.91 (3 H, s, CH_3C), 1.73 (2 H, p, CH_2C), 2.44 (3 H, s, CH_3Ar), 3.31 (4 H, s, CH_2O), 3.49–3.59 (12 H, m, CH_2O), 3.86 (2 H, s, CH_2OTos) and 7.31–7.78 (4 H, dd, Ar); $\delta_C(CDCl_3)$ 17.02 (CH_3C), 21.74 (CH_3C), 30.26 (CH_2C), 40.22 (CH_2–*C*–CH_3), 66.55, 70.31, 70.77, 71.53 and 73.58 (CH_2O), 128.07, 129.84, 132.98 and 144.70 (Ar); ν_{max}(KBr)/cm^{-1} 1603 (C=C stretch) and 1105 (C–O); *m*/*z* (DCI, chloroform) 404 (M^+ + 1, 100%) (Found: C, 56.95; H, 7.65. $C_{19}H_{30}SO_7$ requires C, 56.69; H, 7.66%).

***trans*-6,13-Ditoluene-*p*-sulfonyloxymethyl-6,13-dimethyl-1,4,8,11-tetraoxacyclotetradecane (20)**

This was prepared using the same procedure as for the preparation of **7**, using **12** (750 mg, 2.58 mmol), tosyl chloride (1.5 g, 7.74 mmol) and dry pyridine (10 cm^3). The mixture was poured onto crushed ice (100 g) the precipitated product was filtered off, dried and recrystallised from ethanol to yield a white crystalline solid (1.38 g, 87%), mp 152–153 °C. $\delta_H(CDCl_3)$

0.87 (6 H, s, CH_3C), 2.44 (6 H, s, CH_3Ar), 3.23 (8 H, s, CH_2O), 3.83 (4 H, s, CH_2OTos) and 7.31–7.78 (8 H, dd, Ar); $\delta_C(CDCl_3)$ 16.92 (CH_3C), 21.63 (CH_3Ar), 40.00 (CH_2–C–CH_3), 70.18, 71.18 and 73.47 (CH_2O), 127.73, 129.93, 132.85 and 144.62 (Ar); ν_{max}(KBr) 1604 (C=C stretch) and 1110 (C–O stretch); *m/z* (DCI, chloroform) 618 ($M^+ + 18$, 100%), 601 ($M^+ + 1$, 68) and 429 (44) (Found: C, 56.3; H, 6.9. $C_{28}H_{40}S_2O_{10}$ requires C, 56.0; H, 6.71%).

6-Cyanomethyl-6-methyl-1,4,8,11-tetraoxacyclotetradecane (8)

To a solution of **7** (1.26 g, 3.13 mmol) in dry DMSO (15 cm^3) was added KCN (260 mg, 4.0 mmol) and 18-crown-6 (10 mg) and the resultant solution heated at 150 °C for 14 h. After cooling, the solvent was removed and the residue extracted with dichloromethane by refluxing for 1 h. After filtration the filtrate was concentrated *in vacuo* again yielding a residue which was chromatographed on neutral alumina with 2:1 hexane–ethyl acetate (R_f = 0.67) to yield a white crystalline solid (735 mg, 91%). $\delta_H(CDCl_3)$ 1.05 (3 H, s, CH_3C), 1.75 (2 H, p, CH_2C), 2.33 (2 H, s, CH_2CN), 3.40 (4 H, s, CH_2O), 3.40 (4 H, s, CH_2O) and 3.56–3.64 (12 H, m, CH_2O); $\delta_C(CDCl_3)$ 19.25 (CH_3C), 23.80 (CH_2C), 30.13 (CH_2CN), 38.25 (CH_2–C–CH_3), 66.52, 70.31, 70.77 and 73.05 (CH_2O) and 117.91 (CN); ν_{max}(KBr)/cm^{-1} 2245 (CN stretch) and 1105 (C–O stretch); *m/z* (DCI, chloroform) 275 ($M^+ + 18$, 85%) and 258 ($M^+ + 1$, 100) (Found: C, 60.55; H, 8.9; N, 5.3. $C_{13}H_{23}NO_4$ requires C, 60.68; H, 9.01; N, 5.44%).

***trans*-6,13-Bis(cyanomethyl)-6,13-dimethyl-1,4,8,11-tetraoxacyclotetradecane (13)**

This was prepared using the same procedure as for the preparation of **8** using **20** (1.2 g, 1.91 mmol), KCN (390 mg, 3.6 mmol), 18-crown-6 (10 mg) and DMSO (10 cm^3). The residue was chromatographed on neutral alumina eluting with 3:1 hexane–ethyl acetate (R_f = 0.57) to yield a white crystalline solid. The configuration of the molecule was established by X-ray crystallography (310 mg, 54%). $\delta_H(CDCl_3)$ 1.07 (6 H, s, CH_3C), 2.34 (4 H, s, CH_2CN), 3.39 (8 H, m, CH_2O) and 3.60 (8 H, m, CH_2O); $\delta_C(CDCl_3)$ 19.34 (CH_3C), 23.91 (CH_2CN), 38.20 (CH_2–C–CH_3), 70.47 and 72.99 (CH_2O) and 117.83 (CN); ν_{max}(KBr)/cm^{-1} 2242 (CN stretch) and 1105 (C–O stretch); *m/z* (DCI, chloroform) 311 ($M^+ + 1$, 100%) (Found: C, 61.55; H, 8.25; N, 8.75. $C_{16}H_{26}N_2O_4$ requires C, 61.91; H, 8.44; N, 9.03%).

6-Carboxymethyl-6-methyl-1,4,8,11-tetraoxacyclotetradecane (9)

To a solution of **8** (180 mg, 0.70 mmol) in ethylene glycol (1.5 cm^3) was added an aqueous solution of NaOH (1.0 cm^3; 2 mol dm^{-3}). The resultant solution was then heated at 150 °C for 48 h, cooled, acidified (6 mol dm^{-3} HCl) and then extracted with diethyl ether (2 × 30 cm^3). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield an off-white solid which was not purified further (90 mg, 47%). $\delta_H(CDCl_3)$ 0.95 (3 H, s, CH_3C), 1.70 (2 H, p, CH_2C), 2.28 (2 H, s, CH_2C=O), 3.40 (4 H, s, CH_2O) and 3.58 (12 H, m, CH_2O); $\delta_C(CDCl_3)$ 19.56 (CH_3C), 30.12 (CH_2C), 38.27 (CH_2–C–CH_3) 40.49 (CH_2C=O), 64.66, 70.23, 70.69 and 74.09 (CH_2O) and 175.94 (C=O); ν_{max}(KBr)/cm^{-1} 3500–3100 (O–H stretch), 1710 (C=O stretch) and 1090 (C–O stretch).

***trans*-6,13-Bis(carboxymethyl)-6,13-dimethyl-1,4,8,11-tetraoxacyclotetradecane (21)**

A solution of **13** (160 mg, 0.62 mmol) in 1:1 NaOH (aq., 2 mol dm^{-3}) methoxyethanol (5 cm^3) was refluxed for 2 days. After cooling, the solvent was removed under reduced pressure to yield a residue which was redissolved in H_2O (3 cm^3) and acidified with HCl (6 mol dm^{-3}). After acidification the aqueous phase was extracted with diethyl ether (3 × 30 cm^3), and the ethereal layer dried (MgO_4), filtered and concentrated *in vacuo* to yield an off-white waxy solid which was not purified further (80 mg, 44%). $\delta_H(CDCl_3)$ 0.93 (6 H, s, CH_3C), 2.20 (4 H, s, CH_2CO), 3.33 (8 H, s, CH_2O) and 3.53 (8 H, s, CH_2O); $\delta_C(CDCl_3)$ 19.11 and 19.43 (CH_3C), 38.00, 38.41 (CH_3–C–CH_2), 39.88, 40.23 (CH_2C=O), 70.06 and 73.71 (CH_2O) and 174.71 (C=O); ν_{max}(thin film)/cm^{-1} 3100 (OH stretch) and 1713 (C=O stretch).

6-Dibenzylcarbamoylmethyl-6-methyl-1,4,8,11-tetraoxacyclotetradecane (3)

To a solution of **9** (70 mg, 0.25 mmol) in dry CH_2Cl_2 (2 cm^3) was added dibenzylamine (100 mg, 0.51 mmol) and 4-dimethylaminopyridine (3 mg) and the solution cooled to −10 °C. To this cooled solution was added dicyclohexylcarbodiimide (51 mg, 0.25 mmol). The temperature of the solution was then slowly allowed to rise to room temperature and stirred for 1 h under argon. The precipitated dicyclohexylurea was filtered off and the filtrate concentrated *in vacuo* to yield a colourless residue. This was purified by chromatography on neutral alumina eluting with 3:1 hexane–ethyl acetate (R_f = 0.63) to yield a waxy solid, mp 57–59 °C (35 mg, 31%). $\delta_H(CDCl_3)$ 1.14 (3 H, s, CH_3C), 1.74 (2 H, p, CH_2C), 2.39 (2 H, s, CH_2C=O), 3.46 (4 H, d, CH_2O), 3.57 (12 H, m, CH_2O), 4.57 (4 H, d, CH_2N) and 7.28 (10 H, m, Ar); $\delta_C(CDCl)_3$ 20.26 (CH_2C), 37.30 (CH_2C=O), 39.87 (CH_2–C–CH_3), 48.47 and 50.74 (CH_2N), 69.93, 70.84, 71.09 and 74.76 (CH_2O), 126.91, 127.44, 127.83, 127.90, 128.64, 128.71, 128.89, 129.02, 129.37, 137.46, 138.22 (ArC) and 172.56 (C=O); ν_{max}(thin film)/cm^{-1} 1645 (C=O stretch); *m/z* (DCI, chloroform) 456 ($M^+ + 1$, 100%) (Found: C, 70.8; H, 8.01; N, 2.80. $C_{27}H_{37}NO_5$ requires C, 71.1; H, 8.17; N, 3.07%).

***trans*-6,13-Bis(dibenzylcarbamoylmethyl)-6,13-dimethyl-1,4,8,11-tetraoxacyclotetradecane (4b)**

This was prepared using the same procedure as for the preparation of **3** using the diacid **21** (80 mg, 0.23 mmol), dibenzylamine (90 mg, 0.46 mmol), dicyclohexylcarbodiimide (95 mg, 0.46 mmol) and 4-dimethylaminopyridine (2 mg). This was purified by chromatography on neutral alumina eluting with 3:1 hexane–ethyl acetate (R_f = 0.63) to yield a waxy solid, mp 90–92 °C (35 mg, 31%). $\delta_H(CDCl_3)$ 1.11 (6 H, s, CH_3C) 2.36 (4 H, s, CH_2C=O), 3.40 (8 H, s, CH_2O), 3.50 (8 H, s, CH_2O), 4.50–4.59 (8 H, dd, CH_2N) and 7.27 (20 H, m, ArH); $\delta_C(CDCl_3)$ 19.69 and 19.78 (CH_3C), 36.89 (CH_2C=O), 39.30 (CH_2–C–CH_2), 47.99, 50.26 (CH_2N), 70.25, 74.04 (CH_2O), 126.41, 127.23, 127.45, 128.20, 128.47, 128.84, 137.14, 137.72 (ArC) 172.00 (C=O); ν_{max}(thin film)/cm^{-1} 1645 (C=O stretch); *m/z* (DCI, chloroform) 636 ($M^+ + 1$, 58%), 440 [$M^+ - N(CH_2Ph)_2$, 100%] and 197 [$(PhCH_2)_2N^+ + 1$, 87%] (Found: C, 74.6; H, 7.35; N, 3.6. $C_{44}H_{54}N_2O_6$ requires C, 74.2; H, 7.69; N, 3.96%).

Crystal structure of *trans*-6,13-bis(cyanomethyl)-6,13-dimethyl-1,4,8,11-tetraoxacyclotetradecane (13)

$C_{16}H_{26}N_2O_4$, M = 310.4, monoclinic, space group $P2_1/n$, a = 6.282(2), b = 8.052(2), c = 17.079(3) Å, β = 97.39°, Z = 2, V = 856.7(4) $Å^3$, D_c = 1.203 g cm^{-3}, μ(Mo-Kα) = 0.086 mm^{-1}, crystal size = 0.20 × 0.25 + 0.45 mm, T = 153 K, number of reflections [$F > 4.0\ \sigma(F)$] = 1415, R = 10.53%, wR = 10.26%.

Intensity data were collected on a Rigaku AFC-6S diffractometer in ω–2θ scan mode using Mo-Kα radiation. Full lists of fractional atomic coordinates, bond lengths and angles, and thermal parameters have been deposited as

supplementary material with the Cambridge Crystallographic Data Centre.†

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† For details of the CCDC deposition scheme see 'Instructions for Authors (1995)', *J. Chem. Soc., Perkin Trans. 2*, 1995, issue 1.

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