Comparative Study of Mono- and Di-substituted 14-Crown-4 Derivatives as Lithium Ionophores

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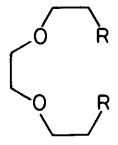
14-Crown-4 derivatives bearing either one or two methoxy, methoxycarbonylmethyl or carbamoylalkyl substituents have been prepared in an attempt to obtain selective ionophores for lithium ions. Complexation with lithium has been monitored by IR and ^{13}C NMR spectroscopy and solvent polymeric membranes have been fabricated and evaluated using the fixed interference method. The highest selectivity for lithium with respect to sodium is observed for a diamide derivative (630:1).

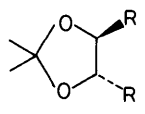
The implementation of electrically neutral, lipophilic ion-complexing agents as sensing ionophores in ion-selective electrodes has been well-established.[1] The potentiometric selectivity of these sensors for a given ion is primarily governed by the complexation specificity of the carrier molecule involved. Several neutral carriers for lithium ion in a lithium ion-selective electrode have been described, all of which exhibit only moderate selectivity for lithium with respect to sodium. Of these, the most promising are *N,N*-dicyclohexyl-*N'*,*N'*-di-isobutyl-*cis*-cyclohexane-1,2-dicarboxamide[2] and 6-dodecyl-6-methyl-1,4,8,11-tetraoxacyclotetradecane[3] which have been reported to give lithium selectivities relative to sodium of 280 and 150, respectively. These values have subsequently been revised independently to 140 and 125.[4]

Although several [14]-O_4 coronands have been prepared and examined in ion-selective electrodes, the substituents have usually been positioned in the trimethylene chain,[5,6] with greater regard for the substituent lipophilicity than for its efficacy in binding lithium efficiently. The series of [14]-O_4 ligands synthesised was chosen so as to vary systematically the nature of the additional donor groups and their number. In the set of monofunctionalised coronands (**17**)–(**23**), the ability of the donor groups preferentially to bind Li^+ over Na^+ was expected to mirror their relative σ-donor ability, *i.e.* amide donors with a high ground-state dipole moment should favour binding to Li^+ over Na^+ (as shown by related work with [12]-N_2O_2 disubstituted coronands[7]) compared with ether or methoxycarbonyl donors. This trend was expected to be accentuated in the *trans* di-substituted series (**10**)–(**16**). In addition, it was hoped that formation of 'sandwich-like' 2:1 complexes with Na^+ and K^+ would be suppressed with this disubstituted coronand, through unfavourable steric interactions between the substituents in formation of the 'sandwich' complex. The *trans*-disubstituted series was C_2-symmetric (and also chiral) in order that both substituents could bind simultaneously to a lithium cation held in the plane of the ring. The length of the donor arm—with one intervening methylene group—was surmised to be most suitable to permit binding of the small lithium cation in a six-ring chelate. The preference of small cations (*e.g.* Li^+) to form more stable complexes with six-ring chelates than larger cations (*e.g.* K^+ and to a lesser extent Na^+) has previously been noted in both macrocyclic chemistry[8] and in other areas of organic chemistry such as enolate association[9] or chelate-controlled stereoselective lithiation.[10]

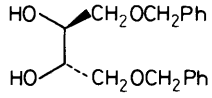


R

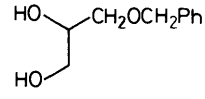
(**1**) CN
(**2**) CO_2Et
(**3**) CH_2OH
(**4**) CH_2Cl



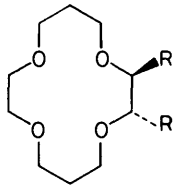
(**5**) CO_2Et
(**6**) CH_2OH
(**7**) CH_2OCH_2Ph



(**8**)

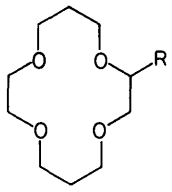


(**9**)



R

(**10**) CH_2OCH_2Ph
(**11**) CH_2OH
(**12**) CH_2OTs
(**13**) CH_2CN
(**14**) CH_2CO_2Me
(**15**) CH_2CO_2H
(**16**) CH_2CONBu_2



R

(**17**) CH_2OCH_2Ph
(**18**) CH_2OH
(**19**) CH_2OTs
(**20**) CH_2CN
(**21**) CH_2CO_2Me
(**22**) CH_2CO_2H
(**23**) CH_2CONMe_2

Synthesis of Ligands.—The chiral benzyloxymethyl 1,2-diols (**8**) and (**9**) afforded convenient starting materials for the introduction of functionality into the macrocycle. Co-cylisation of these diols with 1,10-dichloro-4,7-dioxadecane (**4**) [prepared *via* ethanolysis of the dinitrile followed by $LiAlH_4$ reduction (**1**)] in butan-2-ol in the presence of lithium t-butoxide and lithium bromide afforded the dibenzyl derivatives (**10**) and (**17**) in 51 and 42% yield, respectively. Lithium-templated cyclisation reactions of this type have been reported previously, usually in somewhat lower yield.[3,11] Hydrogenolytic debenzylation

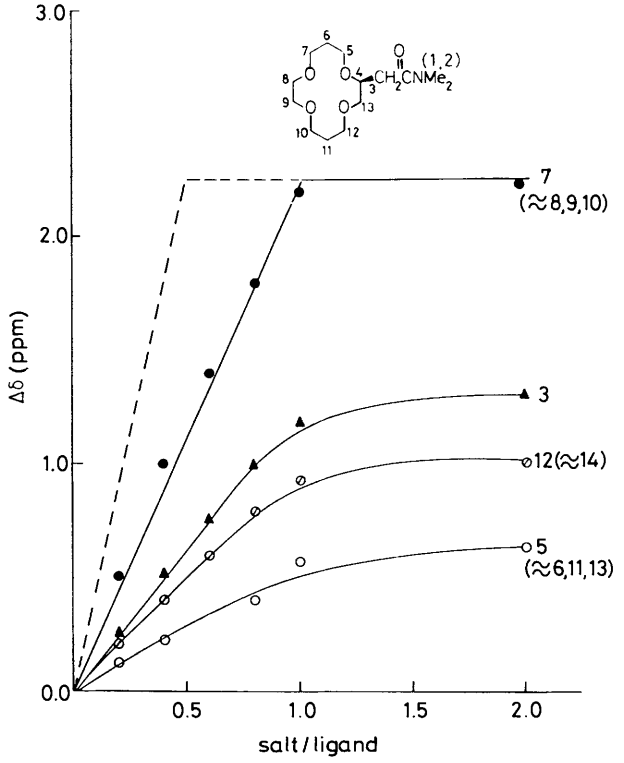


Figure 1. Incremental ^{13}C NMR shifts as a function of added lithium chloride with the monoamide derivative (**23**) (CD_3OD: $CDCl_3$ = 2:1).

Table 1. Calibration of electrodes using a dip-type method (310 K).

Ligand	Donor group(s)	Slope (mV per decade $[Li^+]$)	Limit of $[Li^+]$ detection[a]
Philips 561-Li^+ Ionophore		56	$10^{-5.0}$ ($10^{-2.05}$)
(**17**)	CH_2OCH_2Ph	53	$10^{-4.8}$ ($10^{-2.00}$)
(**10**)	$(CH_2OCH_2Ph)_2$	56	$10^{-4.9}$ ($10^{-2.15}$)
(**11**)	CH_2OH	37	$10^{-4.4}$ —
(**18**)	$(CH_2OH)_2$	32	$10^{-4.3}$ —
(**14**)	CH_2CO_2Me	55	$10^{-4.5}$ ($10^{-2.0}$)
(**21**)	$(CH_2CO_2Me)_2$	53	$10^{-4.6}$ ($10^{-2.05}$)
(**16**)	CH_2CONMe_2	48	$10^{-4.7}$ ($10^{-1.73}$)
(**23**)	$(CH_2CONBu_2)_2$	57	$10^{-5.2}$ ($10^{-2.50}$)

[a] Values are the mean of three separate measurements.
[b] Values in parentheses refer to a constant background of 150 mmol dm^{-3} NaCl, and were not optimised.

proceeded smoothly using Pearlman's catalyst to yield the alcohols (**11**) and (**18**), from which the toluene-*p*-sulphonate derivatives (**12**) and (**19**) were prepared using tosyl chloride in pyridine. Cyanation (KCN in DMSO) followed by acidic methanolysis afforded the desired esters (**14**) and (**21**). Conversion of these esters into the desired amides (**16**) and (**23**) was achieved by acid hydrolysis followed by treatment of the acids (**15**) and (**22**) with PCl_5 and subsequent reaction of the acid chloride with the appropriate amine.

IR and ^{13}C Studies of Complexation.—Solutions of the ligands in a 2:1 $CD_3OD/CDCl_3$ mixture were titrated against added lithium chloride. In all cases examined, the observed shifts of the ligand ^{13}C NMR resonances reached a maximum at 1:1 stoicheiometry. Discrete signals were not observed for the complex and the free ligand at intermediate stoicheiometries consistent with fast exchange between free and complexed ligand on the NMR time-scale (298 K, 62.1 MHz). A typical plot of the ^{13}C NMR shift displacement ($\Delta\delta$) for given carbon atoms in the monoamide (**23**) *vs.* the lithium/ligand ratio is shown in Figure 1. The relatively sharp 'curve-bend' obtained is suggestive of a fairly strong 1:1 complex, although the fact that separate signals were not observed for free and bound ligand implies that log $K \leq 4$. Participation in lithium binding by the amide carbonyl may be inferred from the co-ordination shift ($\Delta\delta$ = 0.9 ppm).

The occurrence of 'axial' donor participation was studied by IR spectroscopy for the esters (**14**) and (**21**), and the amides (**16**) and (**23**). Thin films of their lithium thiocyanate complexes were prepared by evaporation from methanol. Co-ordination shifts in the ester carbonyl stretching frequency were found to be 17 cm^{-1} (to lower frequency) for (**21**) and 13 cm^{-1} for (**14**). For the amides the co-ordination shifts of the carbonyl stretch observed were 15 and 16 cm^{-1} for (**23**) and (**16**), respectively. The observation of only one shifted carbonyl stretching frequency for the disubstituted derivatives is strongly suggestive of simultaneous co-ordination of both donors to the cation. Shifts in the ether carbon–oxygen stretch at *ca.* 1 120 cm^{-1} were also observed upon complexation with lithium. These were 40 cm^{-1} for the monosubstituted derivatives, and 25 cm^{-1} for the disubstituted ligands.

Electrode Calibration and Characterisation.—The selectivities reported for a particular ionophore are dependent upon the precise membrane composition and the composition of the analyte and hence on the method of measurement used for selectivity coefficient determination.[4] The selectivity for Li^+ with respect to Na^+ reported for *N,N*-dicyclohexyl-*N',N'*-di-isobutyl-*cis*-cyclohexane-1,2-dicarboxamide apparently varies from 280 to 70 as the plasticiser is changed, if potassium tetrakis(*p*-chlorophenyl)borate is added and if the separate solution or the fixed interference method is used for determination.[12]

Accordingly, in order to compare results with those previously reported,[3,6] all of the [14]-O_4 ionophores were prepared with the same PVC membrane, using the same plasticiser and lipophilic anion. The cocktail comprised 1.2% ionophore, 0.4% potassium tetrakis(*p*-chlorophenyl)borate, 65.6% *o*-nitrophenyl octyl ether and 32.8% PVC. Electrode characteristics (slopes, limits of detection and selectivity coefficients) were examined comparatively, at first with the fixed interference dip-type method and then the most promising electrodes were evaluated using the same procedure in a flow system. The performance of these new electrodes was compared with that of the commercially available Philips (561-Li^+) ion selective electrode.

Electrodes were examined comparatively by the fixed interference method and selectivities, limits of detection and sensitivities (slopes) were measured potentiometrically. Calibration measurements were performed at 37 °C for which a Nernstian response predicts a 61.5 mV potential difference per decade change in lithium activity. The electrodes were conditioned prior to examination by immersing for 24 h in 10^{-3} mol dm^{-3} LiCl solution. The results of this preliminary screen, carried out using a 'dip-type' method, are summarised in Table 1. The alcohols (**11**) and (**18**) behaved very poorly with poor slopes and modest limits of detection. The esters (**14**) and (**21**) were marginally inferior to the ethers (**10**) and (**17**), with the dibenzyl ether (**10**) exhibiting the most promising behaviour of the four. Of all the electrodes measured, the diamide (**16**) performed best, offering a significant improvement over the commercially available Philips (561-Li^+) electrode both in terms of measured slope and limit of detection. In all cases response times were fast, being no more than 30 s.

The electrodes based on the dibenzyl (**10**), diester (**14**), and

Table 2. Calibration of electrodes using a fixed interference method in a flow system (310 K).[a,*]

Ligand	Donor group	Slope in LiCl[c] (mV/decade)	Slope in interferents	Detection limit[b,d] $[Li^+]$ $[M^{n+}]$	log $K^{POT}_{Li,Na}$
Philips 561 Electrode		61	47	$10^{-4.5}$ $10^{-2.15}$	−1.33
(10)	$(CH_2OCH_2Ph)_2$	59	60	$10^{-5.1}$ $10^{-2.90}$	−2.08
(14)	$(CH_2CO_2Me)_2$	61	26	$10^{-5.0}$ $10^{-1.8}$	−0.98
(16)	$(CH_2CONBu_2)_2$	60	61	$10^{-5.2}$ $10^{-3.6}$	−2.80

[a] In the presence of 150 mmol dm^{-3} NaCl, 4.3 mmol dm^{-3} KCl, 1.26 mmol dm^{-3} $CaCl_2$. [b] Detection limits are given in units of lithium activity in the presence of Li^+ only or in the presence of interferents. [c] Addition of trioctylphosphine oxide improved the slopes for (**10**) and (**16**) by *ca.* 2 mV, but led to diminished limits of detection, $10^{-4.2}$ and $10^{-4.7}$ respectively. [d] Values have been corrected for the effects of ionic strength and assume Na^+ to be the primary interferent ion: they represent therefore minimum values for log $K^{POT}_{Li,Na}$.

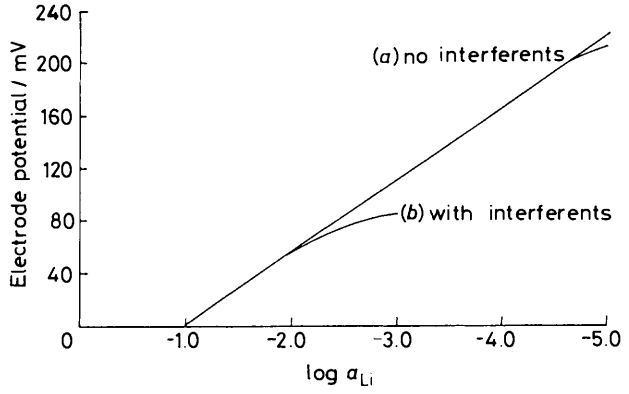


Figure 2. Electrode response of a membrane electrode cell assembly based on (**10**) in pure LiCl (no interferents) and in the presence of 150 mmol dm^{-3} NaCl, 4.3 mmol dm^{-3} KCl and 1.26 mmol dm^{-3} $CaCl_2$ (with interferents).

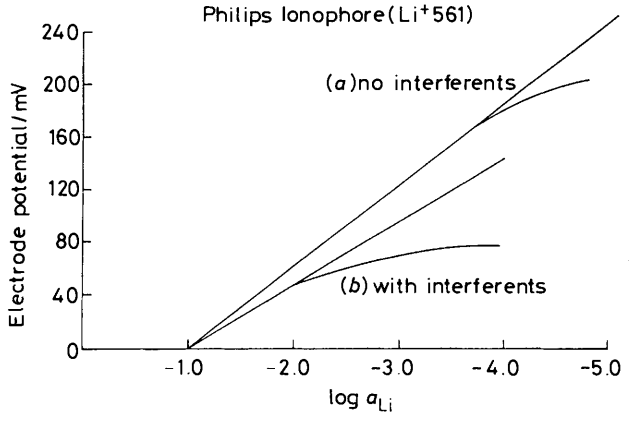


Figure 3. Electrode response of Philips 561 Li^+ electrode.

dibutylamide (**16**) derivatives were examined further in a flow system and compared to the Philips (561-Li^+) electrode. Calibration of the electrode response in pure lithium chloride solution yielded slopes and detection limits superior to those obtained using the dip-type method. Limits of detection were excellent for (**10**) and (**16**), and were slightly less good for (**14**): all were superior to those of the commercial electrode. Addition of trioctylphosphine oxide (TOPO)—promulgated by recent workers in order to enhance Li^+/Na^+ selectivity[3,5]—led to a diminished limit of detection but a slightly improved slope

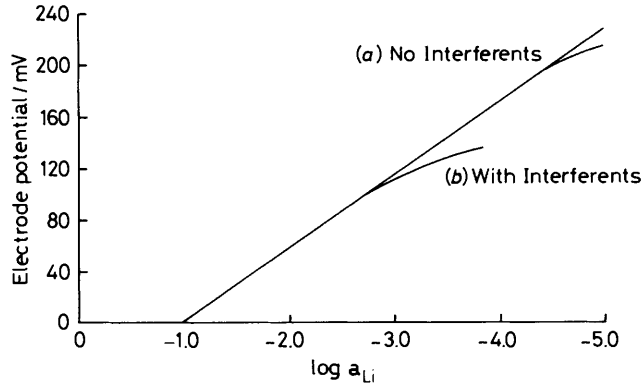


Figure 4. Electrode response of a membrane electrode cell assembly based on (**16**) in the presence and absence of interferents.

(Table 2). The addition of TOPO drastically impaired the performance of the electrode based on the diester (slope reduced to 28 mV per decade $[Li^+]$).

Measurements of lithium selectivity for (**10**), (**14**) and (**16**) (with and without TOPO) and the Philips electrode were made against a fixed background of 150 mmol dm^{-3} sodium chloride, 4.3 mmol dm^{-3} potassium chloride and 1.26 mmol dm^{-3} calcium chloride. Under these conditions, at 37 °C, a 'clinical' background is modelled as these concentrations represent those found typically in serum. For these measurements electrodes were conditioned overnight in 10^{-3} mol dm^{-3} LiCl solution. Electrode responses, in the presence and absence of interferents are depicted for (**10**), (**16**) and the Philips electrode in Figures 2–4. The measured selectivity coefficient for the Philips electrode (log $K^{POT}_{Li,Na}$ = −1.33) compares favourably with that reported by the manufacturers (log = −1.30).

For the dibenzyl and diamide electrodes without TOPO, the slopes in a fixed background of interferents remain the same as those measured in pure lithium chloride solutions (in the range 10^{-1} to *ca.* 10^{-3} mol dm^{-3} Li^+). For the Philips electrode, and particularly for the diester electrode, slopes fall when interferents are present, with concomitant lower limits of detection. The Li/Na selectivity coefficients for the dibenzyl and diamide are clearly higher than those of the Philips electrode, and the value of log $K^{POT}_{Li,Na}$ = 2.80 for the diamide represents an improvement on previously reported values—measured under similar conditions.[4,12] Although the Li/Na selectivity is still lower than that required for the 'ideal' measurement of Li^+ in whole blood (log $K^{POT}_{Li,Na}$ = −4.5), measurements could be performed, using adequate calibration solutions, with some confidence within the clinical lithium ion concentration range (0.5–2 mmol dm^{-3} $[Li^+]$).

The improved performance of the disubstituted ligands compared with the monosubstituted analogues in these

* *Note added in proof:* the diisobutyl analogue of (**16**) gave slopes of 50mV and 61mV in LiCl and interferents, and detection limits of $10^{-4.7}$ and $10^{-4.0}$ for $[Li^+]$ and $[M^{n+}]$, respectively, with a value of log $K^{POT}_{Li,Na}$ = −3.18 (1500:1).

potentiometric experiments bears out the premise that there is a need to suppress competitive 2:1 complex formation with sodium. Furthermore the encouraging performance observed with an electrode based on the diamide (**16**) vindicates the choice of amide donors to enhance Li/Na selectivity. Modifications to the amide disubstituent (*e.g.* cyclohexyl or isobutyl instead of butyl) and variation of the polar donor (phosphonate instead of amide) are being effected with the aim of improving further the Li/Na selectivity.

Experimental

Proton and carbon NMR spectra were recorded on a Bruker AC 250 (250.13 MHz and 62.1 MHz) spectrometer. Chemical shifts are quoted to higher frequency of Me_4Si as an internal standard and are given in ppm, with coupling constants in Hz. IR spectra were recorded on a Perkin-Elmer 580A IR Spectrophotometer, and mass spectra were recorded either in the EI, CI, DCI or FAB mode using a VG 7070E spectrometer. TLC was used (Merck $60F_{254}$) to follow the reactions, and column chromatography was effected using Merck 60 7354 or 9385 for flash chromatography. HPLC analyses were carried out with a Varian 5500 instrument using both ion exchange (TSK DEAE) or reversed-phase (Hypersil 5005) columns for analytical or semi-preparative work, typically using aqueous acetate/CH_3CN gradient elution. Compounds that did not give correct combustion microanalyses were examined for their purity by TLC and/or HPLC and were ≥ 96% homogeneous. Optical rotations were measured with a Perkin-Elmer 141 polarimeter, and combustion analyses were performed by Mrs. M. Cocks (University of Durham). All reactions were effected under an atmosphere of dry nitrogen. Gas chromatography was carried out with a Hewlett-Packard HP 5890 using an SE 30 capillary column.

Potentiometric Studies.—Membrane Preparation. The membranes were made up by dissolving 1.2% sensor, 65.6% plasticizer (ONPOE), 32.8% PVC (high molecular weight Fluka) and 0.4% lipophilic anion (KTpCIPB), with or without 1% TOPO, as required, in 6 cm^3 of spectroscopic grade tetrahydrofuran (THF) which was poured into a 33 mm i.d. 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.[16] 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.

Dip Type Method. Solutions were made up using anhydrous lithium chloride (BDH), sodium chloride (BDH), potassium chloride (BDH) and calcium chloride solution 1 mol dm^{-3} (BDH). The solid alkali metal salts were further dried by being stored in a desiccator over silica gel. All solutions were made up using deionised water (MilliQ).

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). The temperature of the system was maintained at 37 °C using a Techne Tempette junior TE-85 Thermostat bath.

Electrode potentials were measured by dipping both ion selective and reference electrodes into the analyte and recording the limiting potential value. The electrodes were thoroughly rinsed using deionised water between each measurement.

Flow System. A constant-volume cell was used for ion-selective electrodes. It was made from a water-jacketed glass tube with B19 ground-glass joint. Drilled glass stoppers with a wax seal were used for fitting the electrodes.

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

Solutions were made up using anhydrous lithium chloride (BDH), sodium chloride (BDH), potassium chloride (BDH) and calcium chloride solution 1 mol dm^{-3} (BDH). The solid alkali metal salts were further dried by being stored in a desiccator over silica gel. All solutions were made up using deionised water.

1,8-*Dicyano*-3,6-*dioxaoctane* (**1**).—To a stirred solution of aqueous sodium hydroxide (40 cm^3, 2% w/v) and ethane-1,2-diol (24.8 g, 0.2 mol) at 0 °C was added acrylonitrile (43 g, 0.4 mol) over 1 h. The mixture was stirred at room temperature for 24 h, then allowed to stand to aid separation of the lower aqueous layer. The organic layer was dried (K_2CO_3) and purified by distillation to yield a colourless oil (b.p. 90–95 °C, 0.1 mmHg), 28.6 g (85%). $\delta_H(CDCl_3)$ 2.58 (4 H, t, CH_2CN), 3.58 (4 H, t, *J* 6, CH_2O), and 3.53 (4 H, s, CH_2O); $\delta_C(CDCl_3)$ 17.9 (CH_2CN), 64.9 (CH_2O), 69.4 (CH_2O), and 117.7 (CN). ν_{max}(neat) 2 225 (CN), 1 105 (C–OC), and 840 cm^{-1}. *m/z* (CI) 169 ($M^+ + 1$), and 98 ($M^+ - CH_2CH_2CN$).

Diethyl 4,7-*Dioxadecane*-1,10-*dioate* (**2**).—To a solution of conc. sulphuric acid (20 g) in ethanol (100 cm^3) at 0 °C was added (**1**) (50.2 g, 0.3 mol) and the mixture was boiled under reflux for 24 h. After cooling the solvent was removed under reduced pressure, the residue was treated with dichloromethane (30 cm^3) then water (100 cm^3), and the aqueous layer was further extracted with dichloromethane (3 × 20 cm^3). The combined extracts were washed with a dilute brine solution (2 × 20 cm^3), dried ($MgSO_4$) and evaporated to yield a residue which was distilled (70 °C, 0.05 mmHg) to give a colourless oil (65.5 g, 84%). $\delta_H(CDCl_3)$ 1.25 (6 H, t, CH_2C), 2.60 (4 H, t, CH_2CO), 3.75 (4 H, t, *J* 6.4, CH_2O), 3.62 (4 H, s, CH_2O), and 4.15 (4 H, q, CH_2CH_3). $\delta_C(CDCl_3)$ 13.9 (CH_3), 34.8 (CH_2CO), 60.2 (CH_2O), 66.3 (CH_2O), and 171.3 (C=O). ν_{max}(neat) 1 735 (CO), 1 110 (COC), and 840 cm^{-1}; *m/z* (CI, isobutane): Found ($M^+ + 1$) 263.148 740. $C_{12}H_{22}O_6$ requires ($M^+ + 1$) 263.149 463.

1,10-*Dihydroxy*-4,7-*dioxadecane* (**3**).—To a suspension of lithium aluminium hydride (20 g) in dry diethyl ether (50 cm^3) at 0 °C was added (**2**) (38.8 g, 0.148 mol) slowly so as to maintain a gentle reflux. Once addition was complete, the mixture was stirred at room temperature for 24 h, cooled to 0 °C, and distilled water (20 cm^3) was slowly added followed by 15% aqueous sodium hydroxide solution (40 cm^3) then distilled water (20 cm^3). The mixture was efficiently stirred, and the white precipitate was removed by filtration and washed with diethyl ether (6 × 50 cm^3). The combined ether extracts were evaporated to yield a residue which was redissolved in dichloromethane (100 cm^3), filtered, dried (K_2CO_3) and evaporated to yield an oil which was distilled (90 °C, 0.05 mmHg) to give a colourless oil (13.9 g, 51%). $\delta_H(CDCl_3)$ 1.70 (4 H, quint., CH_2C), 3.52 (4 H, t, CH_2O), 3.49 (4 H, s, CH_2O), and 3.60 (4 H, t, CH_2OH). $\delta_C(CDCl_3)$ 31.8 (CH_2C), 59.1 (CH_2O), 68.3, and 69.5 (CH_2O). ν_{max}(neat) 3 500–3 100 (OH, br), 1 105, and 845 cm^{-1} (COC). *m/z* (CI) Found: 179.119 410 ($M^+ + 1$): $C_8H_{18}O_4$ requires 179.120 509.

1,10-*Dichloro*-4,7-*dioxadecane* (**4**).—To a stirred solution of (**3**) (9.2 g, 52 mmol) in dry benzene (50 cm^3) was added pyridine (0.12 mol) and thionyl chloride (14.3 g, 0.12 mol) and the mixture was boiled under reflux for 24 h. The mixture was cooled to 0 °C, hydrochloric acid was added (5 cm^3, 3 mol dm^{-3}), and the organic layer was separated, washed with water (2 × 20 cm^3), dried ($MgSO_4$). The solvents were removed under reduced pressure to yield a pale yellow liquid which was distilled (89 °C, 0.4 mmHg), (6.9 g, 62%). $\delta_H(CDCl_3)$ 1.94, (4 H, tt, *J* 6.1, CH_2C) and 3.55 (12 H, mult., CH_2O + CH_2Cl); $\delta_C(CDCl_3)$ 32.4 (CH_2C), 41.7 (CH_2Cl), 67.3 (CH_2O), and 70.0 (CH_2O). ν_{max}(neat) 1 120 (COC), and 655 cm^{-1} (C–Cl); *m/z* (CI) Found: 214.053 765. $C_8H_{16}Cl_2O_2$ requires 214.052 735.

trans-(4*R*,5*R*)-(−)-Bis(ethoxycarbonyl)-2,2-dimethyl-1,3-dioxolane (**5**) and *trans*-(4*S*,5*S*)-(−)-bis(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane (**6**) were prepared as described previously,[13] and 3-benzyloxymethylpropane-1,2-diol (**9**) was prepared according to the literature method.[14]

(2S,3S)-(−)-1,4-*Bis*(*dibenzyloxymethyl*)-2,2-*dimethyl*-1,3-*dioxolane* (**7**).—A mixture of (**6**) (5 g, 31 mmol), sodium hydroxide (2.95 g, 74 mmol), benzyl chloride (9.0 g, 74 mmol) and tetrapropylammonium bromide (50 mg) in dry THF (200 cm^3) was heated to reflux for 24 h. After cooling and filtration, the filtrate was evaporated and the residue was redissolved in dichloromethane (50 cm^3), washed with water (2 × 10 cm^3), dried ($MgSO_4$) and solvent was removed under reduced pressure. The resultant oil was distilled (115 °C, 0.1 mmHg) to give a colourless oil (7.1 g, 60%). $[\alpha]_D^{20}$ = −8.5° (*c* 1.0 in CH_2Cl_2) $[\alpha]_D^{20}$ (lit.,[15]) −7.5 (*c* = 2.6 in $CHCl_3$) GC analysis indicated that the compound was ≥ 99.7% chemically homogeneous. $\delta_H(CDCl_3)$ 1.44 (6 H, s, Me_2C), 3.61 (4 H, d, CH_2O), 4.00 (2 H, m, CHO), 4.57 (4 H, s, CH_2O), and 7.32 (10 H, br s, Ar). $\delta_C(CDCl_3)$ 26.9 (CH_3), 70.5 (CH_2O), 73.4 ($PhCH_2O$), 77.4 (CHO), 109.5 [CO(O)], 127.8, 128.3 (CH), and 137.9 (arom C). ν_{max}(neat) 1 600 (Ar ring), 1 372, and 1 081 cm^{-1}. *m/z* (CI) 343 (M^+ + 1), 342 (M^+).

(2S,3S)-(−)-1,4-*Bis*(*dibenzyloxymethyl*)*butane*-2,3-*diol* (**8**).—To a solution of (**7**) (15 g, 44 mmol) in acetone (35 cm^3) was added hydrochloric acid (1 mol dm^{-3}, 100 cm^3) and the mixture was heated to reflux for 24 h. After removal of solvent under reduced pressure, the residue was dissolved in dichloromethane (40 cm^3), dried ($MgSO_4$) and evaporated to yield a residue which was chromatographed on silica, eluting with ethyl acetate to give a colourless solid, (12 g, 90%), m.p. 51–52 °C, $[\alpha]_D^{20}$ = −7.5 (*c* 1.0 in CH_2Cl_2) (lit.,[14]); $[\alpha]_D^{20}$ = −5.0 (*c* = 5.0 in $CHCl_3$) m.p. 58–59 °C, GC analysis indicated that the diol was ≥ 99.7% homogeneous]. $\delta_H(CDCl_3)$ 3.60 (4 H, d, CH_2O), 3.87 (2 H, m, CH), 4.54 (4 H, s, CH_2O), and 7.32 (10 H, br s, arom). $\delta_C(CDCl_3)$ 70.4 (CH_2O), 73.4 ($PhCH_2O$), 71.7 (CHO), 127.6, 128.3 (arom CH), and 137.6 (arom q) (Found: C, 71.2; H, 7.42. $C_{18}H_{22}O_4$ requires: C, 71.5; H, 7.28%).

2-*Benzyloxymethyl*-1,4,8,11-*tetraoxacyclotetradecane* (**17**).—Lithium metal (0.38 g, 55.8 mmol) was added to dry butan-2-ol (200 cm^3) and the mixture was stirred at 50 °C until the lithium had dissolved. To this solution was added (**9**) (3.39 g, 18.6 mmol), 1,10-dichloro-4,7-dioxadecane (4 g, 18.6 mmol) and lithium bromide (1.62, 18.6 mmol) and the mixture was stirred under reflux for 14 days. After evaporation of solvent, the residue was treated with water (50 cm^3) and brought to pH 7 with hydrochloric acid (6 mol dm^{-3}). Extraction with dichloromethane (5 × 40 cm^3), followed by an aqueous wash (2 × 20 cm^3), drying ($MgSO_4$) and evaporation yielded a residue which was chromatographed on alumina, eluting with hexane–ethyl acetate (5:1) (R_f = 0.5) to yield a colourless oil (2.5 g, 42%). $\delta_H(CDCl_3)$ 1.73 (4 H, tt, CH_2C), 3.65 (17 H, m, CH_2O + CHO), 4.47 (4 H, s, CH_2Ph), and 7.27 (5 H, br s, arom). $\delta_C(CDCl_3)$ 30.3 (CH_2C), 30.4 (CH_2C); 65.7, 66.6, 67.0, 67.5, 69.8, 70.0, 70.9, 72.5 (CH_2O), 73.2 (CH_2Ph), 77.7 (CHO), 127.5, 128.3 (arom CH), and 138.1 (arom). ν_{max}(neat) 1 600 (ring) and 1 112 cm^{-1} (C–O–C). *m/z* (CI), 325 (M^+ + 1, 100%).

(2S,3S)-(−)-2,3-*Bis*(*benzyloxymethyl*)-1,4,8,11-*tetraoxacyclotetradecane* (**10**).—This was prepared as described for (**17**) using lithium (0.9 g, 129 mmol), butan-2-ol (500 cm^3), (**8**) (13 g, 43 mmol), (**4**) (9.25 g, 43 mmol) and lithium bromide (3.75 g, 43 mmol). Purification by column chromatography on alumina (eluant hexane–ethyl acetate, 3:1) yielded a viscous oil (9.8 g, 51%), $[\alpha]_D^{20}$ = −10.5 (*c* 1.0 in CH_2Cl_2). $\delta_H(CDCl_3)$ 1.77 (4 H, tt, CH_2C), 3.65 (18 H, m, CH_2O + CHO), 4.44 (4 H, s, CH_2Ph), and 7.26 (10 H, s, arom). $\delta_C(CDCl_3)$ 30.5 (CH_2C); 66.0, 66.3, 68.8, 69.9 (CH_2O), 72.4 (CH_2Ph), 79.7 (CHO), 127.0, 127.7, and 137.7 (arom). ν_{max} 1 600 and 1 113 cm^{-1}. *m/z* (CI) 445 (M^+ + 1, 100%), 355 (M^+ − $PhCH_2$, 50%), 337 (M^+ − $PhCH_2O$, 80%), and 245 (M^+ − Bz − BzO, 70%).

2-*Hydroxymethyl*-1,4,8,11-*tetraoxacyclotetradecane* (**18**).—A suspension of (**17**) (5 g, 15.4 mmol), Pearlman's catalyst [*i.e.* $Pd(OH)_2$ on C] (500 mg) and toluene-*p*-sulphonic acid (20 mg) in ethanol (50 cm^3) was shaken under H_2 (3 atm, 25 °C) for 24 h. After filtration and evaporation, the residue was chromatographed on neutral alumina, eluting with ethyl acetate (R_f = 0.3) to give a viscous oil (3.3 g, 92%). $\delta_H(CDCl_3)$ 1.6–1.9 (4 H, m, CH_2C), 2.85 (1 H, s, OH), and 3.2–3.9 (17 H, m, CH_2O, CHO). $\delta_C(CDCl_3)$ 30.3, 30.4 (CH_2C); 62.8 (CH_2OH); 66.1, 66.8, 66.9, 67.5, 69.5, 71.3, 72.5 (CH_2O) and 78.7 (CHO). ν_{max}(neat) 3 600–3 100 (br, OH), 1 120, and 1 090 cm^{-1} (COC). *m/z* (CI) Found: (M^+ + 1): 235.166 990; $C_{11}H_{22}O_5$ requires (M^+ + 1): 235.167 105.

trans-(2S,3S)-(−)-2,3-*Bis*(*hydroxymethyl*)-1,4,8,11-*tetraoxacyclotetradecane* (**11**).—This was prepared as described for (**18**) and the product was purified on alumina, eluting with ethyl acetate (R_f 0.3), to give a colourless oil (1.85 g, 90%), $[\alpha]_D^{20}$ = −11.5° (*c* 1.0 in CH_2Cl_2). $\delta_H(CDCl_3)$ 1.70 (4 H, tt, CH_2C), 2.88 (2 H, s, OH), and 3.41–3.85 (18 H, m, CH_2O + CHO). $\delta_C(CDCl_3)$ 29.8 (CH_2C), 61.5 (CH_2OH), 66.1, 67.4, 70.0, 71.4 (CH_2O), and 78.5 (CHO). ν_{max}(neat) 3 600–3 100 (OH, br), 1 135, and 1 072 cm^{-1} (COC). *m/z* (CI) Found: 265.156 890 (M^+ + 1). $C_{12}H_{25}O_6$ requires (M^+ + 1) 265.154 890.

2-*Toluene*-p-*sulphonyloxymethyl*-1,4,8,11-*tetraoxacyclotetradecane* (**19**).—To a solution of (**18**) (5 g, 21.3 mmol) in dry pyridine (10 cm^3) at −10 °C was added toluene-*p*-sulphonyl chloride (4.4 g, 23.5 mmol) and the mixture was held at −20 °C for 48 h, then poured onto crushed ice (50 cm^3) and treated with hydrochloric acid (6 mol dm^{-3}, 20 cm^3). The acidic aqueous layer was extracted with dichloromethane (5 × 30 cm^3), dried ($MgSO_4$) and solvent was evaporated to give a residue which was chromatographed on silica with dichloromethane to yield a viscous oil (3.7 g, 45%). $\delta_H(CDCl_3)$ 1.5–1.7 (4 H, m, CH_2C), 2.43 (3 H, s, CH_3), 3.25–3.60 (14 H, m, CH_2O), 3.71 (1 H, m, CHO), 3.95 (2 H, d, *J* 5.2, CH_2OTs), 7.28 (2 H, d, *J* 8), and 7.71 (2 H, d). $\delta_C(CDCl_3)$ 21.6 (CH_3), 30.2 (CH_2C); 65.8, 66.3, 66.5, 67.3, 69.3, 69.7, 70.7 (CH_2O), 76.2 (CHO), 127.2, 129.7 (CH); 132.9, and 144.7 (1 q, arom). ν_{max}(neat) 1 125, 1 085 (COC), 1 360, 1 192, and 1 176 cm^{-1} (SO). *m/z* (CI) 389 (M^+ + 1, 100%), and 216 (M^+ − OTs, 30%).

trans-(2S,3S)-(−)-2,3-*Bis*(*toluene*-p-*sulphonyloxymethyl*)-1,4,8,11-*tetraoxacyclotetradecane* (**12**).—This was prepared as described for (**19**) using (**11**) (4 g, 15.2 mmol), pyridine (15 cm^3), and toluene-*p*-sulphonyl chloride (3.2 g, 16.7 mmol). Purification

by column chromatography on silica yielded a colourless solid (4.2 g, 48%), m.p. 74–75 °C, $[\alpha]_D^{20} = -15.0$ (*c* 1.0 in CH_2Cl_2). $\delta_H(CDCl_3)$ 1.40–1.65 (4 H, m, CH_2C), 2.36 (6 H, s, CH_3), 3.20–3.77 (14 H, m, CH_2O + CHO), 4.05 (4 H, d, CH_2OTs) 7.27 (2 H, d, *J* 7.6), and 7.68 (2 H, d). $\delta_C(CDCl_3)$ 21.5 (CH_3), 30.5 (CH_2C), 66.5, 66.6, 68.6, 70.3 (CH_2O), 77.2 (CHO), 127.9, 129.8 (CH arom), 132.6, and 144.9 (q, arom). ν_{max}(Nujol) 1 120, 1 083 (COC), 1 360, 1 185, and 1 178 cm^{-1} (SO). *m/z* (CI) 573 (M^+, 100%), 229 (35%) (Found: C, 54.6, H, 6.32. $C_{26}H_{36}S_2O_{10}$ requires: C, 54.5; H, 6.29%).

2-*Cyanomethyl*-1,4,8,11-*tetraoxacyclotetradecane* (**20**).—To a solution of (**19**) (3.5 g, 9 mmol) in dry DMSO (50 cm^3) was added potassium cyanide (0.98 g, 15 mmol) and the mixture was heated to 95 °C (3 h). After cooling, water (40 cm^3) was added and the solution was extracted with dichloromethane (5 × 20 cm^3). The combined extracts were washed with water (2 × 15 cm^3), dried ($MgSO_4$) and solvent was evaporated to yield a residue which was chromatographed on neutral alumina, eluting with ethyl acetate–hexane (1:4) to give a viscous oil (1.35 g, 62%). $\delta_H(CDCl_3)$ 1.76 (4 H, m, CH_2C), 2.52 (2 H, d, *J* 7, CH_2CN), and 3.30–4.05 (15 H, m, CH_2O + CHO). $\delta_C(CDCl_3)$ 20.8 (CH_2CN), 30.1 (CH_2C), 66.2, 66.4, 67.5, 69.6, 70.2, 70.8, 71.9 (CH_2O), 75.7 (CHO), and 117.7 (CN). ν_{max}(neat) 2 250 (CN), and 1 123 cm^{-1} (COC). *m/z* (CI) 244 (M^+ + 1, 100%).

trans-(2S,3S)-2,3-(−)-*Bis*(*cyanomethyl*)-1,4,8,11-*tetraoxacyclotetradecane* (**13**).—This was prepared as described for (**20**) using (**12**) (5.15 g, 9 mmol), KCN (0.95 h, 14 mmol) and DMSO (50 cm^3). The product was purified by chromatography on alumina, eluting with ethyl acetate–hexane (1:3) to yield a colourless solid (1.2 g, 48%), m.p. 77–78 °C $[\alpha]_D^{20} = -6.5°$ (*c* 1.0 in CH_2Cl_2). $\delta_H(CDCl_3)$ 1.75 (4 H, tt, CH_2C), 2.55 (4 H, m, CH_2CN), and 3.40–3.85 (14 H, m, CH_2O + CHO). $\delta_C(CDCl_3)$ 18.7 (CH_2CN), 30.1 (CH_2C); 66.9, 67.3, 69.5 (CH_2O), 75.7 (CHO), and 117.1 (CN). ν_{max}(Nujol) 2 250 (CN), and 1 023 cm^{-1} (COC). *m/z* (FAB, glycerol) 283 (M^+ + 1, 30%) (Found: C, 59.3; H, 7.85; N, 9.82. $C_{14}H_{22}N_2O_4$ requires: C, 59.6; H, 7.80; N, 9.93%).

2-*Methoxycarbonylmethyl*-1,4,8,11-*tetraoxacyclotetradecane* (**21**).—Through a solution of (**20**) (500 mg, 2.05 mmol) in methanol (30 cm^3) was bubbled dry HCl gas for 1 h. The mixture was stirred under reflux for 5 h, and solvent was removed under reduced pressure to leave a residue which was taken up in water (5 cm^3) and extracted into dichloromethane (3 × 20 cm^3). The extracts were washed with aqueous potassium carbonate solution (10%, 2 × 10 cm^3), dried ($MgSO_4$) and solvent was removed to give a gum which was purified by chromatography on alumina, eluting with ethyl acetate–hexane (1:5) to yield a colourless oil (360 mg, 63%). $\delta_H(CDCl_3)$ 1.68 (4 H, m, CH_2C), 2.36 (2 H, dd, CH_2CO), and 3.50–3.95 (18 H, m, CH_3 + CH_2O + CHO). $\delta_C(CDCl_3)$ 30.6, 30.8, (CH_2C), 37.1 (CH_2CO), 51.7 (OCH_3), 65.8, 66.6, 67.0, 67.2, 70.0, 71.3, 74.0 (CH_2O), 76.5 (CH), and 171.7 (CO). ν_{max}(neat) 1 742 (CO_2Me), and 1 120 cm^{-1} (COC). *m/z* (CI) 277 (M^+ + 1, 100%).

(2S,3S)-(−)-2,3-*Bis*(*methoxycarbonylmethyl*)-1,4,8,11-*tetraoxacyclotetradecane* (**14**).—This was prepared as described for (**21**), to yield a clear oil (320 mg, 52%), $[\alpha]_D^{20} = -39.5$ (*c* 1.0 in CH_2Cl_2). $\delta_H(CDCl_3)$ 1.74 (4 H, m, CH_2C), 2.48 (4 H, dd, CH_2CO), and 3.43–4.0 (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 (CO_2Me). ν_{max}(neat) 1 741 (CO_2Me) and 1 115 cm^{-1} (COC). *m/z* (CI), 349 (M^+ + 1, 100%), 171 (80%).

2-*Carboxymethyl*-1,4,8,11-*tetraoxacyclotetradecane* (**22**).—To a solution of (**21**) (300 mg, 1.1 mmol), in aqueous methanol (10 cm^3, 1:1) was added tetramethylammonium hydroxide (1 g) and the mixture was boiled for 2 h. After removal of the solvent under reduced pressure, the residue was treated with hydrochloric acid (5 cm^3, 6 mol dm^{-3} HCl) and extracted with diethyl ether (6 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and solvent evaporated to yield a colourless glassy solid (250 mg, 86%). $\delta_H(CDCl_3)$ 1.72 (4 H, tt, CH_2C), 2.51 (2 H, dd, CH_2CO), 3.45–3.92 (15 H, m, CH_2O + CHO), and 10.2 (1 H, s, CO_2H). $\delta_C(CDCl_3)$ 30.1 (CH_2C), 37.0 (CH_2CO), 65.7, 66.6, 67.2, 69.5, 70.0, 71.0, 73.5 (CH_2O), 74.9 (CHO), and 175.8 (CO_2H). ν_{max}(Nujol) 3 600–2 600 (OH, br), 1 746 (CO_2H), and 1 120 cm^{-1} (COC). *m/z* (CI) 263 (M^+ + 1, 100%), 245 (M^+ − H_2O, 80%).

(2S,3S)-(−)-*Bis*(*carboxymethyl*)-1,4,8,11-*tetraoxacyclotetradecane* (**15**).—This was prepared as described for (**22**) to give an off-white waxy solid (150 mg, 75%). $\delta_H(D_2O)$ 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), 78.2 (CHO) and 174.8 (CO_2H). ν_{max}(Nujol) 3 600–2 600 (OH, br), 1 750 (CO_2H) and 1 120 cm^{-1} (COC).

2-(N,N-*Dimethylcarbamoylmethyl*)-1,4,8,11-*tetraoxacyclotetradecane* (**23**).—To a solution of (**22**) (440 mg, 1.5 mmol) in dichloromethane (5 cm^3) was added phosphorus pentachloride (285 mg, 1.35 mmol) and the mixture was stirred for 24 h at room temperature. After evaporation to dryness, both IR and ^1H NMR analysis confirmed complete conversion into the acid chloride. The residue was redissolved in dichloromethane (20 cm^3) and a solution of aqueous dimethylamine (30% v/v, 2 cm^3) was added slowly at 0 °C. The mixture was allowed to stir at room temperature for a further 1 h when the organic layer was separated, washed with water (2 × 5 cm^3), dried and evaporated to yield a residue which was chromatographed on silica, eluting with ethyl acetate (R_f *ca.* 0.63), to give a colourless oil (220 mg, 50%). $\delta_H(CDCl_3)$ 1.75 (4 H, tt, CH_2C), 2.52 (2 H, dd, CH_2CO), 2.95 (3 H, s, NMe), 3.03 (3 H, s, NMe), and 3.45–3.95 (15 H, m, CH_2O + CHO). $\delta_C(CDCl_3)$ 30.3, 30.4, (CH_2C), 35.6, 37.5 (CH_3N), 35.8 (CH_2CO), 65.6, 66.6, 67.1, 69.1, 71.0, 73.6 (CH_2O), 75.6 (CHO), and 170.8 (CO). ν_{max}(neat) 1 637 ($CONMe_2$) and 1 120 (COC) cm^{-1}. *m/z* (CI) 290 (M^+ + 1, 100%), 179 (15%), 85 (23%).

trans-(2S,3S)-3(−)-2,3-*Bis*(N,N-*dibutylcarbamoylmethyl*)-1,4,8,11-*tetraoxacyclotetradecane* (**16**).—To a solution of (**15**) (150 mg, 0.47 mmol) in dichloromethane (5 cm^3) was added PCl_5 (95 mg, 0.45 mmol) and the solution was stirred at room temperature for 12 h. This solution was added slowly to a solution of dibutylamine (0.25 g, 1.9 mmol) and triethylamine (0.19 g, 1.9 mmol) in dichloromethane (10 cm^3) at 0 °C. After 2 h of stirring, the solvent was removed under reduced pressure and the residue was partitioned between heptane and water. The organic phase was washed with dilute hydrochloric acid (2 × 5 cm^3) then water (2 × 5 cm^3), dried ($MgSO_4$) and the solvent was evaporated to yield a residue which was chromatographed on neutral alumina, eluting with ethyl acetate–hexane (1:1) to give a colourless oil (153 mg, 60%), $[\alpha]_D^{20} = -33.7°$ (*c* 1.0 in CH_2Cl_2). $\delta_H(CDCl_3)$ 0.85 (12 H, q, *J* 7, CH_3), 1.30 (8 H, m, CH_2CH_3), 1.45 (8 H, m, $CH_2CH_2CH_3$), 1.75 (4 H, tt, CH_2C ring), 2.31 (4 H, dd, CH_2CO), 3.12 (4 H, m, CH_2N), 3.34 (4 H, m, CH_2N), 3.50–3.65 (12 H, m, CH_2O), and 3.82 (2 H, dd, CHO). $\delta_C(CDCl_3)$ 13.8 (CH_3), 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}(neat) 1 638 ($CONBu_2$), and 1 115 cm^{-1} (COC). *m/z* (CI) 543 (M^+ + 1, 55%), 231 [M^+ − $(CONBu_2)_2$, 100%].

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