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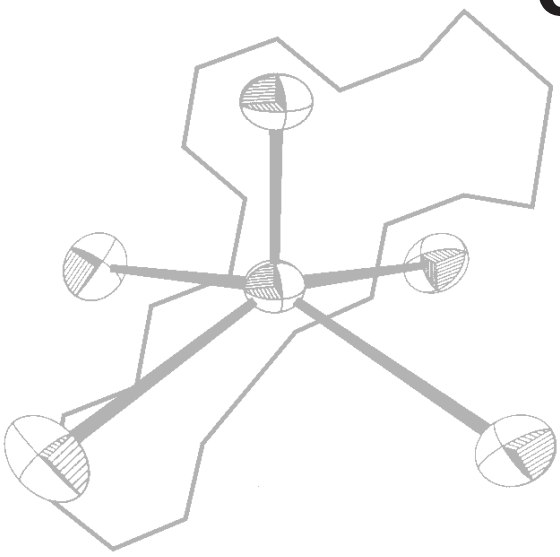

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New Macrocyclic Ligands. VIII* Di- and Tri-linked Macrocyclic Systems Incorporating N_2O_2-Donor Atoms

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The synthesis and characterization of new lipophilic di- and tri-linked O_2N_2-donor macrocycles is reported. The synthesis of the dilinked species involved the initial alkylation of one secondary nitrogen of the parent 15-membered, O_2N_2-donor macrocycle (1) with 2-bromoethanol or with ethylene oxide to yield (2), followed by protection of the appended alcohol group by reaction with t-butyldiphenylsilyl chloride to give (3). Two such moieties were then bridged via a diacylation reaction with $ClCO(CH_2)_8COCl$ to yield the corresponding diamide product (4). Deprotection of the alcohol functions followed by reduction of the both amide linkages resulted in formation of the N,N'-alkyl-linked species (5) incorporating two pendant hydroxyethyl groups. This product was then converted [via the corresponding dichloro derivative (6)] into the diether (7) by condensation with 4-t-butylphenol.

By use of analogous chemistry, the trilinked trismacrocycle species (12), based on a phloroglucinol core, has also been synthesized. An aim of the present study was thus the preparation of new 'linked' macrocyclic systems that might be expected to show higher lipophilicity than their corresponding single-ring systems. These were designed for future use as ionophores in metal ion membrane transport (and solvent extraction) experiments.

Introduction

We have been interested in the design of macrocyclic ring systems for the recognition of small molecules and ions (and especially transition and post transition metal ions).[1] Recently, we have extended these studies to the synthesis of structurally elaborated ligand systems based on macrocyclic rings.[2] Because of their often unique properties,[3] macrocyclic rings are desirable moieties for incorporation in larger multicomponent molecular systems since they often give rise to kinetically and thermodynamically stable complexes that, as a consequence, tend to retain their integrity under a range of conditions.

One category of larger macrocyclic systems is composed of linked ring ligands which are capable of binding simultaneously to two or (less commonly) more metal ions.[4] For example, many covalently linked bis(macrocyclic) ligands incorporating polyaza rings have now been reported.[5] One interest in such systems has reflected their potential for exhibiting cooperative behaviour of the type found in particular metalloenzymes incorporating two metal centres.[6] Recent attention has also been given to such linked species because of the observation that a number of such compounds act as anti-HIV agents, while exhibiting low cytotoxicity.[7] Many linked mixed-donor macrocycles are also known,[4,8] although these are less common than the all-nitrogen derivatives just mentioned.

We now report the synthesis of the new di- and trilinked (lipophilic) macrocycles (7) and (12) (Schemes 1 and 2, respectively). A motivation for this study was to produce linked species that would prove suitable for use as ionophores in solvent extraction studies for the selective extraction of heavy metal ions. In particular, it was of interest (and of potential industrial relevance) to compare the performance of linked ionophores in such studies relative to the behaviour of an equivalent

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concentration of the corresponding monomeric analogue. For this purpose, the related single-ring species (10) (Scheme 2) was also synthesized.

Pendant arm derivatives of the parent N_2O_2-donor macrocycle (1), incorporating hydroxyethyl[9] and 2-pyridyl arms[10] appended to the nitrogen donor(s) of (1) have been synthesized previously in the authors' laboratory. However, such ligands are not lipophilic enough for ideal use as ionophores in membrane ($H_2O/CHCl_3/H_2O$) transport experiments (at least, in the absence of a lipophilic anion). Thus, preliminary experiments indicated[11] that bleeding into the aqueous receiving phase occurs when either of the above ligands was used as the extractant in solvent extraction (water/chloroform) experiments involving the extraction of copper(II) nitrate into the chloroform phase.

Results and Discussion

Single-Ring Macrocycle (10)

The starting point for this synthesis was the *N*-hydroxyethyl macrocycle (2)[9] which has available both a secondary amine and a primary alcohol site for further functionalization (Scheme 2). To ensure selective reaction at the amine site, the alcohol group was first protected by formation of the corresponding t-butyldiphenylsilyl ether derivative (3); the latter was obtained in 89% yield by reaction of (2) with t-butyldiphenylsilyl chloride under standard conditions.[12] *N*-Alkylation of (3) with 1-iodoheptane (acetonitrile/$NaHCO_3$/60°C) was then carried out. Cleavage of the silyl ether group of this product was found to occur readily by acid hydrolysis ($MeOH/H_2O$/conc. HCl, 20 : 5 : 2). However, nucleophilic cleavage ($Bu_4N^+F^-$/tetrahydrofuran)[13] proved to be much less successful; only a very low yield of the hydroxyethyl macrocycle (8) was isolated after chromatographic workup in the latter case.

Reaction of (8) with thionyl chloride in dichloromethane gave the chlorinated derivative (9) in high yield. This product was homogenous by t.l.c. and was used without further purification since attempted chromatography on silica gel led to decomposition. The chloro derivative (9) was used to alkylate 4-t-butylphenol (*N*,*N*-dimethylformamide/NaI/caesium carbonate/60°C) yielding the required 'single-ring' macrocycle (10) in 37% yield. Spectroscopic data were in accord with the proposed structure; in particular, the success of the alkylation procedure was indicated by the downfield shift of the carbinyl methylene ($CH_2C\mathbf{H}_2O$) signal from δ 3·18 for the parent hydroxyethyl macrocycle (2) to δ 3·99 for the phenyl ether (10).

An alternative synthesis of (10) was also attempted starting from the unsubstituted parent macrocycle (1). Direct alkylation of (1) was performed by heating it with 1-iodoheptane in the presence of $NaHCO_3$ in acetonitrile. Reaction of this latter product with 1-(2-bromoethoxy)-4-t-butylbenzene under similar conditions to those just described resulted in formation of (10), but in this case the yield after workup was only 15%.

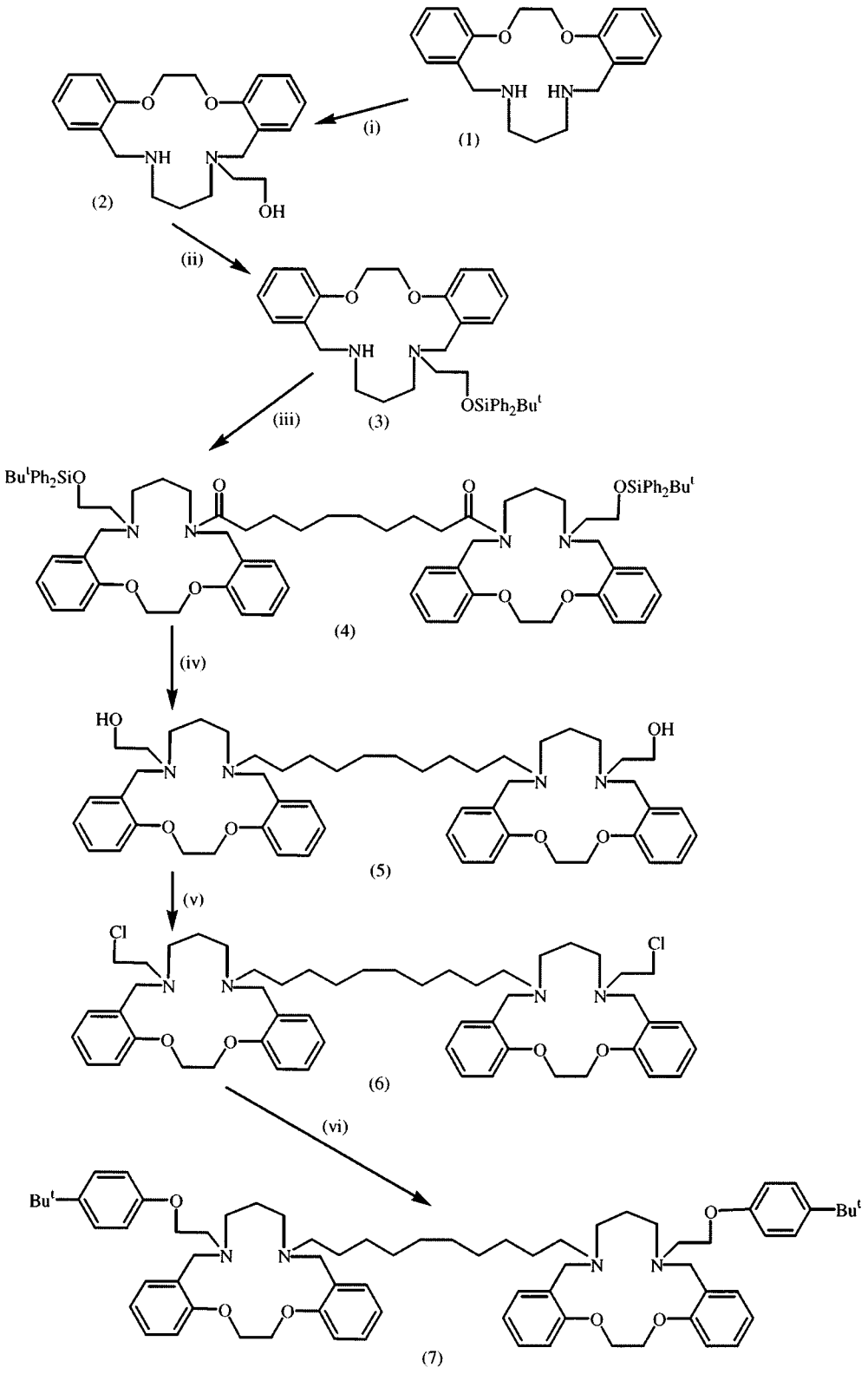
Linked Bismacrocycle (7)

A series of derivatives incorporating two linked macrocyclic rings have been synthesized. Initially, an attempt was made to link the silyl ether (protected) species (3) in an *N*,*N*′-dialkylation procedure employing 1,6-dibromohexane. Under the conditions used (acetonitrile/$NaHCO_3$/60°C), this procedure failed to produce the required product in acceptable yield. Instead, a competing intramolecular alkylation on the same ring nitrogen occurred to afford the corresponding single-ring (spiro) quaternary ammonium salt as the major product. The latter was identified from its ^1H and ^{13}C n.m.r. spectra (including an XHCORR, short-range, n.m.r. experiment) coupled with identification of bromide ion in the product. In contrast, a diacylation procedure employing sebacoyl chloride as the linking reagent was successful in producing the corresponding linked-ring diamide system (4). The reaction was performed in the presence of triethylamine and gave (4) in high yield (*c.* 90%). The ^1H and ^{13}C n.m.r. spectra of this compound were very complex, most likely resulting from the presence of geometric isomers (three possible) due to restricted rotation around the amide C–N bonds. Subsequent reduction of the amide groups with BH_3.thf[14] and hydrolysis of the silyl protecting group during acid workup of the reaction product, gave the diol (5) in *c.* 80% yield. The ^1H and ^{13}C n.m.r. spectra of (5) were strictly comparable to those of the related 'monomeric' precursor (2), except for the presence of signals arising from the 10-carbon linker chain. F.a.b. mass spectrometry and accurate peak matching of the parent ion subsequently confirmed the 'dimeric' nature of (5).

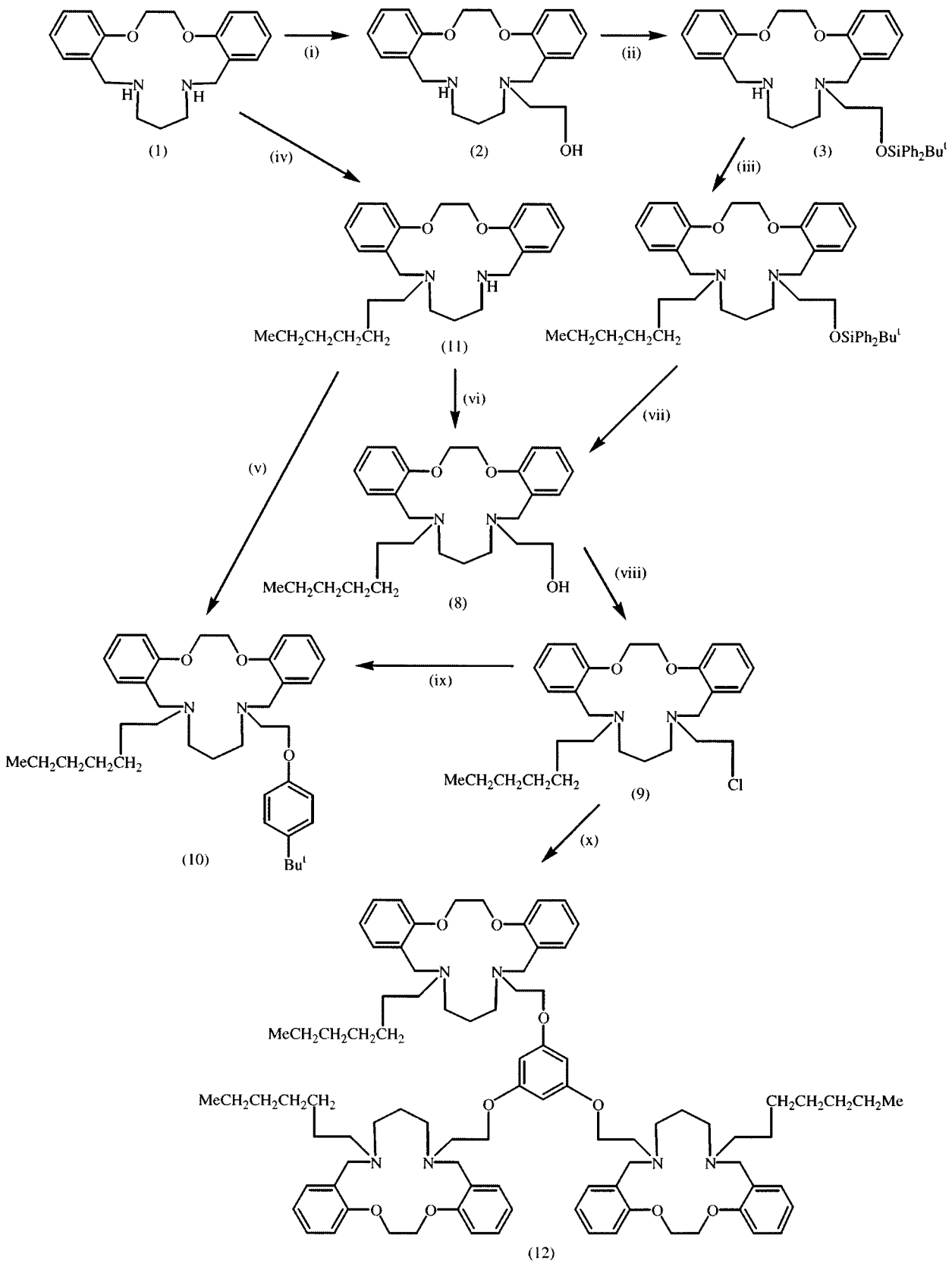
Conversion of (5) into the corresponding bis-4-t-butylphenyl ether (7) was achieved (Scheme 1) by the same procedure used for the preparation of the 'monomeric' analogue (10) (Scheme 2). Compound (7) was obtained as a viscous oil in 33% yield after chromatographic workup. As expected, the ^1H and ^{13}C n.m.r. spectra of this product were both quite similar to those of (10).

Trilinked Macrocycle (12)

The chloroethyl intermediate (9) (Scheme 2) was also used to link three macrocycles of the present type to a tritopic aromatic 'core'. Thus, trialkylation of phloroglucinol with (9) in *N*,*N*-dimethylformamide in the presence of caesium carbonate gave the 'trimer' (14) in moderate yield (34%). The ^1H and ^{13}C n.m.r. spectra of (12) were in accord with the proposed structure. Relative to the ^1H n.m.r. spectrum of (9), the spectrum of (12) contained a 'new' triplet at δ 3·94 for the phenyl ether methylene group ($NCH_2C\mathbf{H}_2OAr$)



Scheme 1. (i) Ethylene oxide, acetone (ref. 9); (ii) t-butyldiphenylsilyl chloride, 4-dimethylaminopyridine, triethylamine, dichloromethane; (iii) sebacoyl chloride, triethylamine, dichloromethane, 0°C; (iv) borane/tetrahydrofuran, reflux, then HCl/MeOH/H_2O; (v) thionyl chloride, dichloromethane; (vi) 4-t-butylphenol, Cs_2CO_3, NaI, *N*,*N*-dimethylformamide, 60°C.



Scheme 2. (i) See Scheme 1; (ii) see Scheme 1; (iii) 1-iodoheptane, $NaHCO_3$, acetonitrile, 60°C; (iv) same as (iii); (v) 1-(2-bromoethoxy)-4-t-butylbenzene, $NaHCO_3$, acetonitrile, 60°C; (vi) 2-bromoethanol, $NaHCO_3$, acetonitrile, reflux; (vii) $HCl/MeOH/H_2O$, reflux; (viii) thionyl chloride, dichloromethane; (ix) 4-t-butylphenol, Cs_2CO_3/NaI, 60°C; (x) phloroglucinol, Cs_2CO_3, *N*,*N*-dimethylformamide, 60°C.

and a 'new' singlet at δ 6·01 for the phloroglucinol aromatic proton. The 'trimeric' composition of (12) was further confirmed by the presence of a molecular ion peak (MH^+) at *m/z* 1436 in its mass spectrum (l.s.i.m.s.).

Experimental

The ^1H and ^{13}C n.m.r. spectra were determined on Bruker AM200 or AM300 spectrometers; all chemical shifts are relative to tetramethylsilane. All n.m.r. spectra were recorded in (D)chloroform solution. Spectral assignments are based on those given previously for the parent ring systems.[15] High-resolution electron impact (e.i.) and liquid secondary ion (l.s.i.) mass spectra were determined at the Central Science Laboratory, University of Tasmania; high-resolution Fourier-transform electrospray (e.s.) spectra were determined at the Australian Institute of Marine Science, Townsville. The fast atom bombardment (f.a.b.) spectrum was determined at the Division of Energy and Fuel Technology, CSIRO, Lucas Heights Laboratories.

All syntheses were carried out under nitrogen.

1-(2-Bromoethoxy)-4-t-butylbenzene

To a mixture of 4-t-butylphenol (18·03 g, 0·12 mol) and 1,2-dibromoethane (35·0 g, 0·19 mol) at the reflux was added a solution of sodium hydroxide (5·4 g, 0·13 mol) in water (38 ml) over 30 min. Refluxing was continued for 20 h, then the reaction mixture was cooled to room temperature. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3×20 ml). The combined organic fractions were then washed with 10% sodium hydroxide (10 ml), dried (anhydrous Na_2SO_4), and distilled under vacuum. The pure *product* was obtained as a colourless oil, b.p. 117°/0·02 mmHg; yield 12·9 g, 42% (Found (e.s.m.s.): *m/z* 279·0349. $C_{12}H_{17}BrO$ (MNa^+) requires 279·0355.) ^1H n.m.r. δ 1·28, s, 9H, $C(CH_3)_3$; 3·55, t, 2H, OCH_2CH_2Br; 4·20, t, 2H, OCH_2CH_2Br; 6·8–7·3, m, 4H, aromatic H. ^{13}C n.m.r. δ 29·2, OCH_2CH_2Br; 31·4, $C(CH_3)_3$; 33·9, $C(CH_3)_3$; 67·8, OCH_2CH_2Br; 114·1, 114·6, 126·2, 143·9, 155·7, aromatic C.

Protection of (2) to Yield (3)

Macrocycle (2)[9] (0·713 g, 2·0 mmol), 4-dimethylaminopyridine (0·0269 g, 0·22 mmol) and triethylamine (0·340 ml, 2·40 mmol) were dissolved in dry dichloromethane (10 ml). To this solution was added t-butyldiphenylsilyl chloride (0·58 ml, 2·30 mmol) dropwise via a syringe. The reaction mixture was stirred at room temperature for 3 h and refrigerated overnight. Extra dichloromethane (20 ml) and saturated aqueous NH_4Cl solution (10 ml) were added, and the aqueous layer was reextracted with dichloromethane (20 ml). The combined dichloromethane extracts were dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation. The resulting oil was chromatographed on silica gel. Elution with 5% MeOH/$CHCl_3$ afforded a colourless oil (1·06 g, 89%) which crystallized upon addition of dry ether. The resulting solid was recrystallized from acetonitrile and light petroleum to give the *silyl ether* (3) as a colourless crystalline solid (as its 2·5 hydrate), m.p. 163–164°C, R_F 0·73 (Found (e.i.m.s.): *m/z* 594·3281. $C_{37}H_{46}N_2O_3Si$ (M^+) requires 594·3278. Found: C, 69·4; H, 7·9; N, 4·0. $C_{37}H_{51}N_2O_{5·5}Si$ requires C, 69·45; H, 8·0; N, 4·4%). I.r. (Nujol) 767, 939, 1245, 1600, 1692, 2918, 3015, 3312 cm^{-1}. ^1H n.m.r. δ 1·00, s, 9H, $SiC(CH_3)_3$; 1·97, quin, 2H, $NCH_2CH_2CH_2N$; 2·63, 2·71, 2·79, 3×br t, 3×2H, $NCH_2CH_2CH_2N$, NCH_2CH_2OSi; 3·58, t, 2H, NCH_2CH_2OSi; 3·67, 4·00, 2×s, 2×2H, $ArCH_2$; 4·20, 4·36, 2×t, 2×2H, OCH_2CH_2O; 6·70–7·61, m, 18H, aromatic H. ^{13}C n.m.r. δ 19·0, $SiC(CH_3)_3$; 22·0, $NCH_2CH_2CH_2N$; 26·8, $SiC(CH_3)_3$; 48·7, 49·3, $NCH_2CH_2CH_2NH$; 52·7, NCH_2CH_2O; 53·5, 57·0, $ArCH_2$; 61·0, NCH_2CH_2O; 65·4, 66·5, OCH_2CH_2O, 110·8, 119·3, 120·4, 121·5, 125·4, 127·7, 129·4, 129·6, 131·3, 132·6, 133·0, 133·3, 135·6, 156·6, 156·9, aromatic C.

Acylation of (3) with Sebacoyl Chloride to Yield Linked Derivative (4)

Macrocycle (3) (0·598 g, 1·0 mmol) and triethylamine (0·167 ml, 1·2 mmol) were dissolved in dry dichloromethane (5 ml) and cooled to 0°C in an ice bath. To this mixture was added a solution of freshly distilled sebacoyl chloride (0·107 ml, 0·5 mmol) in dry dichloromethane (5 ml) via a syringe over 30 min. The mixture was stirred at room temperature for 3 h, while the reaction progress was followed by t.l.c. The solvent was then removed on a rotary evaporator and the resulting oil was distributed between dichloromethane (40 ml) and H_2O (20 ml). The aqueous layer was reextracted with dichloromethane (2×20 ml). The combined dichloromethane layers were dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation. The resulting crude oil was chromatographed on silica gel. Elution with $CHCl_3$ and then 5% MeOH/$CHCl_3$ afforded the *linked macrocycle* (4) as a viscous oil (0·607 g, 89·5%), R_F 0·44 (Found: C, 74·4; H, 7·9; N, 4·0. $C_{84}H_{106}N_4O_8Si_2$ requires C, 74·4; H, 7·9; N, 4·1%. Found (e.s.m.s.): *m/z* 1355·7659. $C_{84}H_{107}N_4O_8Si_2$ (MH^+) requires 1355·7621). The ^1H and ^{13}C n.m.r. spectra of (4) were in accordance with the proposed structure but were too complex for unambiguous interpretation (see Results and Discussion section).

Reduction and Hydrolysis of (4) to Yield (5)

Linked macrocycle (4) (0·321 g, 0·24 mmol) was dissolved in dry tetrahydrofuran (5 ml). To this solution was added borane/tetrahydrofuran complex (1·5 ml, 0·48 mmol) dropwise via a syringe over 20 min. The reaction mixture was refluxed for 6 h. The excess borane/tetrahydrofuran complex was destroyed by the addition of MeOH (1 ml) and the solvent was removed by rotary evaporation. To the residue, 10 ml of MeOH/H_2O/conc. HCl (20 : 5 : 2) were added and the mixture was refluxed for 1 h. The solvent was removed by rotary evaporation and the residue partitioned between H_2O (5 ml) and dichloromethane (20 ml). The aqueous layer was basified with 2 M sodium hydroxide to pH 11–12. The basified layer was extracted with dichloromethane (3×20 ml) and the combined dichloromethane extracts were dried (anhydrous Na_2SO_4). The solvent was then removed by rotary evaporation. The resulting crude *product* (5) (0·162 g, 79%) was homogenous by t.l.c. Final purification was achieved by chromatography on silica gel. Elution with $CHCl_3$ and then 5% MeOH/$CHCl_3$/0·5%NH_4OH afforded (5) as a viscous oil, R_F 0·25 (10% MeOH/$CHCl_3$/1%NH_4OH) (Found (e.s.m.s.): *m/z* 851·5674. $C_{52}H_{75}N_4O_6$ (MH^+) requires 851·5681). Mass spectrum (f.a.b.) *m/z* 851·5, MH^+ (82%), 281·1 (31), 133·0 (70), 107·1 (100). ^1H n.m.r. δ 1·2–1·35, m, 12H, $NCH_2CH_2(CH_2)_6CH_2CH_2N$; 1·65, br quin, 2×2H, $NCH_2CH_2(CH_2)_6$; 1·77, quin, 2×2H, $NCH_2CH_2CH_2N$; 2·47–2·6, m, 2×6H, $NCH_2CH_2CH_2N$, $NCH_2CH_2(CH_2)_6$; 2·70, t, 2×2H, NCH_2CH_2OH; 3·49, s, 2×2H, $ArCH_2$; 3·92, s, 2×2H, $ArCH_2$; 4·37, s, 2×4H, OCH_2CH_2OH; 6·9–7·3, m, 2×8H, aromatic H. ^{13}C n.m.r. δ 23·2, 26·2, 27·3, 29·4, 29·5, 5×CH_2, $NCH_2CH_2CH_2CH_2CH_2$, $NCH_2CH_2CH_2N$; 50·8, 50·9, 51·2, 51·4, 54·0, 54·2, 6×CH_2N; 58·6, NCH_2CH_2OH; 66·1, OCH_2CH_2O; 110·7, 111·3, 120·5, 128·9, 129·8, 132·6, 132·8, 157·1, aromatic C.

Chlorination of (5) to Yield (6)

Linked macrocycle (5) (1·06 g, 1·24 mmol) was dissolved in dry dichloromethane (6 ml) and the solution was cooled (dry ice/acetone bath). To this solution was added freshly distilled thionyl chloride (0·5 ml, 6·78 mmol) dropwise via a syringe. The reaction mixture was allowed to warm to room temperature

over 3 h. Excess thionyl chloride was destroyed by the addition of ethanol (0·235 ml, 4·24 mmol) and the solvent was removed by rotary evaporation. The residue was partitioned between 2 M sodium hydroxide solution (15 ml) and dichloromethane (25 ml) and the organic layer was separated and dried (anhydrous Na_2SO_4). The solvent was removed by rotary evaporation to give the bismacrocycle (6) as a brown oil (0·744 g, 67%). This product was shown to be homogeneous by t.l.c. and was used without further purification. ^{1}H n.m.r. δ 1·2–1·35, br, m, 12H, $NCH_2CH_2(CH_2)_6CH_2CH_2N$; 1·49, br quin, 2×2H, $NCH_2CH_2CH_2$; 1·64, quin, 2×2H, $NCH_2CH_2CH_2N$; 2·3–2·5, m, 2×6H, $NCH_2CH_2CH_2N$, $NCH_2CH_2(CH_2)_6$; 2·79, t, 2×2H, NCH_2CH_2Cl; 3·65, s, 2×2H, $ArCH_2$; 3·68, s, 2×2H, $ArCH_2$; 4·34, br s, 2×4H, OCH_2CH_2O; 6·9–7·3, m, 2×8H, aromatic H. ^{13}C n.m.r. δ 23·6, 27·1, 27·5, 29·6, $NCH_2CH_2CH_2CH_2CH_2CH_2$, $NCH_2CH_2CH_2$; 42·0, NCH_2CH_2Cl; 51·2, 51·4, 52·1, 53·1, 53·4, 55·7, 6×CH_2N; 66·5, OCH_2CH_2O; 110·8, 110·9, 120·5, 127·3, 128·2, 128·5, 131·8, 132·4, 157·0, 157·1, aromatic C.

Linked Macrocycle (7)

Linked macrocycle (6) (2·31 g, 2·60 mmol) was dissolved in dry *N*,*N*-dimethylformamide (15 ml). To this solution were added 4-t-butylphenol (1·20 g, 7·80 mmol), caesium carbonate (2·54 g, 7·80 mmol) and sodium iodide (0·050 g). The reaction mixture was stirred at 60°C for 48 h and the solvent was then removed by rotary evaporation. The residue was dissolved in dichloromethane (50 ml). This solution was washed with 10% sodium hydroxide (50 ml) and the aqueous layer was reextracted with dichloromethane (3×20 ml). The combined dichloromethane extracts were dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation to give a brown oil, which was purified by chromatography on silica gel. Elution with $CHCl_3$ and then 3% MeOH/$CHCl_3$ afforded *linked macrocycle* (7) as a light brown oil (1·06 g, 33%), R_F 0·35 (Found (e.s.m.s.): *m/z* 1115·7565. $C_{72}H_{99}N_4O_6$ (MH^+) requires 1115·7486). ^{1}H n.m.r. δ 1·2–1·25, m, 12H, $NCH_2CH_2(CH_2)_6CH_2CH_2N$; 1·28, s, 18H, $C(CH_3)_3$; 1·53, quin, 2×2H, $NCH_2CH_2CH_2$; 1·73, quin, 2×2H, $NCH_2CH_2CH_2N$; 2·4–2·6, m, 2×6H, $NCH_2CH_2CH_2N$, $NCH_2CH_2CH_2$; 2·88, t, 2×2H, NCH_2CH_2O; 3·6–3·8, m, 8H, $ArCH_2$; 3·97, t, 2×2H, NCH_2CH_2O; 4·3–4·4, br s, 8H, OCH_2CH_2O; 6·75–7·29, m, 24H, aromatics. ^{13}C n.m.r. δ 23·0, 26·7, 27·4, 29·5, 5×CH_2, $NCH_2CH_2CH_2CH_2CH_2CH_2$, $NCH_2CH_2CH_2N$; 31·5, $C(CH_3)_3$; 34·0, $C(CH_3)_3$; 51·2, 51·4, 51·5, 53·4, 6×CH_2N; 66·5, 66·6, NCH_2CH_2O, OCH_2CH_2O; 110·9, 111·0, 113·9, 120·5, 120·6, 126·1, 128·4, 132·1, 157·0, aromatics.

Macrocycle (8)

(A) *From the silyl-protected species (3).* Macrocycle (3) (2·38 g, 4·0 mmol) was dissolved in dry acetonitrile (40 ml). To this warm solution were added 1-iodoheptane (1·31 ml, 5·2 mmol) and $NaHCO_3$ (0·672 g, 8·8 mmol) and the solution was stirred at 60°C for 3 h, then stored in a refrigerator overnight. The solvent was removed by rotary evaporation and the resulting oil was distributed between dichloromethane (160 ml) and H_2O (80 ml). The aqueous layer was reextracted with dichloromethane (2×80 ml), and the combined dichloromethane phases were washed with saturated NaCl solution (120 ml) and then with 0·1 M sodium thiosulfate solution (160 ml). The organic phase was dried (anhydrous Na_2SO_4) and the solvent removed by rotary evaporation. The resulting crude oil was chromatographed on silica gel. Elution with 2·5% MeOH/$CHCl_3$ afforded the *N*-heptyl derivative of the silyl-protected species (3) as a viscous oil (2·04 g), R_F 0·52 (Found (l.s.i.m.s.): *m/z* 693·4444. $C_{44}H_{61}N_2O_3Si$ (MH^+) requires 693·4451). ^{1}H n.m.r. δ 0·85, t, 3H, CH_2CH_3; 1·04, s, 9H, $SiC(CH_3)_3$; 1·2–1·35, m, 8H, $NCH_2CH_2(CH_2)_4CH_3$; 1·60, br quin, $NCH_2CH_2(CH_2)_4CH_3$; 1·65, quin, 2H, $NCH_2CH_2CH_2N$; 2·5–2·65, m, 4H, $NCH_2CH_2(CH_2)_4CH_3$, NCH_2CH_2OSi; 2·82, 3·10, 2×br t, 2×2H, $NCH_2CH_2CH_2N$; 3·61, t, 2H, NCH_2CH_2OSi; 3·67, 4·25, 2×s, 2×2H, $ArCH_2$; 4·27, 4·37, 2×br t, 2×2H, OCH_2CH_2O; 6·77–7·77, m, 18H, aromatic H. ^{13}C n.m.r. δ 13·7, CH_2CH_3; 18·8, $SiC(CH_3)_3$; 21·7, 22·3, 23·3, 26·5, 28·5, 31·3, 6×CH_2, $CH_3(CH_2)_4CH_2CH_2N$, $NCH_2CH_2CH_2N$; 51·3, 51·6, 52·6, 52·7, 54·3, 55·6, 6×CH_2N; 60·5, NCH_2CH_2O; 66·2, 66·6, OCH_2CH_2O; 110·9, 111·2, 118·1, 120·7, 121·4, 125·7, 127·6, 129·3, 129·7, 131·5, 132·2, 133·7, 135·4, 156·6, 157·0, aromatic C.

The above product (1·94 g) was dissolved in 20 ml of MeOH/H_2O/conc. HCl (20 : 5 : 2) and the solution was heated at reflux for 1 h. The solvent was removed by rotary evaporation and the residue taken up in water (10 ml). The aqueous layer was extracted with dichloromethane (3×20 ml) and then basified with 2 M NaOH solution to pH 11–12. The basified layer was extracted with dichloromethane (3×20 ml), and combined dichloromethane phases were dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation. The crude *hydroxyethyl macrocycle* (8) (1·34 g) which resulted was homogeneous by t.l.c. Final purification was achieved by chromatography on silica gel (10% MeOH/$CHCl_3$) to afford (8) as a yellow oil, R_F 0·45 (Found (e.i.m.s.): *m/z* 454·3190. $C_{28}H_{42}N_2O_3$ (M^+) requires 454·3195). ^{1}H n.m.r. δ 0·88, t, 3H, CH_2CH_3; 1·2–1·35, m, 8H, $NCH_2CH_2(CH_2)_4CH_3$; 1·53, br quin, 2H, $NCH_2CH_2(CH_2)_4CH_3$; 1·64, quin, 2H, $NCH_2CH_2CH_2N$; 2·3–2·6, m, 8H, $NCH_2CH_2CH_2$, $NCH_2CH_2(CH_2)_4CH_3$, NCH_2CH_2OH; 3·48, t, 2H, NCH_2CH_2OH; 3·64, 3·75; 2×s, 2×2H, $ArCH_2$; 4·36, s, 2×2H, OCH_2CH_2O; 6·88–7·27, m, 8H, aromatic H. ^{13}C n.m.r. δ 14·0, CH_2CH_3; 22·6, 23·6, 26·8, 27·4, 29·1, 31·8, 6×CH_2, $CH_3(CH_2)_4CH_2CH_2N$, $NCH_2CH_2CH_2N$; 50·7, 50·8, 51·3, 51·7, 53·8, 54·15, 6×CH_2N; 58·8, NCH_2CH_2O; 66·0, 66·2, OCH_2CH_2O; 110·7, 111·1, 120·4, 120·5, 124·8, 126·3, 128·8, 129·9, 132·5, 132·6, aromatic C.

(B) *Directly from (11).* Derivative (11) as its HI salt (0·90 g, 2·0 mmol) was dissolved in acetonitrile (50 ml) to which were added sodium bicarbonate (0·48 g, 5·7 mmol) and 2-bromoethanol (1·8 g, 14·4 mmol). The mixture was refluxed for 72 h, and the solvent was then removed under vacuum. The residue oil was dissolved in dichloromethane (50 ml) and this solution was washed with 10% sodium hydroxide (20 ml). The combined dichloromethane layers were dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation. The resultant oil was chromatographed on silica gel (10% MeOH/$CHCl_3$) to afford (8) as a yellow oil (0·15 g, 20%). The ^{1}H and ^{13}C n.m.r. spectra of this product were identical to those of the product obtained from preparation (A).

Chlorination of (8) to Yield (9)

Macrocycle (8) (0·909 g, 2·0 mmol) was dissolved in dry dichloromethane (10 ml) and the solution was chilled (dry ice/acetone bath). To this chilled solution was added freshly distilled thionyl chloride (0·25 ml, 3·47 mmol) dropwise by means of a syringe. The reaction mixture was allowed to warm to room temperature over 3 h. The excess thionyl chloride was destroyed by addition of ethanol (0·26 ml, 4·42 mmol) and the solvent was removed by rotary evaporation. The residue was distributed between 2 M NaOH (10 ml) and dichloromethane (20 ml) and the aqueous layer was reextracted with dichloromethane (3×20 ml). The combined dichloromethane phases were dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation to give the chloroethyl macrocycle (9) as a brown oil (0·921 g, 94%). This material was homogeneous by t.l.c. and was used without further purification. ^{1}H n.m.r. δ 0·88, t, 3H, CH_2CH_3; 1·2–1·35, m, 8H, $NCH_2CH_2(CH_2)_2CH_3$; 1·49, br quin, 2H, $NCH_2CH_2(CH_2)_4CH_3$; 1·63, quin, 2H, $NCH_2CH_2CH_2N$; 2·35–2·55, m, 8H, $NCH_2CH_2CH_2$, $NCH_2CH_2(CH_2)_4CH_3$; 2·83, t, 2H, NCH_2CH_2Cl; 3·41, t, 2H, NCH_2CH_2Cl; 3·63, 3·69, 2×s, 2×2H, $ArCH_2$; 4·35, s, 4H, OCH_2CH_2O; 6·86–7·27, m, 8H, aromatic H. ^{13}C n.m.r. δ 14·1, CH_2CH_3; 22·6, 23·8, 27·4, 27·5,

29·2, 31·9, 6×CH_2, $CH_3(\mathbf{C}H_2)_4\mathbf{C}H_2CH_2N$, $NCH_2\mathbf{C}H_2CH_2N$; 42·0, 51·3, 51·4, 52·1, 53·6, 55·8, 6×CH_2N; 66·5, 2×CH_2, OCH_2CH_2O; 110·8, 111·9, 120·3, 127·3, 128·1, 128·4, 131·8, 132·3, 157·0, aromatic C.

Macrocycle (10)

(A) *Reaction of 4-t-butylphenol with chloroethyl macrocycle (9) to yield (10).* The chloroethyl macrocycle (9) (0·473 g, 1·0 mmol) was dissolved in dry *N*,*N*-dimethylformamide (5 ml). To this solution were added 4-t-butylphenol (0·167 g, 1·1 mmol), caesium carbonate (0·360 g, 1·1 mmol) and sodium iodide (0·015 g). The reaction mixture was stirred at 60°C for 48 h. The solvent was then removed by rotary evaporation. The residual oil was dissolved in dichloromethane (20 ml). This solution was washed with 10% sodium hydroxide solution (40 ml) and the aqueous layer was re-extracted with dichloromethane (3×15 ml). The combined dichloromethane phases were dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation to yield a brown oil (0·5 g). This material was purified by chromatography on silica gel (elution with $CHCl_3$ and then 3% MeOH/$CHCl_3$) to afford the *4-t-butylphenol ether* (10) as a brown oil (0·221 g, 37%), R_F 0·46 (Found (e.s.m.s.): *m/z* 587·4216. $C_{38}H_{55}N_2O_3$ (MH^+) requires 587·4207). ^{1}H n.m.r. δ 0·87, t, 3H, $CH_2C\mathbf{H}_3$; 1·2–1·35, m, 8H, $NCH_2CH_2(C\mathbf{H}_2)_4CH_3$; 1·29, s, $C(CH_3)_3$; 1·50, br quin, 2H, $NCH_2C\mathbf{H}_2(CH_2)_4CH_3$; 1·71, quin, 2H, $NCH_2C\mathbf{H}_2CH_2N$; 2·40–2·60, m, 6H, $NC\mathbf{H}_2CH_2C\mathbf{H}_2N$, $NC\mathbf{H}_2CH_2(CH_2)_4CH_3$; 2·89, t, 2H, $NC\mathbf{H}_2CH_2O$; 3·68, 3·71, 2×s, 2×2H, $ArC\mathbf{H}_2$; 3·99, t, 2H, $NCH_2C\mathbf{H}_2O$; 4·33–4·35, m, 4H, OCH_2CH_2O, 6·77–7·30, m, 12H, aromatic H. ^{13}C n.m.r. δ 14·1, $CH_2\mathbf{C}H_3$; 22·6, 23·2, 27·3, 27·5, 29·3, 31·9, 6×CH_2, $CH_3(\mathbf{C}H_2)_4\mathbf{C}H_2CH_2N$, $NCH_2\mathbf{C}H_2CH_2N$; 31·5, $C(\mathbf{C}H_3)_3$; 34·0, $\mathbf{C}(CH_3)_3$; 51·2, 51·5, 52·4, 52·6, 52·8, 53·7, 6×CH_2N; 66·6, 66·7, 3×CH_2, $O\mathbf{C}H_2\mathbf{C}H_2O$, $NCH_2\mathbf{C}H_2O$; 110·9, 111·0, 114·0, 120·5, 126·1, 127·6, 128·0, 128·2, 132·1, 143·1, 156·6, 157·0, 157·1, aromatic C.

(B) *Alternative synthesis of (10).* In a second procedure (10) was prepared as follows: (11) as its HI salt (0·245 g, 0·54 mmol) was dissolved in acetonitrile (15 ml) to which were added sodium bicarbonate (0·084 g, 1·0 mmol) and 1-(2-bromoethoxy)-4-t-butylbenzene (0·33 g, 1·3 mmol). The mixture was stirred at 60°C for 24 h and the solvent was then removed under vacuum. The residual oil was dissolved in dichloromethane (50 ml). The solution was washed with 10% sodium hydroxide (10 ml). The combined dichloromethane phases were dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation. The resultant oil was chromatographed on silica gel: first eluted by $CHCl_3$ and then 3% MeOH/$CHCl_3$ to afford (10) as a yellow oil (0·15 g, 15%). The ^{1}H and ^{13}C n.m.r. spectra of this product were identical to those obtained for the product obtained from preparation (A).

Macrocycle (11)

Macrocycle (1) (0·625 g, 2·0 mmol) was dissolved in dry acetonitrile (10 ml). To this solution were added 1-iodoheptane (0·328 ml, 2·3 mmol) and $NaHCO_3$ (0·168 g, 2·0 mmol) and the solution was stirred at 60°C for 3 h. The reaction mixture was washed with 10% sodium hydroxide (10 ml), the aqueous layer was then separated and reextracted with dichloromethane (2×20 ml). The combined dichloromethane phases were washed with 0·1 M sodium thiosulfate solution (20 ml). The organic phase was dried (anhydrous Na_2SO_4) and the solvent removed by rotary evaporation. The resulting crude oil was chromatographed on silica gel. Elution with 5% MeOH/$CHCl_3$ afforded *macrocycle* (11) as a viscous oil which solidified on triturating with diethyl ether as its HI salt. It was recrystallized from ethanol (0·47 g, 41%), R_F 0·31 (Found: C, 57·9; H, 7·2; N, 5·5. $C_{27}H_{39}IN_2O_2$ requires C, 58·0; H, 7·3; N, 5·5%). Mass spectrum (e.s.) *m/z* 411·3, MH^+. ^{1}H n.m.r. δ 0·85, t, 3H, $CH_2C\mathbf{H}_3$; *c.* 1·0–1·3, m, 10H, $NCH_2(C\mathbf{H}_2)_5CH_3$; 1·50, br quin, 2H, $NCH_2C\mathbf{H}_2(CH_2)_4CH_3$; 2·1, quin, 2H, $NCH_2C\mathbf{H}_2CH_2N$; 2·47, 2·57, 2·96, 3×t, 3×2H, $NC\mathbf{H}_2CH_2C\mathbf{H}_2N$, $NC\mathbf{H}_2CH_2(CH_2)_4CH_3$; 3·50, 4·07, 2×s, 2×2H, $ArC\mathbf{H}_2$; 4·45, m, 4H, OCH_2CH_2O; 6·89–7·71, m, 8H, aromatic H. ^{13}C n.m.r. δ 13·7, $CH_2\mathbf{C}H_3$; 21·6, 22·2, 26·5, 28·4, 28·6, 31·1, 6×CH_2, $CH_3(\mathbf{C}H_2)_4CH_2CH_2N$, $NCH_2\mathbf{C}H_2CH_2N$; 48·4, 50·2, 53·2, 53·6, 55·7, 5×CH_2N; 66·4, 66·5, 2×CH_2, OCH_2CH_2O; 110·7, 110·8, 119·8, 120·2, 121·0, 123·0, 129·6, 131·0, 132·7, 132·8, 156·5, 156·6, aromatic C.

Trilinked Macrocycle (12)

Macrocycle (9) (0·71 g, 1·5 mmol) was dissolved in dry *N*,*N*-dimethylformamide (10 ml). To this solution were added phloroglucinol (0·058 g, 0·46 mmol) and caesium carbonate (0·49 g, 1·5 mmol). The reaction mixture was stirred at 60°C for 48 h. The solvent was removed by rotary evaporation and the residual oil was dissolved in dichloromethane (50 ml). This solution was washed with 10% sodium hydroxide (75 ml) and the aqueous layer was extracted with dichloromethane (3×20 ml). The combined dichloromethane phases were washed with H_2O (100 ml), dried (anhydrous Na_2SO_4) and the solvent was removed by rotary evaporation. The resulting oil was purified by chromatography on silica gel (elution with $CHCl_3$ and then 5% MeOH/$CHCl_3$) to give *trilinked macrocycle* (12) as a brown oil (0·22 g, 34%), R_F 0·16 (Found (l.s.i.m.s.): *m/z* 1435·9453. $C_{90}H_{127}N_6O_9$ (MH^+) requires 1435·9665). ^{1}H n.m.r. δ 0·86, t, 3×3H, $CH_2C\mathbf{H}_3$, 1·15–1·35, m, 3×8H, $CH_3(C\mathbf{H}_2)_4CH_2CH_2N$; 1·49, br quin, 3×2H, $CH_3(CH_2)_4C\mathbf{H}_2CH_2N$; 1·70, quin, 3×2H, $NCH_2C\mathbf{H}_2CH_2N$; 2·35–2·55, m, 3×6H, $NC\mathbf{H}_2CH_2C\mathbf{H}_2N$, $CH_3(CH_2)_4CH_2C\mathbf{H}_2N$; 2·88, t, 3×2H, $NC\mathbf{H}_2CH_2O$; 3·66, br s, 3×2H, $ArC\mathbf{H}_2$; 3·75, br s, 3×2H, $ArC\mathbf{H}_2$, 3·94, t, 3×2H, $NCH_2C\mathbf{H}_2O$; 4·33, br s, 3×4H, OCH_2CH_2O; 6·01, s, 3H, C_6H_3; 6·80–7·30, m, 24H, aromatic H. ^{13}C n.m.r. δ 14·0, $C(\mathbf{C}H_3)_3$; 22·5, 23·1, 26·9, 27·3, 29·1, 31·7, $NCH_2(\mathbf{C}H_2)_4\mathbf{C}H_2\mathbf{C}H_3$, $NCH_2\mathbf{C}H_2CH_2N$; 51·2, 51·4, 52·2, 52·8, 53·5, 6×CH_2N; 66·5, 66·6, NCH_2CH_2O, OCH_2CH_2O; 93·9, phloroglucinol CH; 110·8, 110·9, 120·4, 127·4, 128·2, 131·9, 132·1, 156·9, 157·0, 160·54, remaining aromatic C.

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