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New Macrocyclic Ligands. XIII*
Single-Ring and Tri-Linked Macrocyclic Systems Derived from Selectively Protected Cyclam

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The selective use of the tert-butoxycarbonyl protecting group has enabled efficient syntheses of the tri-linked cyclam derivatives (6)–(8). Using a related protecting group strategy, a series of related single-ring, *N*-benzylated cyclam derivatives (1)–(4) has also been prepared.

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Introduction

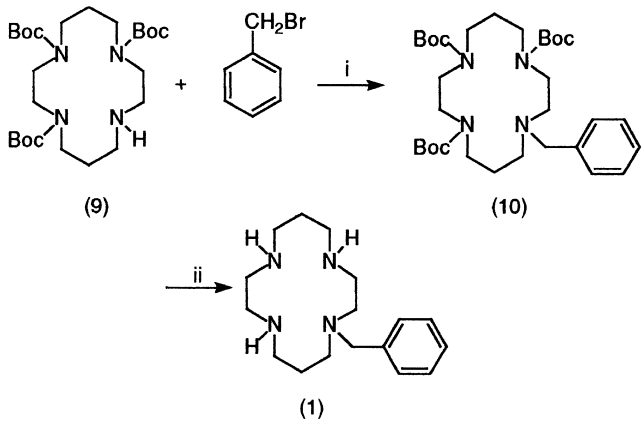
There has been continuing interest in the synthesis of larger supramolecular and supermolecular entities incorporating multi-metal ion binding sites.[1] Arising from their tendency to yield both kinetically and thermodynamically stable metal complexes,[2] macrocyclic rings have frequently been employed as structural components in such systems. One category of this type involves larger structures composed of covalently linked macrocyclic ligand species incorporating nitrogen heteroatoms in their donor sets.[3] While there are now many examples in which two macrocyclic rings of the above type have been linked, systems involving three (or more) linked rings are much less common.[4–9] As a continuation of our previous studies in the area,[8,10–12] we now report the use of protecting group chemistry to prepare the four single-ring cyclam derivatives given by (1)–(4), together with the related tri-linked ring derivatives (6)–(8). The previously reported[13] tetrabenzylated derivative (5) was also synthesised directly from cyclam as part of the present study.

It needs to be noted that the interaction of (5) with particular transition and post-transition metal ions has been carried out by a number of groups,[14–16] and that the rich transition metal coordination chemistry of the parent cyclam macrocycle has been well documented over many years.[2] Cyclam, with its 14-membered ring, tends to form more kinetically and thermodynamically stable complexes than the corresponding N_4-donor rings incorporating other ring sizes. Further, coordination to 1,4,8,11-tetraazacyclotetradecane (cyclam) has been shown to promote access to a number of less common metal oxidation states, including nickel(III), copper(III) and both silver(II) and silver(III).[17]

Results and Discussion

Synthesis of Benzylated Cyclam Derivatives

In the present study, differentially Boc-protected cyclam derivatives have been used as key intermediates in the synthesis of (1)–(4) and (6)–(8).[18] In particular, the tris(*N*-Boc)cyclam species (9)[19] has been employed for many of the syntheses. In an initial study (9) was reacted with benzyl bromide in refluxing acetonitrile over caesium carbonate to yield the mono-*N*-benzylated derivative (10). Deprotection of (10) to give (1) was then achieved in near quantitative yield by hydrolysis by using 3 M HCl–MeOH as shown in Scheme 1. Alternative syntheses of (1) have been reported previously.[20–24]



(9) (10) (1)

Scheme 1. Boc = tert-butoxycarbonyl. *Reagents and conditions*: (i) Cs_2CO_3, dry CH_3CN, reflux; (ii) 3 M HCl–MeOH.

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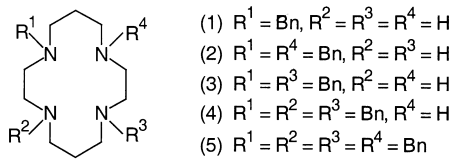
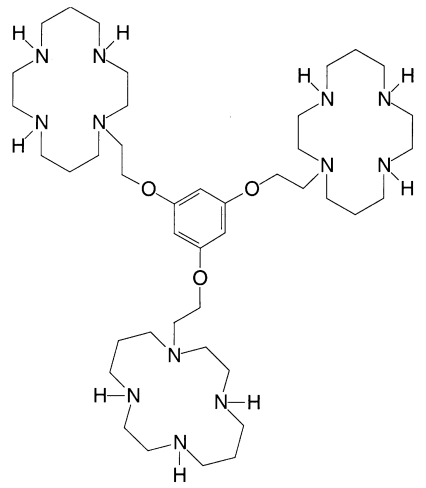
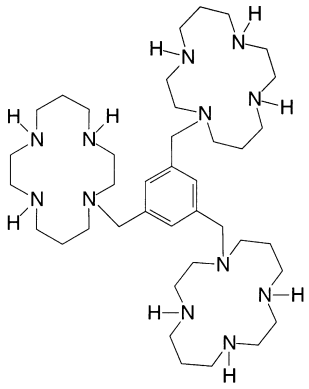




(6)



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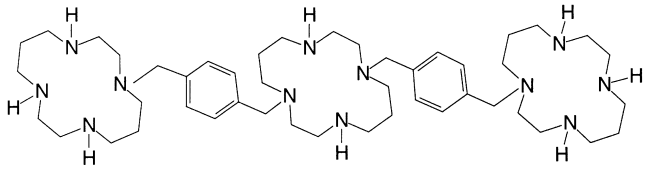
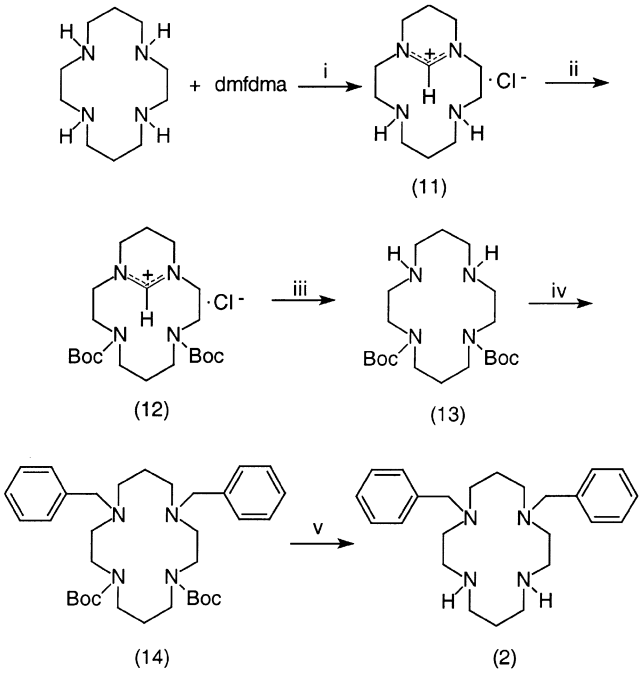


(8)

1,5-Bis-*N*-benzylated cyclam was obtained using a closely related procedure (Scheme 2) to that reported previously[25] for the preparation of the corresponding bis(2-hydroxyethyl) derivative. The addition of one equivalent of dimethylformamidedimethylacetyl (dmfdma) to cyclam in a minimum amount of hot chloroform yielded the formamidinium salt (11), which was obtained as a hygroscopic red-brown glass after removal of the reaction solvent. This



Scheme 2. Boc = tert-butoxycarbonyl; dmfdma = dimethylformamidedimethylacetal. *Reagents and conditions*: (i) CH_3CN, reflux; (ii) $(Boc)_2O$, EtOH, H_2O; (iii) conc. NaOH aqueous solution, EtOH; (iv) $PhCH_2Br$, Cs_2CO_3, dry CH_3CN; (v) 3 M HCl–MeOH.

product was then acylated with two equivalents of $(Boc)_2O$ followed by treatment with conc. NaOH in order to destroy the amidine intermediate (12). Benzylation of this product followed by deprotection of (14) with HCl–MeOH yielded the required *cis*-dibenzylated product (2).

Tris-*N*-benzylated cyclam (4) was also obtained starting from tris-*N*-Boc protected cyclam (9). The latter was initially converted into (15), which contained both Boc and Troc protecting groups. Selective removal of the Boc groups with acid then yielded (16). Tris-*N*-benzylation under basic conditions followed by deprotection of the Troc group resulted in the desired derivative (4) (Scheme 3).

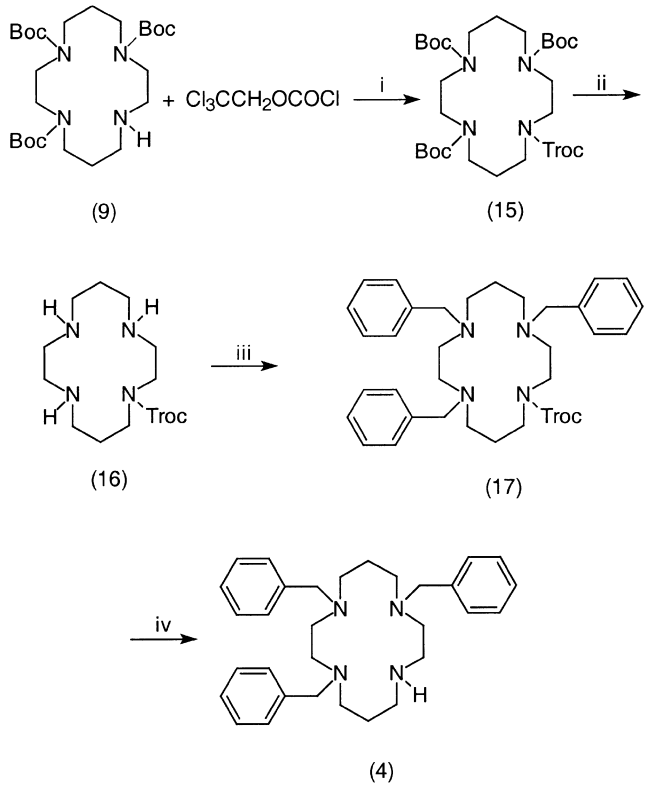
Linked Systems

The attachment of three cyclam molecules to a phloroglucinol (1,3,5-trihydroxybenzene) core was achieved as shown in Scheme 4.

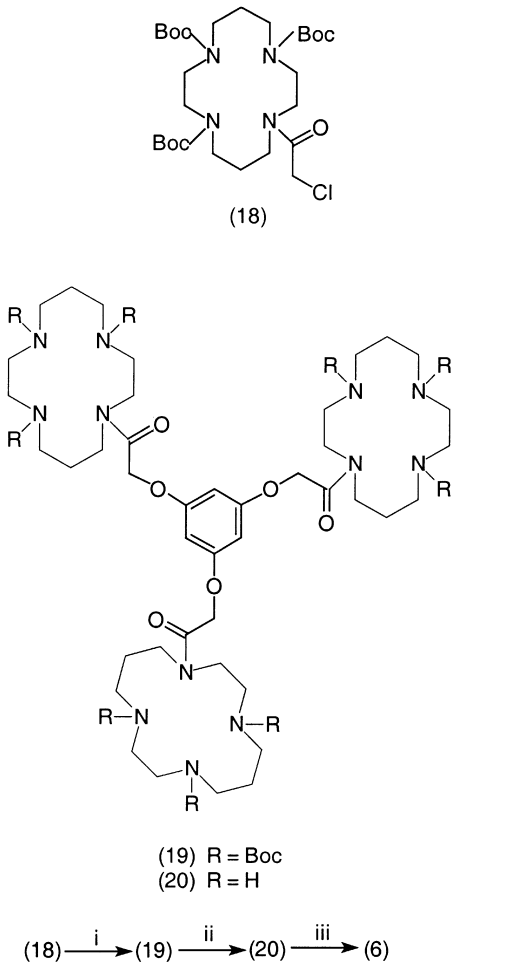
The 1,3,5-tribenzyl-linked compound (7) was obtained in a related manner, which involved the direct acylation of three molecules of (9) with trimesoyl chloride (benzene-1,3,5-tricarbonyl trichloride) as shown in Scheme 5. A brief report of the synthesis of this compound by a different procedure has appeared,[6] with the reported ^1H nuclear magnetic resonance (NMR) and mass spectrometry (MS) data being similar to that obtained in the present study.

The synthesis of (8) was achieved using a procedure that started from the 1,8-bis(*N*-Boc)cyclam derivative (23) (see Scheme 6).

Characterization of the above benzylated and tri-linked cyclam products relied heavily on high-resolution mass spectrometry (HRMS) [electron ionization (EI) and fast-



Scheme 3. Boc = tert-butoxycarbonyl; Troc = 2,2,2-trichloroethoxycarbonyl. *Reagents and conditions*: (i) Et_3N, dry CH_2Cl_2; (ii) 3 M HCl–MeOH; (iii) $PhCH_2Br$, Cs_2CO_3, dry CH_3CN, reflux; (iv) Zn, HOAc.



Scheme 4. Boc = tert-butoxycarbonyl. *Reagents and conditions*: (i) $C_6H_3(OH)_3$, Cs_2CO_3, dimethylformamide; (ii) 3 M HCl–MeOH; iii) $BH_3{\cdot}Me_2S$ then $MeOH/H_2O$/conc. HCl (20 : 10 : 10).

atom bombardment (FAB)] since most of these compounds were either glasses or viscous oils which tenaciously retained the last traces of solvent. All compounds yielded satisfactory HRMS data. In all cases, the ^1H and ^{13}C NMR spectra were consistent with the proposed structures, although in some cases considerable spectral overlap arising from the inherently similar chemical environment of the ring methylene groups of the constituent macrocycles was in evidence. Interpretation of the spectra of particular acylated intermediates tended to be complicated by signal broadening and/or splitting, which was apparently largely caused by slow interconversion of the amide rotamers. However, this situation was generally improved in the final products following deprotection and amide reduction.

Concluding Remarks

A comparative investigation of aspects of the metal binding of the present single-ring and tri-linked derivatized macrocycles is at present underway and the results of this study will be reported in due course.

Experimental

General

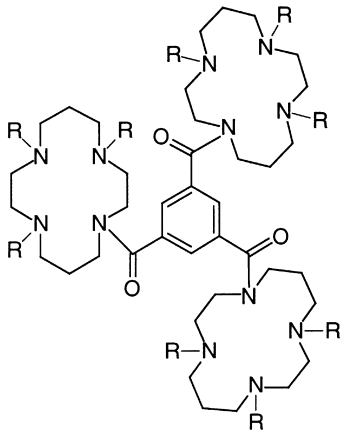
NMR spectra were recorded on Bruker AC-200 and Bruker DPX-400 spectrometers. δ_H values are relative to Me_4Si; δ_C values are relative to $CDCl_3$ at 77.1 ppm, and *J* values are given in Hertz (Hz). HRMS spectra were obtained on a Kratos M25RFA spectrometer and low-resolution MS [electrospray (ES)] on a Finnigan LCQ-8 spectrometer.

Where available, all chemicals were analytical-grade. Dry acetonitrile was prepared by shaking AR-grade acetonitrile with Linde 4-Å molecular sieves, stirring with CaH_2 until no further hydrogen was evolved, and then fractionally distilling over CaH_2. 1,4,8,11-Tetraazacyclotetradecane (cyclam) was prepared using the procedure detailed by Barefield and Wagner.[26] 1,4,8-Tris(tert-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (9) was synthesized by following a literature procedure,[19] as was 1,8-bisbenzyl-1,4,8,11-tetraazacyclotetradecane (3),[27] compound (11),[25] 1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclotetradecane (5),[28–29] 1,4,8-tris(tert-butoxycarbonyl)-11-chloroacetyltetraazacyclotetradecane (18)[12] and 1,8-bis(tert-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (23).[30]

Synthesis

1-Benzyl-4,8,11-tris(tert-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (10)

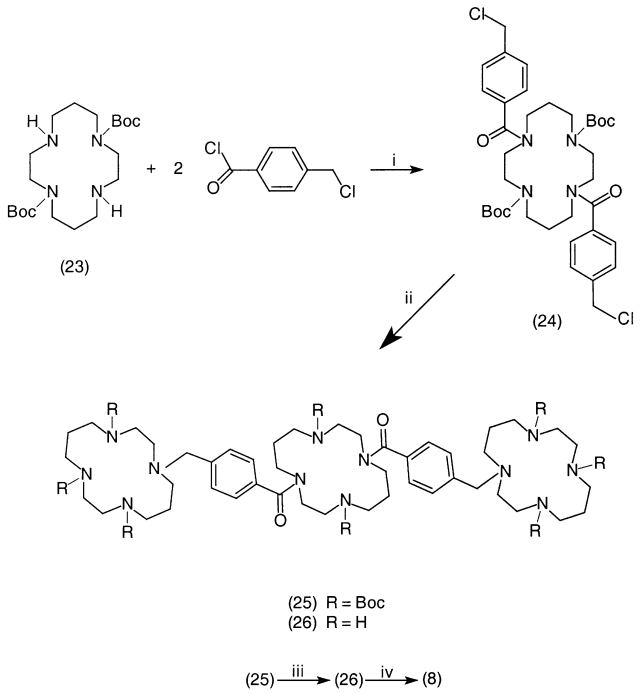
Benzyl bromide (0.342 g, 2.0 mmol) and caesium carbonate (0.977 g, 3.0 mmol) were added to a stirred solution of 1,4,8-tris(tert-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (1.000 g, 2.0 mmol) in dry acetonitrile (30 mL). The resultant mixture was refluxed overnight, filtered through Filter-Aid Celite 521 and washed with hot chloroform (30 mL). The filtrate was taken to dryness on a rotary evaporator to give a colourless viscous oil which was purified by column chromatography on silica gel (with CH_2Cl_2/MeOH/saturated NH_3 aqueous solution, 150 : 1 : 0.5 as eluent) to give (10) as a colourless *oil* (1.06 g, 90%) (Found (EI): M^+, 590.4025. $C_{32}H_{54}N_4O_6$ requires 590.4043). ^1H NMR



(21) R = Boc
(22) R = H

(9) —i→ (21) —ii→ (22) —iii→ (7)

Scheme 5. Boc = tert-butoxycarbonyl. *Reagents and conditions*: (i) $C_6H_3(COCl)_3$, Et_3N, tetrahydrofuran; (ii) 3 M HCl–MeOH; (iii) $BH_3{\cdot}Me_2S$ then MeOH/H_2O/conc. HCl (20 : 10 : 10).



(23) (24)

(25) R = Boc
(26) R = H

(25) —iii→ (26) —iv→ (8)

Scheme 6. Boc = tert-butoxycarbonyl. *Reagents and conditions*: (i) Et_3N, dichloromethane; (ii) Compound (9), Cs_2CO_3, KI, CH_3CN; (iii) 3M HCl–MeOH; (iv) $BH_3{\cdot}Me_2S$, then MeOH/H_2O/conc. HCl (20 : 10 : 10).

($CDCl_3$) δ 1.39, s, 9H, Bu^t; 1.44, s, 9H, Bu^t; 1.47, s, 9H, Bu^t; 1.68, quintet, *J* 6.5 Hz, 2H, $PhCH_2NCH_2C\mathbf{H}_2CH_2NBoc$; 1.88, quintet, *J* 6.8 Hz, 2H, $BocNCH_2C\mathbf{H}_2CH_2NBoc$; 2.39, t, *J* 6.5 Hz, 2H, $PhCH_2NC\mathbf{H}_2$-CH_2CH_2NBoc; 2.61, t, *J* 5.7 Hz, 2H, $PhCH_2NC\mathbf{H}_2CH_2NBoc$; 3.23–3.34, m, 12H, NCH_2; 3.52, s, 2H, $PhCH_2$; 7.18–7.33, m, 5H, ArH. ^{13}C NMR ($CDCl_3$) δ 28.6, 46.0, 47.4, 51.5, 53.2, 59.5, 79.5, 79.7, 127.0, 128.2, 129.2, 138.8, 155.6.

1-Benzyl-1,4,8,11-tetraazacyclotetradecane (1)

The above protected compound (10) (0.800 g, 1.36 mmol) was dissolved in 3 M HCl–MeOH (30 mL) and stirred overnight at room temperature. The white precipitate that formed was filtered off and washed with cold MeOH. It was then dissolved in 10% aqueous NaOH (40 mL) and CH_2Cl_2 (40 mL) was added. The resultant mixture was stirred at room temperature for 0.5 h and the two layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and the solvent was removed to dryness on a rotary evaporator. Compound (1) was obtained as a colourless viscous oil (0.36 g, 92%) (Found (EI): M^+, 290.2474. Calc. for $C_{17}H_{30}N_4$: 290.2470). ^1H NMR ($CDCl_3$) δ 1.67, quintet, *J* 5.3 Hz, 2H, $NCH_2C\mathbf{H}_2CH_2N$; 1.85, quintet, *J* 5.5 Hz, 2H, $PhCH_2NCH_2C\mathbf{H}_2CH_2N$; 2.49–2.85, m, 16H, NCH_2; 3.57, s, 2H, $PhCH_2$; 7.22–7.36, m, 5H, ArH. ^{13}C NMR ($CDCl_3$) δ 26.2, 28.5, 47.4, 47.9, 49.0, 49.2, 49.4, 50.7, 53.4, 54.5, 57.9, 126.9, 128.1, 129.3,138.8.

Compound (12)

To a solution of (11) (0.500 g, 2.02 mmol) in water (10 mL) that had been previously cooled to near-freezing was added $(Boc)_2O$ (0.89 g, 4.08 mmol) in ethanol (10 mL). The reaction vessel was stoppered, the mixture allowed to rise to ambient temperature, and was then stirred for 8 h. The solution was then evaporated on a rotary evaporator to yield (12) as a red-brown viscous *oil* (0.81 g, 90%), which was used without further purification (Found (EI): $[M–Cl]^+$, 411.2967. $C_{21}H_{39}N_4O_4$ requires 411.2971). ^1H NMR (D_2O) δ 1.47, s, 18H, Bu^t; 1.70, quintet, *J* 6.2 Hz, 2H, $BocNCH_2C\mathbf{H}_2CH_2$; 2.20, quintet, *J* 6.0 Hz, 2H, CH^+NCH_2-$C\mathbf{H}_2CH_2N$; 3.22, t, *J* 6.2 Hz, 4H, $BocNC\mathbf{H}_2CH_2C\mathbf{H}_2NBoc$; 3.43–3.56, m, 8H, NCH_2; 3.68, t, *J* 6.0 Hz, 4H, $CH^+NC\mathbf{H}_2CH_2NBoc$; 8.18, s, 1H, CH *ortho*. ^{13}C NMR (D_2O) δ 21.0, 27.5, 30.2, 48.0, 51.1, 52.5, 56.5, 84.7, 154.9, 160.0.

Compound (13)

Compound (12) (0.85 g, 1.9 mmol) was dissolved in ethanol (10 mL) and the solution cooled to 0°C whereupon conc. NaOH solution (10 mL) was added. The mixture was stirred at reflux for 10 h and then cooled. The ethanol was removed on a rotary evaporator and the remaining aqueous phase was extracted with chloroform (8×10 mL). The combined extracts were dried (anhydrous Na_2SO_4), filtered and evaporated to dryness. The resulting brown viscous oil was purified by column chromatography on silica gel (with 1% MeOH/CH_2Cl_2 as eluent) giving the title compound (13) as a pale-yellow sticky *oil* (0.61 g, 80%) (Found (EI): M^+, 400.3051. $C_{20}H_{40}N_4O_4$ requires 400.3050). ^1H NMR ($CDCl_3$) δ 1.45, s, 18H, Bu^t; 1.68, quintet, *J* 5.4 Hz, 2H, $NCH_2C\mathbf{H}_2CH_2N$; 1.95, quintet, *J* 5.6 Hz, 2H, $BocNCH_2$-$C\mathbf{H}_2CH_2$; 2.68–2.76, m, 8H, NCH_2; 3.22–3.32, m, 8H, $BocNCH_2$. ^{13}C NMR ($CDCl_3$) δ 28.4, 29.5, 47.7, 48.9, 49.8, 79.2, 155.9.

Compound (14)

Benzyl bromide (0.45 g, 2.6 mmol) and caesium carbonate (1.92 g, 5.9 mmol) were added to a stirred solution of (13) (0.52 g, 1.3 mmol) in dry acetonitrile (40 mL). The resultant mixture was refluxed overnight, filtered through Filter-Aid Celite 521, and washed thoroughly with hot chloroform (100 mL). The filtrate was taken to dryness on a rotary evaporator to give the crude product as an oil which was purified by column chromatography on silica gel (with CH_2Cl_2/MeOH, 100 : 1 as eluent) to give (14) as a viscous colourless *oil* (0.72 g, 95%) (Found (EI): M^+, 580.3976. $C_{34}H_{52}N_4O_4$ requires 580.3989). ^1H NMR ($CDCl_3$) δ 1.38, s, 18H, Bu^t; 1.58, quintet, *J* 6.2 Hz, 2H, $PhCH_2NCH_2C\mathbf{H}_2CH_2$; 1.96, quintet, *J* 7.0 Hz, 2H, $BocNCH_2C\mathbf{H}_2CH_2$; 2.38, m, 4H, $PhCH_2NC\mathbf{H}_2CH_2C\mathbf{H}_2N$; 2.59, t, *J* 6.2 Hz, 4H, $PhCH_2NC\mathbf{H}_2$; 3.29–3.36, m, 8H, $BocNCH_2$; 7.19–7.26, m, 5H, ArH. ^{13}C NMR ($CDCl_3$) δ 28.4, 46.5, 51.3, 52.8, 59.5, 79.3, 126.8, 128.1, 128.9, 139.5, 155.7.

1,5-Bisbenzyl-1,4,8,11-tetraazacyclotetradecane (2)

The product from the above preparation (14) (0.58 g, 1.0 mmol) was stirred in a solution of 3 M HCl–MeOH (20 mL) overnight at room temperature. The white precipitate was filtered off and washed with cold

MeOH. It was then dissolved in 10% aqueous NaOH (15 mL) and CH_2Cl_2 (30 mL) was added. The resultant mixture was stirred at room temperature for 0.5 h and the two layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and the solvent was removed on a rotary evaporator. The title compound (2) was obtained as a colourless viscous *oil* (0.35 g, 92%) (Found (EI): M^+, 380.2935. $C_{24}H_{36}N_4$ requires 380.2940). ^{1}H NMR ($CDCl_3$) δ 1.63–1.83, m, 4H, $NCH_2CH_2CH_2N$; 2.40–2.56, m, 8H, NCH_2; 2.65–2.79, m, 8H, $PhCH_2NCH_2$; 3.49, s, 4H, $PhCH_2$; 7.17–7.29, m, 10H, ArH. ^{13}C NMR ($CDCl_3$) δ 26.7, 28.1, 47.6, 48.8, 50.7, 53.7, 59.2, 126.9, 128.2, 129.0, 139.6.

1,4,8-Tris(tert-butoxycarbonyl)-11-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (15)

1,4,8-Tris(tert-butoxycarbonyl)cyclam (9) (0.91 g, 1.82 mmol) was dissolved in dry CH_2Cl_2 (40 mL). Triethylamine (0.23 g, 2.27 mmol) and then 2,2,2-trichloroethyl chlorofomate (0.39 g, 1.84 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 6 h. The organic layer was then washed with water (2×20 mL), separated, dried (anhydrous Na_2SO_4) and evaporated on a rotary evaporator. Purification of this material was achieved by column chromatography on silica gel (with CH_2Cl_2/MeOH/saturated NH_3 aqueous solution, 25 : 1 : 0.5 as eluent) to yield the title compound (15) as a colourless viscous *oil* (1.17 g, 95%) (Found (EI): M^+, 674.2592. $C_{28}H_{49}N_4O_8Cl_3$ requires 674.2615). ^{1}H NMR ($CDCl_3$) δ 1.46, s, 27H, Bu^t; 1.75, m, 4H, $NCH_2CH_2CH_2$; 3.30–3.51, m, 16H, NCH_2; 4.74, s, 2H, Cl_3CCH_2OCO. ^{13}C NMR ($CDCl_3$) δ 28.5, 46.4, 47.1, 48.2, 75.2, 79.8, 80.0, 80.1, 95.5, 154.4, 155.6, 155.9.

1-(2,2,2-Trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (16)

Compound (15) (1.01 g, 1.5 mmol) was dissolved in 3 M HCl–MeOH (40 mL) and the solution was stirred overnight at room temperature. The white precipitate was filtered off and washed with cold MeOH. It was then dissolved in 10% aqueous NaOH (30 mL) and CH_2Cl_2 (60 mL) was added. The resultant mixture was stirred at room temperature for 0.5 h and the two layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and the solvent was removed on a rotary evaporator. The title compound (16) was obtained as a colourless viscous *oil* (0.5 g, 89%) (Found (EI): M^+, 374.1037. $C_{13}H_{25}N_4O_2Cl_3$ requires 374.1043). ^{1}H NMR ($CDCl_3$) δ 1.63–1.82, m, 4H, $NCH_2CH_2CH_2$; 2.63–2.79, m, 10H, NCH_2; 2.86–2.91, t, *J* 5.5 Hz, 2H, $TrocNCH_2CH_2$; 3.44, t, *J* 5.5 Hz, 2H, $TrocNCH_2CH_2$ N; 3.54, t, *J* 7.1 Hz, 2H, $TrocNCH_2CH_2CH_2N$; 4.74, s, 2H, Cl_3CCH_2OCO. ^{13}C NMR ($CDCl_3$) δ 29.5, 45.1, 47.0, 47.3, 48.1, 48.5, 49.7, 75.0, 95.8, 154.7.

1-(2,2,2-Trichloroethoxycarbonyl)-4,8,11-trisbenzyltetraazacyclotetradecane (17)

Benzyl bromide (0.63 g, 3.69 mmol) and caesium carbonate (4.09 g, 12.56 mmol) were added to a stirred solution of (16) (0.46 g, 1.23 mmol) in dry acetonitrile (30 mL). The resultant mixture was refluxed for 2 h and then stirred at room temperature overnight, filtered through Filter-Aid Celite 521, and washed thoroughly with hot chloroform. The filtrate was taken to dryness on a rotary evaporator to give a pale-yellow viscous oil which was purified by column chromatography on silica gel (with CH_2Cl_2/MeOH/saturated NH_3 aqueous solution, 200 : 1 : 0.35, as eluent) to give (17) as a white *powder* (0.40 g, 50%) (Found: C, 63.1; H, 6.6; N, 8.6%; (FAB) $[M+H]^+$, 645.2538. $C_{34}H_{43}N_4O_2Cl_3$ requires C, 63.2; H, 6.7; N, 8.7%; $[M+H]^+$, 645.2530). ^{1}H NMR ($CDCl_3$) δ 1.71–1.77, m, 4H, $NCH_2CH_2CH_2$; 2.37–2.58, m, 12H, NCH_2; 3.37–3.45, m, 4H, $TrocNCH_2$; 3.45, s, 2H, $PhCH_2$; 3.50, s, 2H, $PhCH_2$; 3.54, s, 2H, $PhCH_2$; 4.51, s, 1H, Cl_3CCH_2OCO; 4.58, s, 1H, Cl_3CCH_2OCO; 7.18–7.27, m, 15H, ArH. ^{13}C NMR ($CDCl_3$) δ 25.1, 25.5, 26.3, 45.4, 46.1, 47.0, 51.3, 51.7, 52.6, 52.9, 59.9, 74.9, 95.7, 126.9, 128.2, 128.8, 129.2, 139.6, 154.1.

1,4,8-Trisbenzyl-1,4,8,11-tetraazacyclotetradecane (4)

Activated Zn dust (3.27 g, 50 mmol) was added to a solution of (17) (0.65 g, 1.0 mmol) in glacial acetic acid (10 mL). The suspension was stirred at room temperature for 2 h, filtered through Celite and washed with glacial acetic acid, which was then removed under reduced pressure. The residue was partitioned between 10% aqueous NaOH (20 mL) and CH_2Cl_2 (30 mL) at 0°C. The aqueous layer was then extracted with CH_2Cl_2 (2×30 mL) and the combined organic layers were dried (anhydrous Na_2SO_4) then evaporated under reduced pressure to give (4) as a colourless viscous *oil* (0.33 g, 70%) (Found (EI): M^+, 470.3415. $C_{31}H_{42}N_4$ requires 470.3409). ^{1}H NMR ($CDCl_3$) δ 1.68–1.80, m, 4H, $NCH_2CH_2CH_2$; 2.39–2.79, m, 16H, NCH_2; 3.41, s, 2H, $PhCH_2$; 3.56, s, 2H, $PhCH_2$; 3.61, s, 2H, $PhCH_2$; 7.16–7.34, m, 15H, ArH. ^{13}C NMR ($CDCl_3$) δ 25.4, 25.9, 47.0, 48.0, 49.5, 51.8, 52.3, 53.1, 58.3, 59.1, 126.7, 128.0, 129.1, 129.3, 138.6, 139.6.

1,3,5-Tris[(4,8,11-tert-butoxycarbonyl)carbonylmethoxy]benzene (19)

This compound was prepared by an analogous procedure[10] to that described previously and was purified by column chromatography on silica gel (with CH_2Cl_2/MeOH/saturated NH_3 aqueous solution, 50 : 1 : 0.5 as eluent) to give (19) as a white powder (75%) (Found: C, 59.6; H, 8.6; N, 9.3%. Calc. for $C_{87}H_{150}N_{12}O_{24}$: C, 59.8; H, 8.7; N, 9.6%). ^{1}H NMR ($CDCl_3$) δ 1.46, br s, 81H, Bu^t; 1.81, m, 12H, $NCH_2CH_2CH_2$; 3.38, br m, 48H, $NCH_2CH_2CH_2$; 4.62, s, 6H, OCH_2CON; 6.21, s, 3H, core ArH. ^{13}C NMR ($CDCl_3$) δ 27.7, 28.5, 29.0, 45.0, 46.6, 47.1, 47.7, 47.9, 48.5, 49.8, 67.0, 67.4, 80.0, 80.5, 95.3, 155.7, 156.2, 159.9, 167.4. Pronounced broadening of signals in the ^{1}H and ^{13}C NMR spectra of this compound was observed.

1,3,5-Tris[(4,8,11-tetraazacyclotetradec-1-yl)carbonylmethoxy]benzene (20)

Protected triamide (19) (1.75 g, 1.0 mmol) was stirred in a solution of 3 M HCl–MeOH (35 mL) at room temperature overnight. The white powder was filtered off and washed with cold MeOH then basified with 10% aqueous NaOH (50 mL). The basic solution was extracted with chloroform (5×50 mL) and the combined organic extracts were dried (anhydrous Na_2SO_4) and then the solvent was removed on a rotary evaporator. The crude product was dissolved in absolute EtOH (10 mL) and 47% HBr in acetic acid (5 mL) was added at 0°C. The mixture was stirred for 0.5 h and the off-white powder that formed was filtered off and washed thoroughly with cold absolute EtOH, dried, and then redissolved in 10% aqueous NaOH (40 mL). This basic solution was extracted with chloroform (5×50 mL) and the combined extracts were dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. The title compound (20) was isolated as a colourless viscous *oil* (0.72 g, 85%) (Found (FAB): $[M+H]^+$, 847.6236. $C_{42}H_{78}N_{12}O_6$ requires $[M+H]^+$, 847.6245). ^{1}H NMR ($CDCl_3$) δ 1.72, m, 12H, $NCH_2CH_2CH_2$; 2.63–2.90, m, 36H, NCH_2; 3.48, t, *J* 6.5 Hz, 6H, $CH_2CONCH_2CH_2CH_2N$; 3.61, t, *J* 6.9 Hz, 6H, CH_2CONCH_2; 4.65, s, 6H, OCH_2CON; 6.22, s, 3H, ArH. ^{13}C NMR ($CDCl_3$) δ 28.5, 29.1, 29.3, 29.6, 45.2, 47.2, 47.9, 48.6, 49.1, 50.6, 66.7, 67.0, 95.0, 159.8, 167.2, 167.4.

1,3,5-Tris[2-(4,8,11-tetraazacyclotetradec-1-yl)ethoxy]benzene (6)

This product was obtained by an analogous procedure[10] to that described previously and was purified by a similar method to that used for (20). Compound (6) was obtained as a colourless oil (90%) (Found (FAB): $[M+H]^+$, 805.6877. Calc. for $C_{42}H_{84}N_{12}O_3$: $[M+H]^+$, 805.6868). ^{1}H NMR ($CDCl_3$) δ 1.66–1.85, m, 12H, $NCH_2CH_2CH_2$; 2.45–2.81, overlapping m, 48H, $NCH_2CH_2CH_2$; 2.90, t, *J* 5.6 Hz, 6H, OCH_2CH_2N; 4.03, t, *J* 5.6 Hz, 6H, OCH_2CH_2N; 6.07, s, 3H, ArH. ^{13}C NMR ($CDCl_3$) δ 26.4, 28.6, 47.7, 47.9, 48.9, 49.4, 50.8, 51.4, 53.7, 55.6, 65.6, 93.9, 160.7.

1,3,5-Tris[(4,8,11-tert-butoxycarbonyl-4,8,11-tetraazacyclotetradec-1-yl)carbonyl]benzene (21)

This compound was prepared by the method described previously.[10] It was purified by column chromatography on silica gel (with CH_2Cl_2/MeOH/saturated NH_3 aqueous solution, 50 : 1 : 0.5 as eluent) to give (21) as a white powder (90%) (Found: C, 60.7; H, 8.8; N, 9.6%. Calc. for $C_{84}H_{144}N_{12}O_{21}$: C, 60.9; H, 8.8; N, 10.1%). ^{1}H NMR ($CDCl_3$) δ 1.46, s, 81H, Bu^t; 1.79, m, 12H, $NCH_2CH_2CH_2$; 3.18–3.60, overlapping m, 48H, $NCH_2CH_2CH_2$; 7.52, s, 3H, ArH. ^{13}C NMR ($CDCl_3$) δ 27.2,

28.5, ca. 44–50 (broad overlapping signals), 80.0, 125.9, 137.3, 155.5, 155.9, 169.9. Pronounced broadening of signals in the ^{1}H and ^{13}C NMR spectra of this compound was observed.

1,3,5-Tris[(4,8,11-tetraazacyclotetradec-1-yl)carbonyl]benzene (22)

This compound was prepared and purified (89%) by a similar method to that employed for the synthesis of (20) (Found (FAB): $[M+H]^+$, 757.5909. $C_{39}H_{72}N_{12}O_3$ requires $[M+H]^+$, 757.5929). ^{1}H NMR ($CDCl_3$) δ 1.64, m, 12H, $NCH_2CH_2CH_2$; 2.60–2.81, overlapping m, 36H, NCH_2; 3.44–3.63, overlapping m, 12H, CH_2NCO; 7.41, s, 3H, ArH. ^{13}C NMR ($CDCl_3$) δ 29.4, 45.4, 47.7, 48.1, 48.8, 49.4, 49.6, 50.7, 125.5, 137.7, 170.3. Pronounced broadening of signals in the ^{1}H NMR spectrum of this compound was observed.

1,3,5-Tris[(4,8,11-tetraazacyclotetradec-1-yl)methyl]benzene (7)

The title compound was prepared and purified (90%) by a similar method to that used for (6) (Found (FAB): $[M+H]^+$, 715.6552. Calc. for $C_{39}H_{78}N_{12}$: $[M+H]^+$, 715.6551). ^{1}H NMR ($CDCl_3$) δ 1.69, quintet, *J* 6.0 Hz, 6H, $NCH_2CH_2CH_2$; 1.85, quintet, *J* 5.8 Hz, 6H, $NCH_2CH_2CH_2$; 2.42–2.83, overlapping m, 48H, NCH_2; 7.13, s, 3H, ArH. ^{13}C NMR ($CDCl_3$) δ 26.3, 28.8, 29.6, 47.4, 48.0, 48.9, 49.1, 49.5, 50.7, 50.9, 52.6, 54.5, 57.8, 129.4, 137.9. Pronounced broadening of signals in the ^{1}H NMR spectrum of this compound was observed.

[1,8-bis(tert-butoxycarbonyl)-4,11-bis(chloromethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecane (24)

1,8-Bis(tert-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (23) (1.2 g, 3.0 mmol) was dissolved in dry CH_2Cl_2 (50 mL). Triethylamine (0.79 g, 7.8 mmol) and then 4-(chloromethyl)benzoyl chloride (1.25 g, 6.6 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 12 h and the organic layer was then washed with water (2×30 mL), dried (anhydrous Na_2SO_4), and the solvent was removed on a rotary evaporator. Purification of this compound was achieved by column chromatography on silica gel (with CH_2Cl_2/MeOH/saturated NH_3 aqueous solution, 100 : 1 : 0.5, as eluent) to give (24) as a white *powder* (1.91 g, 90%) (Found: C, 61.2; H, 7.0; N, 7.8. $C_{36}H_{50}N_4O_6Cl_2$ requires C, 61.3; H, 7.1; N, 7.9%). ^{1}H NMR ($CDCl_3$) δ 1.26, br s, 9H, Bu^t; 1.46, br s, 9H, Bu^t; 1.90, m, 4H, $NCH_2CH_2CH_2$; 3.26–3.63, overlapping m, 16H, NCH_2; 4.58, s, 4H, $ArCH_2Cl$; 7.41, m, 8H, ArH. ^{13}C NMR ($CDCl_3$) δ 27.4, 28.4, ca. 44–50 (broad overlapping signals), 80.3, 126.8, 128.7, 136.5, 138.7, 155.4, 156.0, 171.4. Pronounced broadening of signals in the ^{1}H and ^{13}C NMR spectra of this compound was observed.

Compound (25)

Compound (24) (1.06 g, 1.5 mmol) was added to a suspension of 1,4,8-tris(tert-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (1.65 g, 3.3 mmol), caesium carbonate (1.22 g, 3.7 mmol) and sodium iodide (0.091 g, 0.6 mmol) in dry acetonitrile (30 mL). The reaction mixture was refluxed for 24 h then the suspension was filtered through Filter-Aid Celite 521 and the residue was washed with hot chloroform. The combined organic phase was evaporated on a rotary evaporator and the crude product was purified by column chromatography on silica gel (with CH_2Cl_2/MeOH/saturated NH_3 aqueous solution, 100 : 1 : 0.5, as eluent) to give (25) as a white *powder* (1.96 g, 80%) (Found: C, 61.2; H, 8.3; N, 9.7. $C_{86}H_{144}N_{12}O_{18}\cdot 0.75CH_2Cl_2$ requires C, 61.4; H, 8.6; N, 9.9%). ^{1}H NMR ($CDCl_3$) δ 1.46, br s, 72H, Bu^t; 1.68, m, 4H, $PhCH_2NCH_2CH_2CH_2N$; 1.91, m, 8H, $BocNCH_2CH_2CH_2NBoc$, $CONCH_2CH_2CH_2N$; 2.40, m, 4H, $ArCH_2NCH_2CH_2CH_2N$; 2.64, m, 4H, $ArCH_2NCH_2CH_2NBoc$; 3.37, overlapping m, 40H, $BocNCH_2$; 3.57, br s, 4H, $ArCH_2N$; 7.31, m, 8H, ArH. ^{13}C NMR ($CDCl_3$) δ 26.5, 28.5, ca. 46–50 (broad overlapping signals), 51.6, 52.8, 59.3, 79.6, 80.3, 126.5, 129.0, 135.2, 140.4, 155.6, 171.9. Pronounced broadening of signals in the ^{1}H and ^{13}C NMR spectra of this compound was observed.

Compound (26)

This *compound* was prepared and purified (90%) by a similar procedure to that used for (20) (Found: C, 59.1; H, 8.6; N, 17.2. $C_{46}H_{80}N_{12}O_2\cdot 1.5CH_2Cl_2$ requires C, 59.4; H, 8.7; N, 17.5%). ^{1}H NMR ($CDCl_3$) δ 1.68, m, 6H, $NCH_2CH_2CH_2$; 1.85, m, 6H, $NCH_2CH_2CH_2$; 2.53–2.81, overlapping m, 40H, NCH_2; 3.42–3.70, overlapping m, 8H, $CONCH_2$; 3.59, s, 4H, $ArCH_2N$; 7.33–7.41, m, 8H, ArH. ^{13}C NMR ($CDCl_3$) δ 26.2, 28.6, 46.3, 47.3, 48.0, 48.9, 49.2, 49.3, 50.7, 53.4, 54.9, 57.6, 126.4, 129.0, 135.6, 140.2, 172.2. Pronounced broadening of signals in the ^{1}H NMR spectrum of this compound was observed.

Compound (8)

This compound was prepared and purified (91%) by a similar procedure to that used for (6) (Found (FAB): $[M+H]^+$, 805.6999. $C_{46}H_{84}N_{12}$ requires $[M+H]^+$, 805.7020). ^{1}H NMR ($CDCl_3$) δ 1.66, m, 6H, $NCH_2CH_2CH_2$; 1.82, m, 6H, $NCH_2CH_2CH_2$; 2.49–2.74, m, 48H, NCH_2; 3.55, s, 4H, $ArCH_2N$; 3.70, s, 4H, $ArCH_2N$; 7.20–7.29, m, 8H, ArH. ^{13}C NMR ($CDCl_3$) δ 25.8, 26.2, 28.6, 47.4, 47.6, 47.9, 48.9, 49.3, 50.0, 50.6, 51.5, 53.0, 53.2, 53.9, 54.5, 57.4, 129.0, 129.3, 135.7, 137.4. The product was further characterized as its hydrobromide salt which was obtained by dropwise addition of conc. HBr to an absolute EtOH solution of the above product. This crude salt was purified by recrystallization from H_2O/EtOH to yield fine colourless *crystals* (Found: C, 30.8; H, 5.8; N, 8.9. $C_{46}H_{96}N_{12}Br_{12}\cdot 3H_2O.0.5HAc$ requires C, 30.4; H, 5.6; N, 9.0%). ^{1}H NMR (D_2O) δ 2.21, br m, 12H, $NCH_2CH_2CH_2$; 3.42, br m, 32H, NCH_2; 3.63, br m, 16H, $ArCH_2NCH_2$; 4.46, br s, 8H, $ArCH_2N$; 7.67, m, 8H, ArH. ^{13}C NMR (D_2O) δ 17.6, 19.5, 21.4, 21.8, 22.0, 40.7, 44.2, 44.8, 47.7, 50.6, 57.1, 60.1, 60.7, 134.1, 134.5.

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