# Syntheses of C- and *N*-Functionalised Derivatives of 1,5,9-Triazacyclododecane

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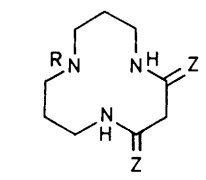
The synthesis of a series of di- and tri-*N*-substituted triazacyclododecane ligands has been effected through the intermediacy of monotosylamide derivatives. A C-functionalised aminobenzyl [12]-$N_3$ tris(carboxymethyl) derivative has been prepared permitting subsequent linkage to a protein.

The synthesis of functionalised azacoronands has been the subject of recent interest because of their ability to selectively bind cationic species.[1,2] Most work has concentrated on the synthesis of C- and *N*-functionalised derivatives of 1,4,8,11-tetra-azacyclotetradecane, in view of the applications of these functionalised ligands in tumour targeting,[3] ion selection,[4] and electrocatalysis.[5] There has been much less work reported on the selective synthesis of functionalised triazacoronands, although the utility of derivatives of [12]-$N_3$ systems as 'proton sponges' has been noted.[6] Recently reported syntheses of derivatives of the [12]-$N_3$ ring system have involved selective protection of a ring precursor[7] prior to Richman–Atkins cyclisation, or have involved the intermediacy of tricyclic orthoamides.[9]

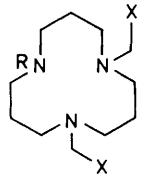
During the course of an effort to investigate the co-ordination chemistry of *N*-functionalised hexadentate macrocyclic ligands, we have developed short syntheses of a series of *N*- and C-substituted [12]-$N_3$ ligands. A particular motivation for this work was the kinetic stability *in vivo* of the $^{111}$In complex ($^{111}$In is a γ-emitter [$t_{\frac{1}{2}}$ = 2.81 days] of use in diagnostic nuclear medicine) of the [12]-$N_3$ triacetate derivative.[10] This stimulated the need to synthesize a C-functionalised derivative bearing an exocyclic amine group for linkage to a protein (antibody).

Reaction of 1,5,9-triazanonane with diethyl malonate in boiling ethanol afforded the diamide (**1**) in moderate yield and tosylation yielded the *N*-tosylamide (**2**), thereby effectively distinguishing one nitrogen from the other two. Borane reduction of (**2**) gave the *N*-tosyl triamine which was separately dialkylated with ethyl bromoacetate or *N*,*N*-dimethylbromoacetamide to give (**4**) and (**6**) in good yield. Detosylation (HBr–AcOH–PhOH) afforded the pentadentate diacid and diamide ligands (**5**) and (**7**). Earlier workers had noted the difficulty (and had not succeeded) in preparing the [12]-$N_3$ triacetate derivative (**9**) by direct reaction of chloroacetic acid with triazacyclododecane in the presence of base.[11] Such problems were obviated by forming (**9**) *via* hydrolysis of the triester (**8**) which was readily accessible by alkylation of triazacyclododecane with ethyl bromoacetate in ethanol in the presence of caesium carbonate. Similarly the neutral triamide (**10**) was prepared by alkylation of the parent triamine with *N*,*N*-dimethylbromoacetamide (EtOH, $Cs_2CO_3$, 75%).

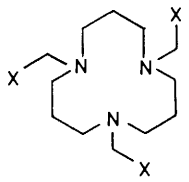
The synthesis of C-functionalised derivatives of [12]-$N_3$ rings may be accomplished either by reaction of a substituted malonate with 1,5,9-triazanonane or through the addition reaction of the amine with an αβ-unsaturated ester[12] (*e.g.* substituted cinnamates or coumarins). Reaction of the *p*-cyanobenzyl derivative of diethyl malonate with triazanonane gave the diamide (**11**) which was separated by chromatography on silica. Direct reduction of (**11**) with borane–tetrahydrofuran yielded not the expected tetra-amine (**14a**), but the boron complex (**14b**). In this compound, the boron is efficiently bound in the plane of the triaza ring to form a robust neutral complex. The boron complex of 1,5,9-triazacyclododecane has previously



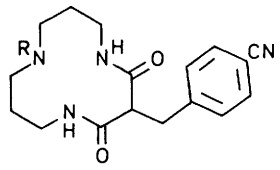
(**1**) R = H, Z = O
(**2**) R = Ts, Z = O
(**3**) R = Ts, Z = $H_2$



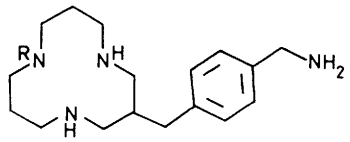
(**4**) R = Ts, X = $CH_2CO_2Et$
(**5**) R = H, X = $CH_2CO_2H$
(**6**) R = Ts, X = $CONMe_2$
(**7**) R = H, X = $CONMe_2$



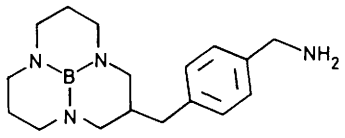
(**8**) X = $CO_2Et$
(**9**) X = $CO_2H$
(**10**) X = $CONMe_2$



(**11**) R = H
(**12**) R = Ts

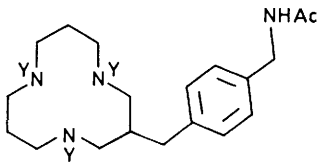


(**13**) R = Ts
(**14a**) R = H

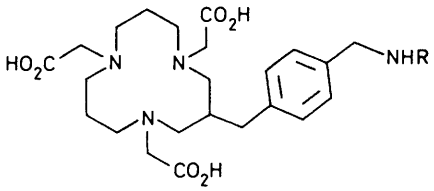


(**14b**)

been reported following exhaustive reaction of the amine with $B(OMe)_3$:[13] borane reduction of the diamide (**1**) affords an alternative route to this boron complex. Tosylation of (**11**) prior to borane reduction obviated the formation of this resilient boron complex, and led to formation of the *N*-tosylamide (**13**). Detosylation with hydrogen bromide in the presence of phenol yielded the tetra-amine (**14a**). The ring nitrogens are conveniently protected from electrophilic attack




(**15**) Y = H
(**16**) Y = $CH_2CO_2Et$




(**17**) R = H
(**18**) R = CO⟨⟩$CH_2$N⟨O, O⟩

by protonation ($pK_a$ = 13.2 and 7.4 for the parent amine[14]) permitting selective acylation of the exocyclic amine. Acetylation of (**14a**) using *p*-nitrophenyl acetate in an aqueous dioxane solvent (pH = 6.8) gave the acetamide (**15**) in good yield (91%). Trialkylation of the secondary amine sites with ethyl bromoacetate in ethanol in the presence of caesium carbonate gave the triester (**16**) (61%) and acid hydrolysis (6M HCl) afforded the amino acid (**17**) quantitatively. The complexation (with $^{111}In$) and conjugation of (**17**) to a monoclonal antibody [*via* (**18**)] to yield a kinetically stable conjugate has been reported elsewhere.[10] The further complexation behaviour and basicity of ligands (**5**), (**7**), (**9**), and (**10**) will be reported subsequently.

## Experimental

Proton and carbon-13 n.m.r. spectra were recorded on a Bruker AC250 (250.13 and 62.1 MHz) spectrometer. Chemical shifts are quoted to higher frequency of $Me_4Si$ and are given in p.p.m. with coupling constants in Hz. I.r. spectra were recorded on a Perkin-Elmer 580A i.r. spectrophotometer and mass spectra were recorded either in the e.i., c.i., d.c.i., or f.a.b. mode with a VG 7070E spectrometer. T.l.c. was used to monitor reactions and column chromatography on silica was effected using Merck 60 7354 or 9385 for flash chromatography and on alumina using Merck neutral alumina, previously treated with ethyl acetate. H.p.l.c. analyses were carried out with a Varian 5500 instrument using both ion exchange (TSK-DEAE) or reverse-phase (Hypersil 5005) columns for analytical or semi-preparative work typically with aqueous $NH_4$ OAc/MeCN gradient elution. Microanalyses were performed by Mrs. M. Cocks, University of Durham. Compounds that did not give correct microanalyses or high resolution spectra were checked for their purity by h.p.l.c. and were ≥97% pure.

1,5,9-*Triazacyclododecane*-2,4-*dione* (**1**).—A solution of 1,5,9-triazanonane (13.1 g, 0.1 mol) and diethyl malonate (16 g, 0.1 mol) in ethanol (1.2 $dm^3$) was boiled under reflux for 5 days. After removal of solvent, the residue was chromatographed on silica gel ($NH_4OH$–$H_2O$: 1→5%; MeOH 59→55%; $CH_2Cl_2$ 40%) to yield a colourless solid, m.p. 152—154 °C [$R_F$ = 0.7 (1% $NH_4OH$, 59% MeOH, 40% $CH_2Cl_2$)], 2.82 g (14%) (Found: C, 49.0; H, 8.75; N, 20.9. Calc. for $C_9H_{17}H_3O_2$: C, 49.2; H, 8.55; N, 21.1%); *m/z* ($NH_3$, c.i.) 200 ($M^+$ + 1) and 199 ($M^+$); $\delta_H(CDCl_3)$ 8.56 (2 H, br t, NHCO), 3.40 (4 H, dt, $CH_2NHCO$), 3.13 (2 H, s, $CH_2CO$), 2.76 (4 H, t, $NCH_2CH_2$), 1.85 (1 H, br s, NH), and 1.66 (4 H, quint, $CH_2CH_2CH_2$).

9-(p-*Tolylsulphonyl*)-1,5,9-*triazacyclododecane*-2,4-*dione* (**2**).—To a solution of (**1**) (0.5 g, 2.5 mmol) in dry pyridine (20 $cm^3$) was added toluene-*p*-sulphonyl chloride (0.75 g, 4 mmol) and the solution was held at 4 °C for 24 h. It was then poured onto ice–water and the precipitate was filtered off. The residue was dissolved in dichloromethane (100 $cm^3$), and the solution dried ($K_2CO_3$), filtered, and evaporated to yield an off-white solid which was recrystallised from hot methanol (466 mg, 53%), m.p. >260 °C (Found: C, 54.2; H, 6.2; N, 11.6. Calc. for $C_{16}H_{23}N_3O_4S$: C, 54.4; H, 6.52; N, 11.9%) *m/z* (e.i.) 353 ($M^+$), 352 ($M^+$ − 1), and 198 ($M^+$ − Ts); $\delta_H(CDCl_3)$ 7.65 (2 H, d, ArH), 7.28 (2 H, d, ArH), 6.40 (2 H, br s, NHCO), 3.29—3.14 (8 H, m, $CH_2NTs$ + $CH_2N$), 2.43 (3 H, s, $CH_3$), 1.75 (4 H, quint, $CH_2CH_2CH_2$); $\nu_{max.}$(KBr) 3 310w (NHCO) 1 680, 1 650s, 1 620s, 1 560, and 1 160 $cm^{-1}$.

9-p-*Tolylsulphonyl*-1,5,9-*triazacyclododecane* (**3**).—To a slurry of (**2**) (0.5 g, 1.41 mmol) in tetrahydrofuran (15 $cm^3$) was added borane•THF (50 $cm^3$; 1M), and the mixture was heated to reflux for 24 h. After this excess of borane was destroyed with methanol, solvents were removed under reduced pressure, and the residue was treated with hydrochloric acid (6M; 20 $cm^3$) and heated to 100 °C (3 h). After the solution had been cooled and basified to pH 14 (KOH), it was extracted with chloroform (3 × 30 $cm^3$) and the extract dried ($K_2CO_3$), filtered, and evaporated to yield a colourless glass (0.41 g, 89%); $\delta_H(CDCl_3)$ 7.65 (2 H, d, ArH), 7.27 (2 H, d, ArH), 3.21 (4 H, t, $CH_2NTs$), 2.76 (8 H, t + t, $CH_2N$), 2.40 (3 H, s, $ArCH_3$), 2.21 (2 H, s, NH), 1.73 (6 H, quint + quint, $CH_2C$); $\delta_C(CDCl_3)$ 142.9(s), 139.5(s); 129.4, 127.3(d); 47.1, 45.5, 45.2 (t, $CH_2N$); 27.5, 26.9 (t, $CH_2C$); 21.4(q); $\nu_{max.}$(KBr) 3 300br (NH), 2 920, 2 810 (CH), and 1 600w, 1 160s $cm^{-1}$; *m/z* (c.i.) 326 ($M^+$ + 1), 325 ($M^+$), and 170 (Found: 325.182 689. $C_{16}H_{27}N_3SO_2$ requires 325.182 399).

1,5-*Bis*(*ethoxycarbonylmethyl*)-9-(p-*tolylsulphonyl*)-1,5,9-*triazacyclododecane* (**4**).—To a solution of (**3**) (0.3 g, 0.92 mmol) in ethanol (10 $cm^3$) was added caesium carbonate (0.63 g, 1.93 mmol) and ethyl bromoacetate (0.33 g, 1.98 mmol), and the mixture was heated at reflux (18 h). After removal of solvent, the residue was chromatographed on silica gel (5% MeOH–$CH_2Cl_2$) to yield a colourless oil (0.344 g, 75%), $R_F$ (10% MeOH–$CH_2Cl_2$) 0.74; *m/z* ($NH_3$, c.i.) 499 ($M^+$ + 2), 498 ($M^+$ + 1), 410, and 342 (Found : *M*, 497.256 248. $C_{24}H_{39}H_3SO_6$ requires 497.255 958); $\delta_H(CDCl_3)$ 7.70 (2 H, d, *J* 8.2), 7.28 (2 H, d), 4.11 (4 H, q, $CH_2O$), 3.48 (4 H, t, $CH_2N$), 3.16 (4 H, s, $CH_2CO$), 2.59 (4 H, br t), 2.52 (4 H, br t), 2.41 (3 H, s), 1.55 (4 H, m, $CH_2C$), 1.49 (2 H, m), and 1.24 (6 H, t, $CH_3CH_2$); $\delta_C(CDCl_3)$ 171.5(s), 142.6(s), 138.5(s); 129.5, 126.9(d); 60.2 ($CH_2O$), 54.5, 52.6, 47.3, 42.2 ($CH_2N$); 24.1, 24.0 ($CH_2C$); 21.4, ($ArCH_3$), 14.2 ($CH_3CH_2$).

1,5-*Bis*(*carboxymethyl*)-1,5,9-*triazacyclododecane* (**5**).—To a solution of (**4**) (0.3 g, 0.6 mmol) in HBr–acetic acid (45% w/v) (25 $cm^3$) was added phenol (0.6 g) and the mixture was heated at 110 °C for 100 h. A fine precipitate was removed by filtration on cooling, and was washed with diethyl ether (2 × 5 $cm^3$) and dried *in vacuo*, (0.23 g, 76%). This was the dihydrobromide of (**5**); $\delta_H(D_2O)$ 4.06 (4 H, s, $CH_2CO_2H$), 3.51—3.19 (12 H, m, $CH_2N$), and 2.35—2.01 (6 H, m, $CH_2C$); $\delta_C(D_2O)$ 173.8(s); 57.2, 55.3, 54.5 ($CH_2N$); 47.2 ($CH_2CO$); 22.9, 22.7 ($CH_2C$); *m/z* (c.i.) 288 ($M^+$ + 1), 287 ($M^+$), 244, 230, and 194.

1,5-*Bis*(*dimethylamidomethyl*)-9-(p-*tolylsulphonyl*)-1,5,9-

*triazacyclododecane* (**6**).—To a solution of (**3**) (700 mg, 2.15 mmol) in dry acetonitrile (15 $cm^3$) was added caesium carbonate (2.1 g, 65 mmol), and *N,N*-dimethylbromoacetamide (1.07 g, 6.5 mmol) and the mixture was heated at reflux for 48 h. It was then cooled, filtered, and evaporated under reduced pressure and the residue was chromatographed on neutral alumina (eluting with ethyl acetate) to yield a colourless oil (0.65 g, 61%), $R_F$(EtOAc) 0.40; *m/z* (d.c.i.) 496 ($M^+ + 1$), 495 ($M^+$), 340 ($M^+ - Ts$) (Found: $M^+$, 495.286 927; $C_{24}H_{41}N_5O_4S$ requires 495.286 715); $\nu_{max.}$(KBr) 1 645vs, 1 600m, 1 335s, and 1 165s $cm^{-1}$; $\delta_H(CDCl_3)$ 7.59 (2 H, d, *J* 8.1), 7.19 (2 H, d), 3.37 (4 H, t, $CH_2NTs$), 3.09 (4 H, s, $CH_2CO$), 2.94 (6 H, s, NMe), 2.88 (6 H, s, NMe), and 1.47 (6 H, m, $CH_2C$); $\delta_C(CDCl_3)$ 170.5(s); 142.7, 137.8(s); 129.4, 126.9(d); 56.2 ($CH_2CO$); 52.0, 48.7, 42.6 ($CH_2N$); 36.8, 35.4 (NMe); 23.7, 23.8 ($CH_2C$), 21.4 ($ArCH_3$).

1,5-*Bis*(*dimethylaminomethyl*)-1,5,9-*triazacyclododecane* (**7**).—To a solution of (**6**) (600 mg, 1.2 mmol) in HBr–acetic acid (45% w/v; 15 $cm^3$) was added phenol (0.34 g, 3.6 mmol) and the mixture was heated at 80 °C for 3 days. After removal of solvent, the residue was taken up in hydrochloric acid (1M; 10 $cm^3$) and the solution washed with diethyl ether (3 × 10 $cm^3$) and dichloromethane (2 × 10 $cm^3$) and then rendered basic (pH 13 with KOH); it was then extracted with dichloromethane (3 × 10 $cm^3$). The extract was dried ($K_2CO_3$) and evaporated and the residue was chromatographed on neutral alumina [eluted initially with ethyl acetate to remove (**6**), and then 10% MeOH–$CH_2O_2$] to yield a colourless oil (140 mg, 34%), $R_F$ 0.50 (10% MeOH–$CH_2Cl_2$); *m/z* (d.c.i.) 342 ($M^+ + 1$) and 341 ($M^+$) (Found: $M^+$, 341.279 076 7. $C_{17}H_{35}N_5O_2$ requires 341.279 075 7); $\nu_{max.}$(film) 3 400br (NH) and 1 635s (CO) $cm^{-1}$; $\delta_H$ 3.11 (4 H, s, $CH_2CO$), 3.04 (6 H, s, $CH_3N$), 2.96 (6 H, s, $CH_3N$), 2.66 (4 H, t, *J* 5.5, $CH_2N$), 2.56 (4 H, m, $CH_2N$), 2.43 (4 H, t, *J* 7.2), and 1.83 (6 H, m, $CH_2C$); $\delta_C(CDCl_3)$ 169.9(s), 55.1 (t, $CH_2CO$), 51.3 ($CH_2N$), 46.7, 45.5 ($CH_2NH$); 35.6, 34.8 (NMe), 22.2, 21.4 ($CH_2C$).

1,5,9-*Tris*(*ethoxycarbonylmethyl*)-1,5,9-*triazacyclododecane* (**8**).—To a solution of 1,5,9-triazacyclododecane (0.34 g, 2 mmol) in ethanol (25 $cm^3$) was added caesium carbonate (2.0 g, 6.2 mmol) and ethyl bromoacetate (1.05 g, 6.2 mmol) and the mixture was heated to reflux (18 h). It was then cooled, filtered, and evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 $cm^3$) and the solution washed with water (2 × 10 $cm^3$), dried, and evaporated to yield a residue which was purified by chromatography on neutral alumina (eluant 2% MeOH–$CH_2Cl_2$) to yield a colourless oil (220 mg, 28%); *m/z* (c.i., isobutane) 430 ($M^+ + 1$), 429 ($M^+$), 344, 256, and 130 (Found: $M^+$, 429.283 696: $C_{21}H_{39}N_3O_6$ requires 429.283 886); $\nu_{max.}$(film) 1 745 (CO), 1 370, 1 270, 1 205, 1 185, 1 140s, and 1 035s $cm^{-1}$; $\delta_H(CDCl_3)$ 4.16 (6 H, q, $CH_2O$), 3.23 (6 H, s, $CH_2CO$), 2.65 (12 H, t, $CH_2N$), 1.60 (6 H, quint, $CH_2C$), and 1.26 (9 H, t, $CH_3$); $\delta_C(CDCl_3)$ 59.4 ($CH_2O$); 55.0, 48.4, ($CH_2N$); 21.1 ($CH_2C$), 13.4 ($CH_3$).

1,5,9-*Tris*(*carboxymethyl*)-1,5,9-*triazacyclododecane* (**9**).—A solution of (**8**) (200 mg) in hydrochloric acid (6M; 10 $cm^3$) was heated to reflux for 6 h and solvent removed to yield a colourless glassy solid; $\nu_{max.}$(KBr) 3 600—2 800br and 1 740 ($CO_2H$) $cm^{-1}$; $\delta_H(D_2O)$ 4.08 (6 H, s, $CH_2CO$), 3.48 (12 H, t, $CH_2N$), and 2.31 (6 H, quint, $CH_2C$); *m/z* (d.c.i.) 346 ($M^+ + 1$) and 345 ($M^+$).

1,5,9-*Tris*(*dimethylamidomethyl*)-1,5,9-*triazacyclododecane* (**10**).—To a solution of 1,5,9-triazacyclododecane (250 mg, 1.46 mmol) in dry ethanol (15 $cm^3$) was added caesium carbonate (1.42 g, 4.4 mmol) and *N,N*-dimethylbromoacetamide (0.73 g, 4.4 mmol) and the mixture was heated to reflux for 24 h. The mixture was cooled, filtered, and evaporated under reduced pressure and the residue was dissolved in hydrochloric acid (1M; 4 $cm^3$), and washed with dichloromethane (3 × 10 $cm^3$). The solution was basic (pH ≥13) with KOH and then extracted with dichloromethane (4 × 10 $cm^3$). Evaporation of the extract gave a residue which was purified by chromatography on neutral alumina (eluant $CH_2Cl_2$→2% MeOH–$CH_2Cl_2$) to yield a colourless oil (466 mg, 75%), $R_F$ 0.5 [2% MeOH–$CH_2Cl_2$]); $\nu_{max.}$(film) 1 650 (CO) $cm^{-1}$; $\delta_H(CDCl_3)$ 3.27 (6 H, s, $CH_2CO$), 3.10 (9 H, s, $CH_3N$), 2.96 (9 H, s, $CH_3N$), 2.61 (12 H, t, $CH_2N$, *J* 5.9), and 1.63 (6 H, quint, $CH_2C$); $\delta_C(CDCl_3)$ 46.6 ($CH_2N$), 36.8, 35.2 (NMe), 21.5 ($CH_2C$); *m/z* ($NH_3DCI$) 427 ($M^+ + 1$) and 426 ($M^+$) (Found: $M^+$, 426.331 751. $C_{21}H_{42}N_6O_3$ requires 426.331 840).

3-(p-*Cyanobenzyl*)-1,5,9-*triazacyclododecane*-2,4-*dione* (**11**).—To a solution of 1,5,9-triazanonane (5.5 g, 40 mmol) in ethanol (1.5 $dm^3$) was added diethyl *p*-cyanobenzylmalonate (11 g, 40 mmol) and the mixture was heated to reflux for 15 days. After this it was evaporated under reduced pressure and the residue was chromatographed on silica (eluant 1% $NH_4OH$, 39% MeOH, 60% $CH_2Cl_2$) to yield a colourless solid ($R_F$ 0.4) which was recrystallised from hot ethanol (2.2 g, 18%), m.p. 264—265 °C (Found: C, 64.6; H, 7.07; N, 18.0%. $C_{17}H_{22}N_4O_2$ requires C, 65.0; H, 7.01; N, 17.8%); *m/z* ($NH_3$, c.i.) 315 ($M^+ + 1$) and 316 ($M^+ + 2$); $\nu_{max.}$(KBr) 3 280br s, 2 230 (CN), 1 660, 1 640, 1 610, and 1 120 $cm^{-1}$; $\delta_H(CDCl_3)$ 7.53 (2 H, d), 7.50 (2 H, br, NHCO), 7.34 (2 H, d), 3.65 (2 H, m), 3.34 (2 H, d, $ArCH_2$), 3.23 (1 H, t), 3.21 (2 H, m), 2.85 (2 H, m), 2.68 (2 H, m), 1.73 (2 H, m), and 1.56 (3 H, s + m, NH + $CH_2C$).

3-(p-*Cyanobenzyl*)-9-(p-*tolylsulphonyl*)-1,5,9-*triazacyclo dodecane*-2,4-*dione* (**12**).—To a solution of (**11**) (1.57 g, 5 mmol) in dichloromethane (150 $cm^3$) was added triethylamine (1.0 g, 10 mmol) and toluene-*p*-sulphonyl chloride (1.35 g, 7.5 mmol) and the mixture was heated to reflux for 18 h. It was then evaporated and the residue was purified by flash chromatography on silica (10% MeOH–$CH_2Cl_2$) to yield a colourless solid (2.1 g, 90%), m.p. 258—260 °C (Found: C, 61.7; H, 6.19; N, 11.7%. $C_{24}H_{28}N_4O_4S$ requires: C, 61.5; H, 6.02; N, 11.9%); *m/z* ($NH_3$, c.i.), 469 ($M^+ + 1$) and 468 ($M^+$); $\nu_{max.}$(KBr) 3 300 (NHCO), 2 215 (CN), 1 670, 1 640 (CO), 1 530, and 1 160 $cm^{-1}$; $\delta_H(CDCl_3)$ 7.74 (2 H, d), 7.65 (2 H, d), 7.43 (4 H, m), 3.49—3.11 (9 H, m), 2.91—2.82 (2 H, m), 2.47 (3 H, s, $CH_3$), 1.74 (2 H, m), and 1.60 (2 H, m).

3-(p-*Aminomethylbenzyl*)-9-(p-*tolylsulphonyl*)-1,5,9-*triaza-cyclododecane* (**13**).—To a slurry of (**12**) (2 g, 4.27 mmol) in tetrahydrofuran (10 $cm^3$) was added borane–THF (1M; 60 $cm^3$) and the mixture was heated at reflux for 48 h. Excess of borane was destroyed with methanol (0 °C) after which the mixture was evaporated under reduced pressure and the residue heated to reflux in 6M HCl (50 $cm^3$) for 3 h. After removal of water from the mixture, the residue was redissolved in aqueous base (pH ≥ 13, KOH) and extracted with dichloromethane (4 × 50 $cm^3$). The combined extracts were dried ($K_2CO_3$) and evaporated to yield a colourless oil (1.71 g, 90%); *m/z* (c.i.) 445 ($M^+ + 1$), 444 ($M^+$), 324, and 289 ($M^+ - Ts$) (Found: $M^+$, 444.256 190 3. Calc. for $C_{24}H_{36}N_4O_2S$: 444.256 187 0); $\nu_{max.}$(film) 3 300, 1 590, 1 330, and 1 160 $cm^{-1}$; $\delta_H(CDCl_3)$ 7.67 (2 H, d), 7.29 (2 H, d), 7.23 (2 H, d), 7.11 (2 H, d), 3.83 (2 H, s, $CH_2NH_2$), 3.27—3.16 (4 H, m, $CH_2NTs$), 2.87—2.72 (4 H, m, $CH_2NH$, 2.67—2.52 (4 H, m, $CH_2NH$), 2.46 (2 H, d, $CH_2Ar$), 2.42 (3 H, s, $CH_3$), 2.17—1.91 (5 H, m, CHC + NH), and 1.78—1.68 (4 H, m, $CH_2C$); $\delta_C(CDCl_3)$ 143.2(s), 129.6(s), 129.0(d), 127.1(d); 51.8(t), $CH_2N$, 46.1, 45.9, 45.2 ($CH_2N$); 38.3 (d, CH), 37.7 (t, $CH_2Ar$); 26.6 ($CH_3Ar$); 21.5 ($CH_2C$).

3-*Aminomethylbenzyl*-1,5,9-*triazacyclododecane* (**14a**).—To a solution of (**13**) (1.7 g, 3.82 mmol) in HBr–acetic acid (45% w/v; 80 $cm^3$) was added phenol (2 g) and the mixture was heated to reflux for 24 h. Upon cooling a precipitate formed and this was filtered off and washed with diethyl ether (3 × 20 $cm^3$) to yield the trihydrobromide as a colourless solid (1.58 g, 67%), m.p. (decomp.) 248—249 °C; *m/z* (d.c.i.) 293 ($M^+ + 1$) and 292 ($M^+$); $\nu_{max.}$(KBr) 3 600—3 300br (NH), 2 890s, and 1 585m $cm^{-1}$; $\delta_H(D_2O)$ 7.11 (2 H, d), 7.06 (2 H, d), 3.76 (2 H, s, $CH_2N$), 3.13—2.78 (12 H, m), 2.56 (2 H, d, $CH_2Ar$), 2.29 (1 H, m, CH), and 1.81—1.68 (4 H, m); $\delta_C(D_2O)$ 138.3(s), 130.2(s); 130.0(d), 129.4(d), 50.6(t), 46.0(t), 40.7(t), 35.7(t), 33.7(d), 19.1(t).

*Boron Complex of* (**14a**)*: Compound* (**14b**).—To a suspension of (**11**) (750 mg, 2.39 mmol) in dry tetrahydrofuran (10 $cm^3$) was added borane·THF (1M; 30 $cm^3$) and the mixture was heated to reflux for 48 h. The mixture was cooled, excess of borane was destroyed by careful addition of methanol, and solvents were removed under reduced pressure. The residue was redissolved in 6M hydrochloric acid (20 $cm^3$) and heated to reflux for 3 h. Water was removed from the mixture and the residue redissolved in 20% KOH (10 $cm^3$) and extracted with dichloromethane (5 × 20 $cm^3$). The combined extracts were dried ($K_2CO_3$) and evaporated to leave a pale yellow oil which crystallised from toluene–ether as a colourless solid (609 mg, 85%), m.p. 69—70 °C (Found: C, 68.8; H, 9.31; B, 3.85; N, 18.4. Calc. for $BC_{17}H_{27}N_4C$, 68.5; H, 9.06; N, 18.8; B, 3.69%); $\delta_H(CDCl_3)$ 7.22—7.11 (4 H, m), 3.61 (2 H, s, $CH_2NH_2$), 2.43—2.65 (12 H, m), 2.57 (2 H, d, $CH_2Ar$), 2.27 (1 H, m, CH), and 1.98—1.78 (4 H, m, $CH_2C$); $\delta_C(CDCl_3)$ 140.5(s), 138.8(s), 126.8(d), 126.6(d), 52.9 (t, $CH_2NH_2$) 47.4(t), 45.8(t), 38.1(d), 37.7(t), 26.5(t).

3-(*Acetamidomethylbenzyl*)-1,5,9-*triazacyclododecane* (**15**).—To a solution of (**14a**) (420 mg, 0.74 mmol) in a 1M piperazine-1,4-bis(ethanesulphonic acid) buffer (pH 6.8, 10 $cm^3$) was added *p*-nitrophenyl acetate (400 mg, 2.22 mmol) in dioxane (10 $cm^3$) and the solution was held at 35 °C for 48 h. After cooling, the solution was extracted with diethyl ether (4 × 40 $cm^3$) and its pH was raised to 14 (KOH pellets); it was then extracted with dichloromethane (5 × 30 $cm^3$). The combined extracts were dried ($K_2CO_3$), filtered, and evaporated to yield a colourless oil (206 mg, 91%); *m/z* ($NH_3$, c.i.) 334 ($M^+ + 2$), 333 ($M^+ + 1$), and 332 ($M^+$); $\delta_H$ 7.25 (2 H, d), 7.16 (2 H, d), 6.86 (1 H, br t, NHCO), 4.39 (2 H, d, $CH_2NH$), 2.87—2.53 (14 H, m, $CH_2N + CH_2Ar$), 2.17 (1 H, m, CH), 2.02 (3 H, s, $CH_2CO$), and 1.85—1.40 (7 H, m, $CH_2C$ + NH); $\delta_C(CDCl_3)$ 170.6(s), 139.6(s), 135.8(s), 129.0(d), 127.7(d), 54.5 (t, $CH_2NHAc$), 48.7(t), 47.1(t), 43.8(t), 38.2(d), 34.6(t), and 23.0(t); $\nu_{max.}$(film) 1 660 (CO) and 1 610 (NH bend) $cm^{-1}$.

3-*Acetamidomethylbenzyl*-1,5,9-*Tris*(*ethoxycarbonylmethyl*)-1,5,9-*triazacyclododecane* (**16**).—To a solution of (**15**) (332 mg, 1 mmol) in dry ethanol (12 $cm^3$) was added caesium carbonate (1.0 g, 3.1 mmol) and ethyl bromoacetate (0.52 g, 3.2 mmol) and the mixture was heated to reflux for 24 h. It was then cooled, filtered, and evaporated under reduced pressure and the residue was redissolved in dichloromethane (20 $cm^3$). This solution was washed with water (3 × 5 $cm^3$), dried ($K_2CO_3$), and evaporated to yield a residue which was purified by chromatography on alumina (eluant 2% MeOH in $CH_2Cl_2$) to give a colourless oil (395 mg, 60%); *m/z* ($NH_3$; c.i.) 592 ($M^+ + 1$) and 591 ($M^+$) (Found: $M^+$, 590.367 482. Calc. for $C_{31}H_{50}N_4O_7$ 590.367 950); $\nu_{max.}$(film) 3 280m (NH), 2 920 (CH), 1 735 (ester CO), 1 660 (amide CO), and 1 610 $cm^{-1}$; $\delta_H(CDCl_3)$ 716 (4 H, m), 5.80 (1 H, br s, NH), 4.39 (2 H, d, $CH_2NH$), 4.13 (6 H, q, $CH_2O$), 3.23 (4 H, s, $CH_2CO$), 3.19 (2 H, s, $CH_2CO$), 2.85—2.53 (8 H, m, $CH_2N$), 2.45—2.23 (7 H, m, $CH_2N + CH + CH_2Ar$), 2.02 (3 H, s, $CH_3CO$), 1.78—1.66 (4 H, m, $CH_2C$), and 1.29—1.23 (6 H + 3 H, t + t, $CH_3$); $\delta_C(CDCl_3)$ 171.8(s), 171.6(s), 140.8(s), 135.2(s), 129.5(d), 127.6(d), 60.3 (t, $CH_2O$), 56.5 (t, $CH_2NHAc$), 56.1 (t, $CH_2CO$), 55.3 (t, $CH_2CO$), 49.9(t), 47.6(t), 43.6(t), 37.9(d), 35.3(t), 23.2(t), 21.9(t), and 20.8(q).

3-*Aminomethylbenzyl*-1,5,9-*tris*(*carboxymethyl*)-1,5,9-*triazacyclododecane* (**17**).—A solution of (**16**) (200 mg) in 6M hydrochloric acid (5 $cm^3$) was heated to reflux for 16 h. Solvent was removed to yield a glassy solid; *m/z* (f.a.b., *m*-nitrobenzyl alcohol) 465 ($M^+ + 1$) and 464 ($M^+$); $\nu_{max.}$(KBr) 3 400—2 800br (NH + OH), 1 740 ($CO_2H$), and 1 605m $cm^{-1}$; $\delta_H(D_2O)$ 7.50 (2 H, d, *J* 7.1), 7.43 (2 H, d), 4.24 (2 H, s, $CH_2CO_3$) 4.12 (2 H, s, $CH_2CO$), 3.93—3.15 (17 H, m), 2.78 (2 H, m), and 2.28 (4 H, m); $\delta_C(D_2O)$ 170.1(s), 137.6(s), 129.8(s), 127.8(d), 126.2(d), 59.1(t), 53.5(t), 53.4(t), 50.9(t), 41.3(t), 35.1(d), 32.1(t), and 18.6(t). This compound was ≥98% homogeneous as deduced by h.p.l.c. (Synchropak, TSK DEAE, aqueous ammonium acetate pH 7 MeCN).

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