An Efficient Route to Symmetrically and Unsymmetrically Substituted Azamacrocyclic Ligands

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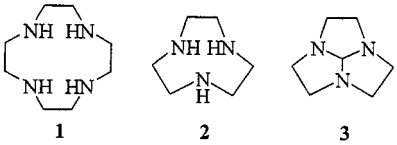
Keywords: Macrocycles / Aza compounds / Polyazacycloalkanes / Nitrogen heterocycles

An extremely efficient cyclisation protocol has been developed for the synthesis of symmetrically (**6**) and unsymmetrically substituted (**7**) derivatives of 1,4,7-triazacyclononane (**2**). The optimised conditions can be successfully applied to the synthesis of larger macrocycles **15a** and **18a**. In contrast, the protocol is not generally applicable with benzylamine, and the cyclic carbamates **16** and **19**, rather than larger azamacrocycles, are formed, indicating that cyclisation in CH_3CN using K_2CO_3 is highly specific to the formation of **7**.

Introduction

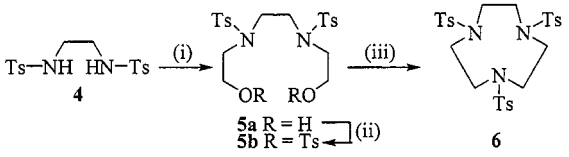
The synthesis and application of *N*-functionalised nitrogen macrocycles continues to be an area of considerable interest.[1,2] This is due to the diverse array of properties that their metal complexes have found; for example, in coordination chemistry,[3] catalysis,[4] and medical applications.[5] Although such ligands are known, their syntheses are not always trivial, as they frequently rely on statistical reactions and the separation of complex reaction mixtures. In addition, the preparation of suitable open-chain starting materials can often be more difficult than the subsequent cyclisation reactions, as has recently been noted.[6] Arguably the greatest success in this diverse area has been achieved in the selective alkylation of tetraazamacrocycles, particularly cyclen (**1**), through judicious control of reaction conditions such as pH.[7,8] Considerably less success has been achieved with the related triazamacrocycles, particularly 1,4,7-triazacyclononane (**2**). Several procedures have been reported based on the statistical alkylation of the free macrocycle,[9,10] dialkylation of the mono-tosylamide[4,11,12] or derivitisation of the orthoamide **3**.[13–15] Although successful, we felt that a more appealing strategy would be to use a cyclisation protocol that would lead directly to the desired substitution pattern in the macrocyclic ring, rather than these reported procedures.



1 **2** **3**

Results and Discussion

By adapting reported procedures that use Cs_2CO_3 as the base in DMF,[16] cyclisation of tosylamide with **5b** produced the desired macrocycle, **6**, in acceptable yield, although it was contaminated with other unidentified side products (Scheme 1). This was not much improved by the use of K_2CO_3 in the same solvent, which gave an isolated yield of the macrocycle of 52%, after flash chromatography. The synthetic route proved to be incredibly efficient, however, when the solvent was changed to acetonitrile, with **6** being formed quantitatively as judged by ^1H NMR spectroscopy. Simple filtration followed by crystallisation from ethanol led to analytically pure **6** in 97% yield. The advantages of this protocol lie in the clean reaction and the ease of workup when acetonitrile is used rather than DMF. This appears to be one of the most efficient methods that has been reported for the synthesis of **6** with an overall yield of 80% in four steps.



Scheme 1. *Reagents and conditions*: (i) ethylene carbonate, K_2CO_3, DMF, 94%; (ii) TsCl, Et_3N, DMAP(cat), CH_2Cl_2, 88%; (iii) $TsNH_2$, K_2CO_3, CH_3CN, 97%

The analogous reaction using benzylamine was less straightforward (Scheme 2). The attempted displacement and cyclisation of **5b** with benzylamine in DMF gave, in addition to small quantities of the desired unsymmetrically substituted macrocycle **7a**, a number of other identifiable materials, **5a** and **8**, **9a**, **10** and **11**, in varying quantities. These materials were always isolated no matter what efforts were made to dry the solvent.[17] The formation of all of these materials can be readily rationalised as there is precedent for the formation of analogous species; however, we are not aware of any reports of them being formed in such significant quantities under such standard reaction conditions for the formation of azamacrocycles. We have been unable to prevent hydrolysis reactions occurring under these reaction conditions and, as a consequence, **5a** is always formed. The formation of enamines **8** and **9a** presumably

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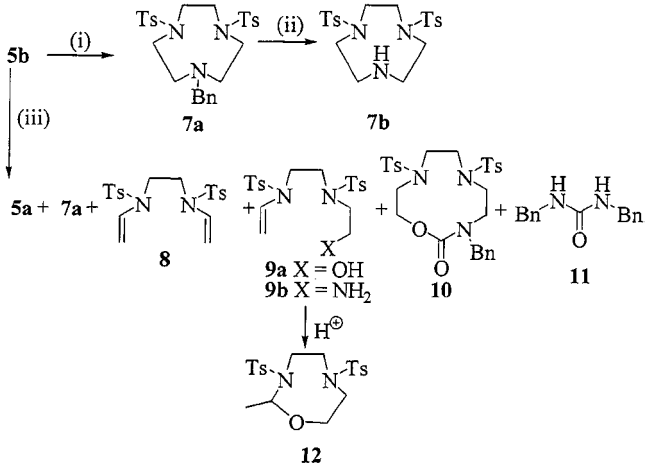
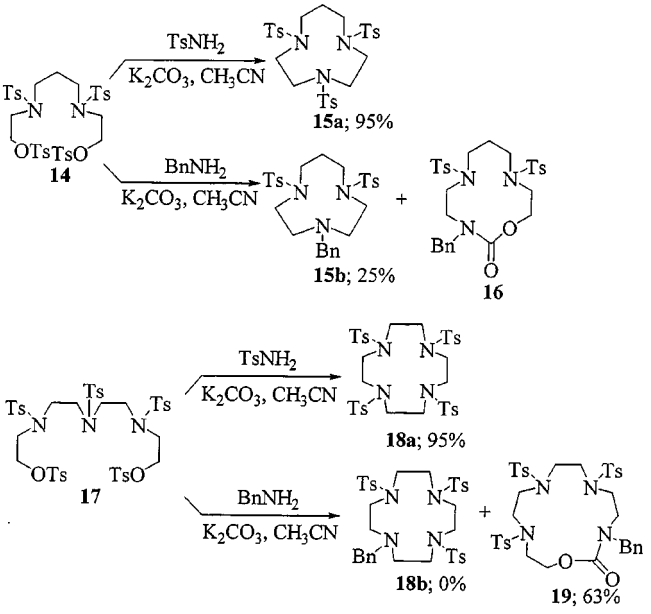


Scheme 2. *Reagents and conditions*: (i) $BnNH_2$, K_2CO_3, CH_3CN, 70%; (ii) Pd/C, H_2, AcOH, 96%; (iii) $BnNH_2$, M_2CO_3 (M = K or Cs), DMF

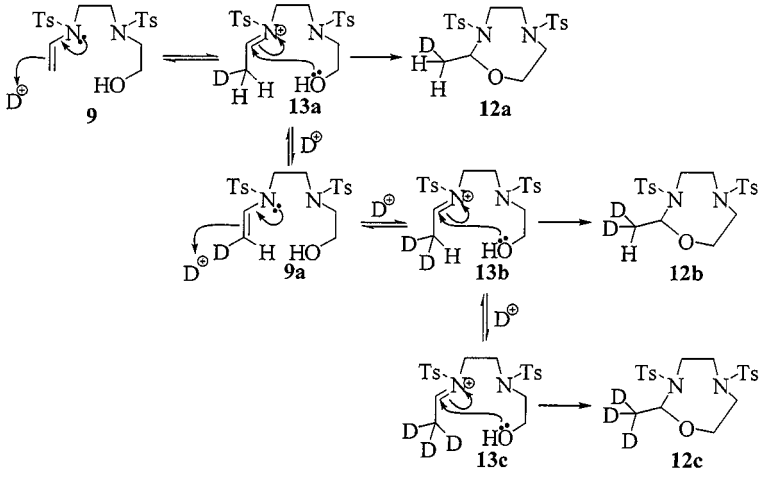
results from competitive elimination and hydrolysis reactions of **5b**,[18] and the formation of species like **10** and **11** by the known reaction of amine nucleophiles with carbonate.[19−22] Similarly, when K_2CO_3 was used in DMF the same materials could be identified. We are confident that the structure is **9a** rather than the similar amine **9b**,[23] confirmation of which came from the intramolecular cyclisation of **9a** to hemiaminal **12**. We were keen to further substantiate our proposal that the cyclisation reaction proceeds via a mechanism involving general acid catalysis. Isotopic studies into the intramolecular cyclisation of enamine **9a** in the presence of D^+ did lend support to our previous proposal that the cyclisation reaction proceeds via the iminium ion **13a**, as shown in Scheme 3. The quadruplet of the C*H*CH_3 for hemiaminal **12** in the ^{1}H NMR spectrum rapidly became extremely complex on addition of D^+, suggesting that a number of species were formed. Multiple incorporation of deuterium in **12a−c** was confirmed by high resolution mass spectrometry, and this presumably results from the reversible addition of D^+ to enamine **9a** prior to the cyclisation step as shown.

Following the effectiveness of the combination of acetonitrile and K_2CO_3 for the formation of **6** we investigated whether a similarly favourable improvement for the synthesis of **7a** might be observed. To our delight a ^{1}H NMR spectrum of the crude reaction mixture indicated that **7a** had been produced exclusively and could be readily purified by crystallisation from ethanol in 70% yield. The benzyl-protected amine in **7a** was readily deprotected under standard conditions[6,24] to yield the required unsymmetrically substituted derivative **7b** in high yield. Solvent purity appears to be the key to this reaction; no sign of any of the previous unwanted side-products **5a** or **8−11** were observed with freshly distilled dry acetonitrile.

We were interested to see whether this route could be extended to larger macrocyclic rings and investigated the synthesis of other N_3 and N_4 azamacrocycles using these optimised conditions (Scheme 4). The tosylamides **14**[25]



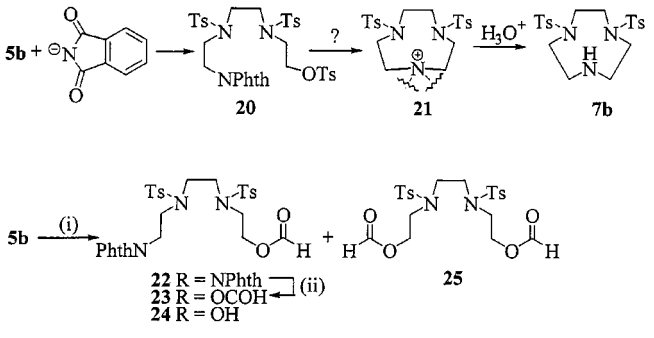
Scheme 4. Investigations into the synthesis of larger N_3- and N_4-azamacrocycles



Scheme 3. Proposed mechanism to account for the multiple incorporation of deuterium during the cyclisation of **9a** to **12**

and **17**[26] were prepared as reported and then reacted with tosylamide or benzylamine. Cyclisation reactions using tosylamide proved to be incredibly efficient for both the 10-membered N_3-macrocycle **15a**[27] and the cyclen derivative **18a**,[28] which were both isolated in 95% yield. Unfortunately, when the analogous reactions were investigated with benzylamine the results were less impressive. For the reaction with **14** the macrocycle **15b**[29] could be isolated by column chromatography in low yield. In addition, other inseparable side products were present, one of which we believe to be the carbamate **16** (HRMS gives M + H^+ 586.2063, $C_{29}H_{36}N_3O_6S_2^+$ requires 586.2046). For the analogous reaction with **17**, none of the desired N_4-macrocycle **18b**[30] could be obtained. However, carbamate **19** was isolated in 63% yield. It seems clear from these results that the cyclisation protocol developed for benzylamine is specific to the synthesis of the unsymmetrically substituted nine-membered macrocycle **7a**.

In view of the adventitious hydrolysis reactions that persistently occurred in DMF, despite extensive efforts to prevent them, we wondered whether it might be possible to use this to our advantage and develop a direct route to **7b**. We thus investigated whether the phthalimide lone pair in **20** might be sufficiently nucleophilic to undergo the desired cyclisation step; facile hydrolysis would then give **7b** directly (Scheme 5). Potassium phthalimide was thus reacted with **5b** in DMF. The desired reaction did not occur, although we were rather surprised to find that not only was the predictable substitution product **22** produced, but that other unexpected materials (**23** and **25**) were also isolated. The complex reaction mixture was extremely difficult to separate by column chromatography and **23** and **25** were largely inseparable. However, by converting **23** to **24** (and **25** to **5a**) they could be unambiguously identified. Although it is known that formates can be formed from tosylates in DMF, these reports are largely isolated to steroid chemistry.[31] Furthermore we have never observed the formation of formates in any other reactions performed in DMF in the absence of phthalimide. We therefore believe that phthalimide is integral to the formation of the formate, and investigations into its role are currently underway in our laboratories.



Scheme 5. *Reagents and conditions*: (i) KNPhth, DMF; (ii) KOH, MeOH

Conclusion

We have developed an incredibly efficient cyclisation procedure for the synthesis of symmetrically (**6**) and unsymmetrically substituted (**7**) nine-membered azamacrocycles. It appears that the reaction conditions can be readily applied to the preparation of larger macrocyclic rings when tosylamide is used in the ring closing step. However, when benzylamine is used, the reaction proves to be highly sensitive to the size of the macrocyclic ring, with nine-membered rings being highly favoured. When attempts are made to increase the ring size by even a single CH_2 unit, the yield of the desired macrocycle is reduced to 25%.

Experimental Section

General Remarks: All reagents were purchased from either Aldrich or Lancaster and were used without further purification unless otherwise stated. For high yielding and efficient cyclisation reactions it is essential that both DMF and acetonitrile are dry and freshly distilled. DMF was refluxed overnight with triphenylchlorosilane in an atmosphere of nitrogen and then distilled from 4 Å molecular sieves under reduced pressure. CH_3CN was refluxed overnight with CaH_2 in an atmosphere of nitrogen and then distilled from CaH_2. Benzylamine was dried over KOH pellets prior to use. Nitrogen for inert atmosphere use was purified by passing it through anhydrous manganese(II) oxide, 3 Å molecular sieves and highly reduced chromium adsorbed onto a silica support. Thin layer chromatography (TLC) was performed on either silica gel 60 F_{254} plates (Merck) or neutral aluminium oxide 60 F_{254}150 plates (Merck). Flash chromatography was performed on either silica gel 60 F_{254}, 230−400 mesh (Merck) or neutral aluminium oxide 60 F_{254} (Merck). Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were obtained using a Carlo Erba 1106 elemental analyser. ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions on a JEOL JNM-EX spectrometer at 270 MHz and at 67.9 MHz respectively, unless otherwise stated, and were referenced to residual $CHCl_3$ as the internal standard. *J* values are given in Hertz. IR spectra were recorded on a Perkin−Elmer 1720X FT-IR spectrometer with a solid state ATR attachment. UV spectra were recorded on a Hewlett−Packard 8453 diode array UV/Vis spectrophotometer. Mass spectra were recorded on a VG Instruments ZAB-SE using xenon gas at 8 kV in a matrix of 3-nitrobenzyl alcohol (MNBA) and sodium iodide (FAB) or on a V.G. BIO-Q instrument (CI, NH_3).

Tosylamide **4** was prepared as previously reported.[27] The macrocyclic precursors **5**,[29] **14**[25] and **17**[26] have previously been reported although the procedure described herein is considerably more efficient, particularly for **5**. These were prepared in an identical manner that is typified by the preparation of **5a** and **5b**. Compounds **6**,[27] **15a**,[27] **15b**,[6] **18a**[27] and **18b**[30] were checked for their integrity by comparison with the data which have previously been reported. Analytical data are presented for any compound for which incomplete characterization was originally reported.

3,6-Di(tosyl)-3,6-diazaoctane-1,8-diol (5a): A solution of **4** (40.00 g, 108.6 mmol), ethylene carbonate (38.24 g, 434.2 mmol) and potassium carbonate (33.01 g, 238.8 mmol) in DMF (220 cm^3) was heated at reflux overnight. After cooling to room temperature, the solvent was evaporated under reduced pressure and the yellow solid

obtained triturated with distilled water (200 cm^3). The white powder that formed was separated by filtration and recrystallised from boiling ethanol to yield **5a** as white crystals (46.6 g, 94%). m.p. 153−155 °C. ^1H NMR: δ = 2.42 (s, 6 H, Ar-CH_3), 2.94 (br. s, 2 H, O*H*), 3.23 (t, *J* = 5.0 Hz, 4 H, TsN-CH_2-CH_2-OH), 3.39 (s, 4 H, TsN-CH_2-CH_2-NTs), 3.80 (t, *J* = 5.0 Hz, 4 H, CH_2-OH), 7.30 (d, *J* = 8.5 Hz, 4 H, CH_3CC-*H*), 7.70 (d, *J* = 8.5 Hz, 4 H, SO_2CC-*H*). − ^{13}C NMR: δ = 21.5 (2 × s), 50.3 (2 × d), 53.1 (2 × d), 61.0 (2 × d), 127.3 (4 × t), 129.8 (4 × t), 134.9 (2 × q), 143.8 (2 × q). − IR: $\tilde{\nu}_{max}$ = 3345 (OH), 1326 (SO_2), 1146 (SO_2) cm^{-1}. − MS (FAB): *m*/*z* (%) = 589 (26) [M + Cs^+], 479 (80) [M + Na^+], 457 (80) [M + H^+], 439 (10) [M^+ − OH], 286 (100). − HRMS: calcd. for $C_{20}H_{29}N_2O_6S_2$ 457.1467; found 457.1481 [M + H^+]. − $C_{20}H_{28}N_2O_6S_2$ (456.58): calcd. C 52.6, H 6.2, N 6.1; found C 52.8, H 6.3, N 6.3.

3,6-Di(tosyl)-3,6-diazaoctane-1,8-di(toluene-4-sulfonate) (5b): A solution of **5a** (38.68 g, 84.71 mmol), *p*-toluenesulfonyl chloride (35.53 g, 186.37 mmol), triethylamine (28.40 mL, 203.31 mmol) and DMAP (103 mg, 0.85 mmol) in CH_2Cl_2 (1000 cm^3) was stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure and the yellow solid obtained triturated with a 10% solution of HCl (400 cm^3). The solid was collected by filtration, washed with distilled water and purified by crystallisation from hot ethanol to give **5b** as white crystals (57.03 g, 88%). m.p. 144−146 °C. − ^1H NMR: δ = 2.44 (s, 12 H, Ar-CH_3), 3.30 (s, 4 H, TsN-CH_2-CH_2-NTs), 3.35 (t, *J* = 5.3 Hz, 4 H, TsN-CH_2-CH_2-OTs), 4.13 (t, *J* = 5.2 Hz, 4 H, TsN-CH_2-CH_2-OTs), 7.33 (d, *J* = 8.3 Hz, 8 H, CH_3CC*H*), 7.71 (d, *J* = 8.3 Hz, 4 H, SO_2CC*H*), 7.76 (d, *J* = 8.3 Hz, 4 H, SO_2CC*H*). − ^{13}C NMR: δ = 21.5 (2 × s), 21.6 (2 × s), 49.4 (2 × d), 49.8 (2 × d), 69.0 (2 × d), 127.4 (4 × t), 128.0 (4 × t), 130.0 (8 × t), 132.3 (2 × q), 134.9 (2 × q), 144.0 (2 × q), 145.2 (2 × q). − IR: $\tilde{\nu}_{max}$ = 1355 (OSO_2), 1326 (NSO_2), 1173 (OSO_2), 1149 (NSO_2) cm^{-1}. − MS (FAB): *m*/*z* (%) = 897 (100) [M + Cs^+], 787 (28) [M + Na^+], 765 (34) [M + H^+], 593 (53) [M^+ − OTs]. − HRMS: calcd. for $C_{34}H_{41}N_2O_{10}S_2$ 765.1644; found 765.1674 [M + H^+]. − $C_{34}H_{40}N_2O_{10}S_4$ (764.95): calcd. C 53.4, H 5.3, N 3.7; found C 53.4, H 5.6, N 3.1.

1,4,7-Tri(tosyl)-1,4,7-triazacyclononane (6): A solution of **5b** (1.00 g, 1.30 mmol), tosylamide (0.25 g, 1.43 mmol) and potassium carbonate (396 mg, 2.87 mmol) in dry acetonitrile (15 cm^3) was stirred at reflux under an atmosphere of nitrogen for six days. After cooling to room temperature, the inorganic salts were removed by filtration and the filtrate evaporated under reduced pressure to leave a white powder. This was purified by crystallisation from hot ethanol to give **6** as white crystals (750 mg, 97%).

1-Benzyl-4,7-di(tosyl)-1,4,7-triazacyclononane (7a): A solution of **5b** (1.00 g, 1.30 mmol), benzylamine (157 μL, 1.43 mmol) and potassium carbonate (396 mg, 2.87 mmol) in dry acetonitrile (15 cm^3) was stirred at reflux under an atmosphere of nitrogen for six days. After cooling to room temperature, the inorganic salts were removed by filtration and the filtrate evaporated under reduced pressure to leave a white powder. This was purified by crystallisation from hot ethanol to give **7a** as white crystals (480 mg, 70%). m.p. 149−151 °C. − ^1H NMR: δ = 2.36 (s, 6 H, ArCH_3), 3.09 (br. m, 4 H, TsNCH_2CH_2NBn), 3.20 (br. m, 4 H, TsNCH_2CH_2NBn), 3.42 (s, 4 H, TsNCH_2CH_2NTs), 3.71 (s, 2 H, NCH_2Ph), 7.16−7.31 (m, 9 H, Ar-*H*), 7.59 (d, *J* = 8.3 Hz, 4 H, SO_2CC*H*). − ^{13}C NMR δ = 21.5 (2 × s), 51.5 (2 × d), 52.4 (2 × d), 54.6 (2 × d), 62.0 (d), 127.1 (5 × t), 128.3 (2 × t), 129.1 (2 × t), 129.7 (4 × t), 135.3 (2 × q), 139.5 (q), 143.4 (2 × q). − UV/Vis (CH_2Cl_2): λ_{max} (ε) = 232 nm (24800). − IR: $\tilde{\nu}_{max}$ = 1339 (SO_2), 1153 (SO_2) cm^{-1}. − MS (FAB): *m*/*z* (%) = 550 (11) [M + Na^+], 528 (62) [M + H^+], 372 (74) [M^+ − Ts], 216 (100). − HRMS: calcd. for $C_{27}H_{34}N_3O_4S_2$ 528.1991; found 528.1982 [M + H^+]. −$C_{27}H_{33}N_3O_4S_2$ (527.70): calcd. C 61.4, H 6.3, N 7.9, S 12.1; found C 61.1, H 6.4, N 7.7, S 11.9.

1,4-Di(tosyl)-1,4,7-triazacyclononane (7b): Pd/C (41 mg, 0.038 mmol) was added to a solution of **7a** (101 mg, 0.19 mmol) in glacial acetic acid (5 cm^3) and the atmosphere saturated with hydrogen. The mixture was stirred at room temperature overnight. The reaction mixture was filtered through a Celite pad which was then washed with methanol (5 cm^3) and ethyl acetate (5 cm^3). The filtrate was concentrated under reduced pressure and the yellow solid obtained was dissolved in $CHCl_3$ (10 cm^3) and stirred vigorously with a 10% solution of NaOH (10 cm^3). After 1 hour the two layers were separated and the aqueous layer extracted with $CHCl_3$ (3 × 5 cm^3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give **7b** (80 mg, 96%) as a white solid whose analytical data were consistent with the reported data.[32]

Alternative Procedure for the Synthesis of 7a: A solution of **5b** (1.00 g, 1.30 mmol), benzylamine (157 μL, 1.43 mmol) and cesium carbonate (940 mg, 2.86 mmol) in dry DMF (15 cm^3) was stirred at reflux under an atmosphere of nitrogen for six days. After cooling to room temperature, the inorganic salts were removed by filtration and the filtrate evaporated under reduced pressure to leave a yellow solid which was purified by column chromatography on silica gel [petroleum ether (40:60)/ethyl acetate, 3:1] to give **7a** (20 mg, 3%) as a white solid. In addition to **7a** the following compounds could also be isolated: **5a** (160 mg, 28%), **8** (20 mg, 2%), **9a** (60 mg, 11%), **10** (200 mg, 27%), **11** (traces)[33,34] and **12** (90 mg, 15%).

3,6-Di(tosyl)-3,6-diaza-1,7-octadiene (8): The dielimination product **8** could also be prepared directly: Potassium *tert*-butoxide (322 mg, 2.87 mmol) was added to a solution of **5b** (1.00 g, 1.31 mmol) in DMF (20 cm^3) and the resultant mixture was stirred at 100 °C under an atmosphere of nitrogen for 20 hours. After cooling to room temperature, the solvent was evaporated. The yellow solid obtained was dissolved in CH_2Cl_2 (20 cm^3) and washed with a 10% solution of HCl (20 cm^3). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic layers were dried over $MgSO_4$ and concentrated. The solid obtained was recrystallised from ethyl acetate to give **8** as white crystals (510 mg, 93%). m.p. 184−186 °C. − ^1H NMR: δ = 2.42 (s, 6 H, ArCH_3), 3.51 (s, 4 H, TsNCH_2), 4.40 (dd, *J* = 9.3, 1.8 Hz, 2 H, TsN-CH=CH_{cis}), 4.58 (dd, *J* = 15.7, 1.8 Hz, 2 H, TsN-CH=CH_{trans}), 6.88 (dd, *J* = 15.7, 9.3 Hz, 2 H, TsN-C*H*=C), 7.30 (d, *J* = 8.3 Hz, 4 H, CH_3CC*H*), 7.64 (d, *J* = 8.3 Hz, 4 H, SO_2CC*H*). − ^{13}C NMR: δ = 21.5 (2 × s), 41.4 (2 × d), 92.7 (2 × d), 126.8 (4 × t), 129.9 (4 × t), 131.6 (2 × t), 135.5 (2 × q), 144.1 (2 × q). − IR: $\tilde{\nu}_{max}$ = 1624 (C=C), 1352 (SO_2), 1152 (SO_2) cm^{-1}. − MS (FAB): *m*/*z* (%) = 443 (10) [M + Na^+], 421 (90) [M + H^+], 265 (100) [M^+ − Ts]. − HRMS calcd. for $C_{20}H_{25}N_2O_4S_2$ 421.1243; found 421.1256 [M + H^+]. − $C_{20}H_{24}N_2O_4S_2$ (420.55): calcd. C 57.1, H 5.8, N 6.7; found C 57.8, H 6.0, N 6.7.

3,6-Di(tosyl)-3,6-diaza-8-octen-1-ol (9): ^1H NMR: δ = 2.43 (s, 6 H, ArCH_3), 3.12−3.40 (m, 4 H, TsNCH_2CH_2NTs), 3.52−3.67 (m, 2 H, TsNC$H_2$$CH_2$OH), 3.79 (t, *J* = 5.1 Hz, 2 H, CH_2OH), 4.39 (dd, *J* = 9.3, 1.8 Hz, 1 H, TsNCH=CH_{cis}), 4.58 (dd, *J* = 15.7, 1.8 Hz, 1 H, TsNCH=CH_{trans}), 6.87 (dd, *J* = 15.7, 9.3 Hz, 1 H, TsNC*H*=CH_2), 7.26−7.42 (m, 4 H, Ar-*H*), 7.51−7.79 (m, 4 H, Ar-*H*). −^{13}C NMR: δ = 21.6 (2 × s), 44.4 (d), 47.6 (d), 53.0 (d), 61.3 (d), 92.3 (d), 126.9 (2 × t), 127.3 (2 × t), 129.9 (2 × t), 130.0 (2 × t), 131.8 (t), 135.1 (q), 135.4 (q), 143.9 (q), 144.2 (q). − IR: $\tilde{\nu}_{max}$ = 3317

(OH), 1623 (C=C), 1334 (SO_2), 1153 (SO_2) cm^{-1}. − MS (FAB): *m/z* (%) = 461 (100) [M + Na^+], 439 (47) [M + H^+]. − HRMS: calcd. for $C_{20}H_{26}N_2NaO_5S_2$ 461.1181; found 461.1169 [M + Na^+].

3-Benzyl-6,9-di(tosyl)-1-oxa-3,6,9-triazacycloundecan-2-one (10): M.p. 117−118 °C. − ^{1}H NMR: δ = 2.45 (s, 6 H, ArC*H*$_3$), 2.98−3.22 (s, 2 H, BnNC*H*$_2$), 3.27−3.61 (m, 8 H, C*H*$_2$NTs), 4.30−4.48 (m, 2 H, C*H*$_2$OCO), 4.56 (br. s, 2 H, NC*H*$_2$Ph), 7.30−7.52 (m, 9 H, Ar-*H*), 7.66−7.73 (m, 4 H, Ar-*H*). − ^{13}C NMR: δ = 21.5 (2 × s), 42.6 (d), 48.0 (d), 49.0 (d), 49.9 (d), 51.1 (d), 53.2 (d), 65.7 (d), 127.1 (2 × t), 127.5 (2 × t), 127.6 (2 × t), 128.0 (2 × t), 128.7 (2 × t), 129.9 (t), 129.9 (2 × t), 133.7 (q), 135.1 (q), 136.8 (q), 143.8 (q), 143.9 (q), 155.6 (q). − IR: $\tilde{\nu}_{max}$ = 1698 (C=O), 1333 (SO_2), 1155 (SO_2) cm^{-1}. − MS (FAB): *m/z* (%) = 594 (71) [M + Na^+], 572 (100) [M + H^+], 416 (59) [M^+ − Ts]. − HRMS: calcd. for $C_{28}H_{34}N_3O_6S_2$ 572.1889; found 572.1869 [M + H^+].

2-Methyl-3,6-di(tosyl)-1-oxa-3,6-diazacyclooctane (12): M.p. 124−127 °C. −^{1}H NMR: δ = 1.01 (d, *J* = 5.8 Hz, 3 H, CHC*H*$_3$), 2.42 (s, 6 H, ArC*H*$_3$), 3.14−3.50 (m, 4 H, C*H*$_2$), 3.56−3.80 (m, 3 H), 3.87−4.06 (m, 1 H), 5.26 (q, *J* = 5.8 Hz, 1 H, C*H*CH$_3$), 7.30 (d, *J* = 7.9 Hz, 4 H, CH$_3$CC*H*), 7.68 (d, *J* = 8.1 Hz, 4 H, SO$_2$CC*H*). − ^{13}C NMR: δ = 18.6 (s), 21.5 (2 × s), 43.4 (d), 49.0 (d), 49.2 (d), 67.2 (d), 84.7 (t), 126.8 (2 × t), 127.0 (2 × t), 129.7 (2 × t), 129.8 (2 × t), 136.3 (q), 137.3 (q), 143.3 (q), 143.7 (q). − IR: $\tilde{\nu}_{max}$ = 1318 (SO_2), 1153 (SO_2) cm^{-1}. − MS (FAB): *m/z* (%) = 461 (15) [M + Na^+], 439 (41), [M + H^+], 283 (14) [M^+ − Ts], 241 (100). − HRMS: (FAB) calcd. for $C_{20}H_{26}N_2O_5S_2Cs$ 571.0337; found 571.0304 [M + Cs^+]; (CI) calcd. for $C_{20}H_{27}N_2O_5S_2$ 439.1361; found 439.1350 [M + H^+].

Deuterium Labelling Study: [D_4]acetic acid (0.18 cm^3 of a 0.13 M solution in $CDCl_3$) was added to a solution of **9a** (10 mg, 23 μmol) in $CDCl_3$ (0.5 cm^3) and the reaction mixture monitored by NMR intermittently for a period of several hours. The solvent was evaporated and the resultant oil analysed by mass spectrometry.− MS (FAB): *m/z* (%) = 572 (100), [M + Cs^+], 461 (19), [M + Na^+]. − HRMS: *m/z* (FAB): **12a**: calcd. for $C_{20}H_{25}DN_2O_5S_2Cs$ 572.0400; found 572.0374 [M + Cs^+]. **12b**: calcd. for $C_{20}H_{24}D_2N_2O_5S_2Cs$ 573.0463; found 573.0500 [M + Cs^+]. **12c**: calcd. for $C_{20}H_{23}D_3N_2O_5S_2Cs$ 574.0526; found 574.0514 [M + Cs^+].

3-Benzyl-6,9,12-tri(tosyl)-1-oxa-3,6,9,12-tetrazacyclotetradecan-2-one (19): Tosylamide **14** (600 mg, 6.2 × 10^{-4} mol) was reacted with benzylamine (75 μL, 6.9 × 10^{-4} mol) under identical conditions to those described for **5a** (vide infra). The crude reaction mixture was purified by column chromatography on silica gel [ethyl acetate/petroleum ether (40:60), 1:1]. The major fractions containing **19** were combined and the solvents evaporated. The solid which resulted was purified by recrystallisation from ethanol giving **19** as a white solid (300 mg, 63%). m.p. 105−106 °C. −^{1}H NMR: δ = 2.37 (s, 3 H, ArC*H*$_3$), 2.38 (s, 3 H, ArC*H*$_3$), 2.40 (s, 3 H, ArC*H*$_3$), 3.05−3.51 (m, 14 H, NC*H*$_2$), 4.28−4.30 (m, 2 H, OC*H*$_2$), 4.47 (s, 2 H, NC*H*$_2$Ph), 7.20−7.45 (m, 11 H, Ar-*H*), 7.52−7.86 (m, 6 H, Ar-*H*). − ^{13}C NMR (250 MHz): δ = 21.4 (3 × s), 45.4 (d), 47.7 (d), 48.5 (d), 49.8 (3 × d), 50.6 (d), 51.3 (d), 65.2 (d), 127.2 (3 × t), 127.4 (3 × t), 127.6 (2 × t), 128.2 (t), 128.7 (3 × t), 129.8 (5 × t), 134.5 (q), 135.3 (q), 137.0 (q), 143.7 (2 × q), 143.9 (2 × q), 155.7 (q). − IR: $\tilde{\nu}_{max}$ = 1698 (CO), 1337 (SO_2), 1152 (SO_2) cm^{-1}. − MS (FAB): *m/z* (%) = 791 (100) [M + Na^+], 769 (26) [M + H^+]. − HRMS: calcd. for $C_{37}H_{45}N_4O_8S_3$ 769.2400; found 769.2423 [M + H^+].

Reaction of Potassium Phthalimide with 5b: Potassium phthalimide (266 mg, 1.43 mmol) was added portionwise within 3 hours to a boiling solution of **5b** (1.00 g, 1.30 mmol) in DMF (150 cm^3) under nitrogen. The mixture was stirred at reflux for 3 days and, after cooling to room temperature, the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (50 cm^3) and washed with a 10% solution of hydrochloric acid (50 cm^3). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 cm^3) and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography on silica gel [petroleum ether (40:60)/ethyl acetate, 3:2] to yield **22** (130 mg, 14%), **23** (160 mg, 23%), **25** (20 mg, 5%), and unchanged **5b** (300 mg, 30%). Amide **23** could not be separated from **25** by column chromatography, although early fractions did contain pure **25**. The signals due to **23** could be identified by elimination of signals due to **25** from the spectra of the mixture. Moreover the structural integrity of **23** was further clarified by hydrolysis to produce **24** which was readily separable by column chromatography from **5a** (produced by hydrolysis of **25**).

3,6-Di(tosyl)-3,6-diazaoctane-1,8-diphthalimide (22): M.p. 210−211 °C. −^{1}H NMR: δ = 2.36 (s, 6 H, ArC*H*$_3$), 3.43 (t, *J* = 5.5 Hz, 4 H, TsNC*H*$_2$CH$_2$NPhth), 3.61 (s, 4 H, TsNC*H*$_2$C*H*$_2$NTs), 3.94 (t, *J* = 5.5 Hz, 4 H, TsNCH$_2$C*H*$_2$NPhth), 7.25 (d, *J* = 8.9 Hz, 4 H, Ar-*H*), 7.68−7.95 (m, 12 H, Ar-*H*). − ^{13}C NMR: δ = 21.5 (2 × s), 36.7 (2 × d), 48.2 (2 × d), 49.3 (2 × d), 123.3 (4 × t), 127.4 (4 × t), 129.8 (2 × q, 4 × t), 132.0 (2 × q), 133.9 (4 × t), 135.2 (2 × q), 143.5 (2 × q), 168.2 (4 × q). − IR: $\tilde{\nu}_{max}$ = 1710 (CO), 1330 (SO_2), 1146 (SO_2) cm^{-1}. − MS (FAB): *m/z* (%) = 737 (42) [M + Na^+], 715 (52) [M + H^+], 307 (100). − HRMS: calcd. for $C_{36}H_{35}N_4O_8S_2$ 715.1896; found 715.1906 [M + H^+].

3,6-Di(tosyl)-3,6-diazaoctane-1,8-diformate (25): M.p. 151−153 °C. −^{1}H NMR: δ = 2.44 (s, 6 H, ArC*H*$_3$), 3.39 (s, 4 H, TsNC*H*$_2$C*H*$_2$NTs), 3.43 (t, *J* = 5.4 Hz, 4 H, TsNC*H*$_2$CH$_2$OCHO), 4.33 (t, *J* = 5.4 Hz, 4 H, C*H*$_2$OCHO), 7.32 (d, *J* = 8.4 Hz, 4 H, CH$_3$CC*H*), 7.70 (d, *J* = 8.4 Hz, 4 H, SO$_2$CC*H*), 8.02 (s, 2 H, *H*COO). − ^{13}C NMR: δ = 21.5 (2 × s), 48.8 (2 × d), 49.6 (2 × d), 62.1 (2 × d), 127.2 (4 × t), 129.9 (4 × t), 135.3 (2 × q), 144.0 (2 × q), 160.6 (2 × t). − IR: $\tilde{\nu}_{max}$ = 1715 (CO), 1340 (SO_2), 1149 (SO_2) cm^{-1}. − MS (FAB): *m/z* (%) = 535 (47) [M + Na^+], 513 (57) [M + H^+], 256 (100) [M^{2+}]. − HRMS: calcd. for $C_{22}H_{29}N_2O_8S_2$ 513.1365; found 513.1345 [M + H^+].

3,6-Di(tosyl)-3,6-diaza-8-phthalimido-1-octyl formate (23): M.p. 208−210 °C. −^{1}H NMR: δ = 2.32 (s, 3 H, ArC*H*$_3$), 2.44 (s, 3 H, ArC*H*$_3$), 3.25−3.61 (m, 8 H, NTsC*H*$_2$), 3.85 (t, *J* = 5.6 Hz, 2 H, C*H*$_2$NPhth), 4.35 (t, *J* = 5.3 Hz, 2 H, C*H*$_2$OCOH), 7.18 (d, *J* = 8.5 Hz, 2 H, Ar-*H*), 7.36 (d, *J* = 8.1 Hz, 2 H, Ar-*H*), 7.62 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.66−7.92 (m, 6 H, Ar-*H*), 8.05 (s, 1 H, *H*COO). − ^{13}C NMR: δ = 21.6 (2 × s), 21.6 (d), 36.6 (d), 48.0 (d), 48.8 (d), 49.2 (d), 62.2 (d), 123.3 (2 × t), 127.2 (2 × t), 127.4 (2 × t), 129.8 (2 × t), 130.0 (2 × t), 132.0 (2 × q), 134.0 (2 × t), 135.4 (2 × q), 143.7 (q), 143.9 (q), 164.7 (t), 168.2 (2 × q). − IR: $\tilde{\nu}_{max}$ = 1707 (CO), 1335 (SO_2) cm^{-1}. 1150 (SO_2) = MS (FAB): *m/z* (%) = 636 (47) [M + Na^+] 614 (100) [M + H^+], 458 (24) [M^+ − Ts]. − HRMS calcd. for $C_{28}H_{32}N_3O_8S_2$ 614.1631; found 614.1651 [M + H^+].

3,6-Di(tosyl)-3,6-diaza-8-phthalimido-octan-1-ol (24): Solid KOH (16 mg, 0.29 mmol) was added to a solution of **23** (160 mg, 0.26 mmol) in methanol (5 cm^3) and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (10 cm^3) and washed with a 10% solution of HCl (10 cm^3). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure. The solid obtained was

recrystallised from boiling ethanol to give **24** as a white powder (130 mg, 85%). ^{1}H NMR: δ = 2.34 (s, 3 H, ArCH_3), 2.45 (s, 3 H, ArCH_3), 3.30 (t, J = 5.0 Hz, 2 H, TsNCH_2), 3.42 (t, J = 5.7 Hz, 2 H, TsNCH_2), 3.52 (s, 4 H, 2 × TsNCH_2), 3.72−3.90 (m, 4 H, CH_2OH and PhthNCH_2), 7.20 (d, J = 8.1 Hz, 2 H, Ar-H), 7.36 (d, J = 8.1 Hz, 2 H, Ar-H), 7.65 (d, J = 8.3 Hz, 2 H, Ar-H), 7.68−7.84 (m, 6 H, Ar-H). − ^{13}C NMR: δ = 21.6 (2 × s), 36.5 (d), 47.7 (d), 49.3 (d), 50.0 (d), 52.9 (d), 61.8 (d), 123.3 (2 × t), 127.2 (2 × t), 127.4 (2 × t), 129.8 (2 × t), 129.9 (2 × t), 131.9 (2 × q), 134.0 (2 × t), 135.3 (q), 135.4 (q), 143.6 (q), 143.7 (q), 168.2 (2 × q). − IR: $\tilde{\nu}_{max}$ = 3494 (OH), 1711 (CO), 1333 (SO_2), 1142 (SO_2) cm^{-1}. − MS (FAB): m/z (%) = 608 (100) [M + Na$^+$], 586 (70) [M + H$^+$]. − HRMS: calcd. for $C_{28}H_{32}N_3O_7S_2$ 586.1682; found 586.1685 [M + H$^+$].

Acknowledgments

We are grateful to The Nuffield Foundation, The University of London Central Research Fund and The Royal Society for financial support. We are also grateful to Dr K. Welham and Mr. M. Cocksedge of the School of Pharmacy, University of London for access to the University of London Inter Collegiate Research Service (ULIRS) mass spectrometry facility. We are grateful to Queen Mary, University of London, for a studentship (SP).

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Receive June 5, 2001
[O01268]