# *N*-Benzyloxycarbonylaziridine in the Syntheses of 2-Aminoethyl Armed Lariats and Selectively *N*-Protected Polyazacrown Ethers

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The 15- and 18-membered mono- and bi-bracchial *N*-aminoethylene armed lariats **6**, **7** and **8** have been synthesized by alkylations of parent azacrowns using *N*-benzyloxycarbonylaziridine **2** and subsequent removal of Z-protecting groups by catalytic hydrogenolysis. Extraction experiments with $M^+$-picrates ($M^+ = Li^+$, $Na^+$, $K^+$ and $Cs^+$) showed medium efficacy of **6**, **7** and **8** and only slight selectivity of **6** for $Cs^+$. The syntheses of selectively *N*-protected polyazacrowns 10-benzyl-1,4-dioxa-7,10,13-triazacyclopentadecane **12**, 10,19-dibenzyl-1,4,13,16-tetraoxa-7,10,19,22-tetraazacyclotetracosane **16** and 4,16-dibenzyl-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane **21** exemplify the application of *N*-benzyloxycarbonylaziridine **2** as a suitable building block for preparations of selectively *N*-protected polyaza-macrocycles.

In the recent years a great number of azacrown macrocycles bearing functionalized pendant arms have been synthesized.[1] This type of compound named lariat ethers,[1] bind metal cations more strongly than their parent azamacrocycles by using co-operatively the macro-ring and the pendant arm donors.[2–4] In addition to metal cation binding the lariats with suitably functionalized pendant arms may also bind organic anions. We have recently shown that dipeptide derived lariats having pendant arms with hydrogen bond donor and acceptor sites function as metal cation and amino acid or dipeptide carboxylate common carriers.[5a,b] In connection with these studies we became interested in syntheses of *N*-aminoethylene armed lariats whose primary amino group may serve for the attachment of different lateral binding and recognition sites.

In this paper we report the efficient syntheses of 15- and 18-membered mono- and bi-bracchial *N*-aminoethylene armed lariats by the *N*-alkylation of the parent azacrowns using *N*-benzyloxycarbonylaziridine **2**. The extraction efficiency of such lariats towards $Li^+$, $Na^+$, $K^+$ and $Cs^+$ picrates was tested and compared to that of the unarmed parent azacrowns and their alkyl ether armed analogues. The facile aziridine **2** ring opening by the nucleophilic attack of primary or secondary amine nitrogens gives $PhCH_2OCONHCH_2CH_2NHR$ and $PhCH_2OCONHCH_2CH_2NR_2$ structural fragments, respectively. Such fragments may be very useful in syntheses of polyazacrowns and macrocyclic polyamines. Herein we also present some examples of the preparation of selectively *N*-protected polyazacrowns based on the application of *N*-benzyloxycarbonylaziridine **2** as a building block.

## Results and Discussion

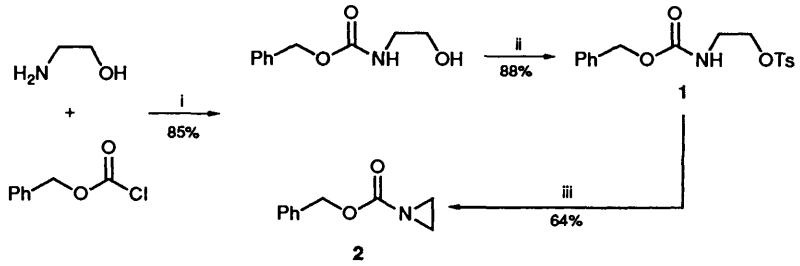
*Syntheses of* N-*Aminoethylene Armed Lariats.*—Several multistep procedures for the preparation of *N*-aminoethylene armed azamacrocycles have been described. All of them start from parent azamacrocycle onto which the 2-aminoethyl arm was attached: (*a*) by Strecker synthesis (HCOH, NaCN, $NaHSO_3$) followed by catalytic hydrogenation of the intermediate *N*-cyanomethyl derivative;[6–8] (*b*) by *N*-alkylation using *N*-bromoethylenephthalimide and subsequent hydrazinolysis;[9] (*c*) by acylation with *N*-tosylglycine, followed by $LiAlH_4$ reduction of the formed amide and removal of tosyl group in the last step;[10] and (*d*) by alkylation using *N*-tosylaziridine and removal of the tosyl group.[11]

The most convenient *N*-tosylaziridine method[11] suffers from the relatively difficult removal of tosyl group in the last step which needs prolonged heating in 32% hydrobromic acid–acetic acid–phenol mixture. Thus, using an *N*-carbamoylaziridine instead *N*-tosylaziridine would be advantageous due to the much easier removal of a carbamoyl protecting group. In this respect the benzyloxycarbonyl group would be especially appropriate since it can be removed in neutral media by catalytic hydrogenolysis, usually in quantitative yield.[12]

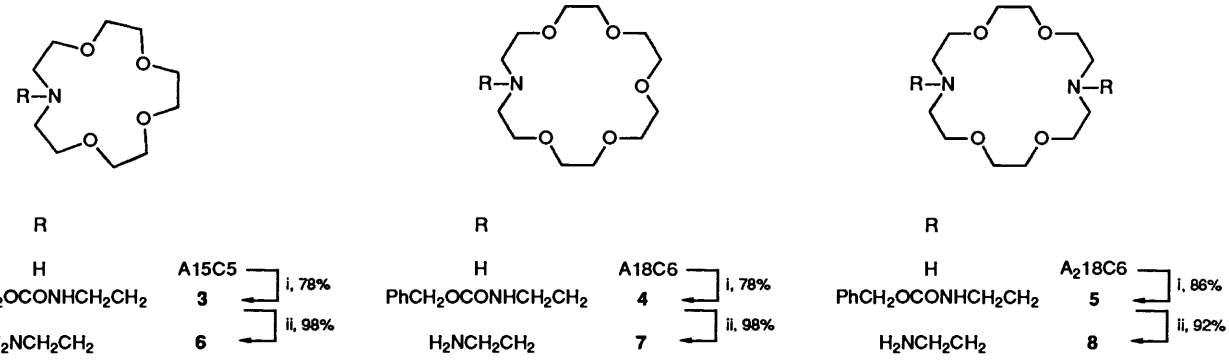
The preparation of *N*-benzyloxycarbonylaziridine **2** is claimed in the patent literature only.[13] The aziridine **2** in the present work was prepared from *N*-Z, *O*-Ts protected ethanolamine derivative **1** and NaH in dry THF (64% yield; Scheme 1).

We have found that aza-15-crown-5 (A15C5),[14] aza-18-crown-6 (A18C6) and 4,13-diaza-18-crown-6 ($A_2$18C6) can be *N*-alkylated in good yield using 50% stoichiometric excess of aziridine **2** (Scheme 2). The *N*-protected lariats **3**, **4** and **5** have been obtained in this way in yields of 78, 65 and 85%, respectively, after purification by flash chromatography ($CH_2Cl_2$–2% MeOH). Hydrogenolytic removal of *N*-protecting groups in the last step gave *N*-(2-aminoethyl) armed lariats **6**, **7** and **8** in quantitative yields.

*Extractions of* $M^+$-*Picrates*[15] *by Lariats* **6**, **7** *and* **8**.—In contrast to lariats bearing alkyl ether pendant arms[1] little is




**Scheme 1** *Reagents and conditions:* i, $NaHCO_3$, 0 °C; ii, TsCl, $Et_3N$–$CH_2Cl_2$, 0 °C; iii, NaH, THF, 45 °C, 15 h




**Scheme 2** *Reagents and conditions:* i, 2, $CH_3CN$–PhMe (1:1), 80 °C, 48 h; ii, $H_2$, 10% Pd/C, MeOH, 3–4 h

**Table 1** Extractions of $M^+$-picrates by *N*-aminoethylene- and *N*-methoxyethylene-armed lariats and their unarmed parent azacrowns

| Compound | $M^+$ extracted (%) | | | |
|---|---|---|---|---|
| | $Li^+$ | $Na^+$ | $K^+$ | $Cs^+$ |
| A15C5[a] | 6.1 | 7.4 | 0.9 | 0.0 |
| A18C6 | 0.0 | 7.7 | 10.5 | 8.4 |
| $A_2$18C6 | 4.9 | 0.0 | 0.5 | 5.4 |
| A15C5-$(CH_2)_2$OMe[b,c] | 3.9 | 8.9 | 3.4 | 5.9 |
| A18C6-$(CH_2)_2$OMe[b,c] | 0.0 | 7.4 | 28.6 | 0.0 |
| $A_2$18C6-$(CH_2)_2$OMe$]_2$[b,c] | 7.5 | 10.4 | 22.8 | 2.7 |
| **6** | 15.7 | 13.7 | 15.2 | 34.3 |
| **7** | 27.3 | 21.3 | 21.9 | 29.3 |
| **8** | 44.7 | 51.0 | 55.0 | 56.9 |
| **5** | 0.0 | 0.0 | 0.0 | 0.0 |

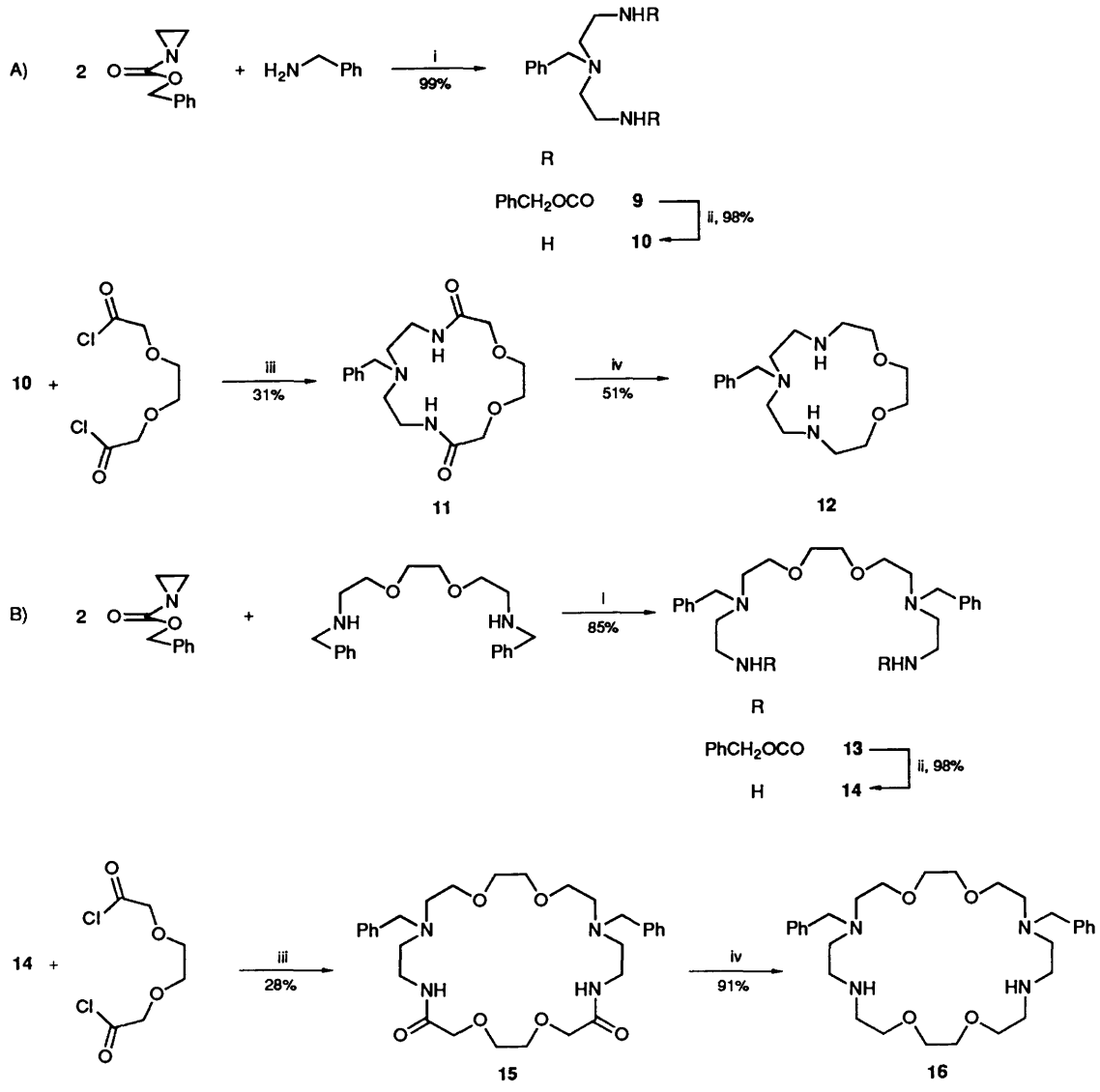
[a] Abbreviations as in ref. 14. [b] Prepared as in ref. 26. [c] Abbreviation denotes the lariat having *N*-pivot methoxyethylene arm.

known about the metal cation binding or extraction properties of the aminoalkyl armed lariats. However, it was reported that *N*,*N*-bis(3-aminopropyl)-4,13-diaza-18-crown-6 extracts $Li^+$, $Na^+$, $K^+$ and $NH_4^+$ picrates from water into a dichloromethane layer with high efficiency;[9] for all examined picrates 100% extraction was measured, thus showing a lack of any selectivity. This intriguing result made it of interest to test the extraction abilities of lariats **6**, **7** and **8** bearing one or two shorter aminoethylene arms attached onto 15- or 18-membered azacrown rings. For comparison purposes the extraction abilities of alkyl ether lariats, *N*-methoxyethylene-A15C5, *N*-methoxyethylene-A18C6 and *N*,*N*′-bis(methoxyethylene)-$A_2$18C6 as well as those of unarmed parent azacrowns, A15C5, A18C6 and $A_2$18C6 have also been determined. The results of the extraction experiments with $Li^+$, $Na^+$, $K^+$ and $Cs^+$-picrates expressed as percentages of the cation extracted from water to chloroform layer are collected in Table 1. Generally, the lariants **6**, **7** and **8** were considerably more efficient extractants than their unarmed parent macrocycles A15C5, A18C6 and $A_2$18C6. Such a result could be expected from the enhanced donor character of the lariat macro-ring tertiary amine nitrogens.[16] However, the lariat **5** which differs from **8** only by having *N*-protected amino groups on the pendant arms completely loses the extraction ability. This result together with the found extraction efficiency order of **8** > **7** > **6** shows the importance of the side arm primary amino donors for the extraction ability of 2-aminoethyl armed lariats. In addition **6**, **7** and **8** were also found to be superior to their alkyl ether analogues $MeO(CH_2)_2$-Al5C5, $MeO(CH_2)_2$-Al8C6 and $[MeO(CH_2)_2]_2$-$A_2$18C6, respectively. This interesting result is somewhat unexpected since it is known that the substitution of an oxygen for nitrogen donor in the crown ring results in the decrease of binding and extraction ability of alkali cations.[17] The explanation of this result is not straightforward. However, it is known that the extraction equilibrium is considered to consist of three constituent equilibria: the distribution of the ligand between the aqueous and organic phase; the complexation of the metal cation in water; and the extraction of the ligand–cation ion pair from water into the organic phase.[15] It is possible that one of the constituent equilibria is more favourable for aminoethylene than for methoxyethylene armed lariats resulting in the increased overall extraction efficiency.

The lariats **6**, **7** and **8** exhibited poor extraction selectivity. Nevertheless, slight selectivity for $Cs^+$ was observed for one armed **6** having the smallest 15-membered ring: $Cs^+/Li^+$ = 2.2; $Cs^+/Na^+$ = 2.5; $Cs^+/K^+$ = 2.3.

*Syntheses of Selectively* N*-Protected Polyazacrowns.*—Synthetic paths leading to the selectively *N*-protected polyazacrowns or polyazamacrocycles are of current interest in the field of supramolecular chemistry allowing preparations of unsymmetrically functionalized receptor molecules.[11,18,19] The most widespread methods for preparations of azacrowns or macrocyclic polyamines are: (*a*) macrocyclizations by reacting acyclic ω,ω′-tosylamines with alkyl sulfates under basic conditions followed by detosylation in the last step; and (*b*) macrocyclizations by reacting acyclic ω,ω′-diamines with ω,ω′-diacid chlorides and subsequent reduction of macrocyclic lactams.[20] Both, the detosylation and lactam reduction, however, are unselective. Thus, in the syntheses of selectively *N*-protected azacrowns the preparations of acyclic precursors containing a mixture of *N*-protecting groups is necessary. In this respect, the combinations of *N*-protecting groups such as tosyl–benzoyl,[21] tosyl–benzyl or tosyl–ethyloxycarbonyl[22] and tosyl–diethoxyphosphoryl[18] have been used. In all of these examples the detosylation under relatively drastic conditions remains as a problem in the last synthetic step.

Herein, we report on the syntheses of the selectively *N*-benzyl-protected azacrowns **12**, **16** and **21** (Schemes 3 and 4). The syntheses are based on preparations of suitable acyclic polyamino precursors **9**, **13** and **18** containing the combination of benzyloxycarbonyl and benzyl *N*-protecting groups. Both protecting groups are known to be easily removed, usually quantitatively, by hydrogenolysis in the presence of Pd/C catalyst.[12] We found however, that the hydrogenolysis of **9**, **13** or **18** performed by bubbling the stream of hydrogen through their MeOH solutions removed benzyloxycarbonyl groups only giving selectively *N*-benzyl protected acyclic polyamines **10**, **14** and **19**, respectively, in quantitative yields. Macrocyclizations of **10**, **14** or **19** by reaction with diglycoloyl or triglycoloyl chloride in high dilution conditions gave macrocyclic di- or tetra-lactams **11**, **15** and **20** in moderate yields. Lactams were reduced either



**Scheme 3** *Reagents and conditions:* i, $CH_3CN$–PhMe (2:1), 80 °C, 3 days; ii, $H_2$, Pd/C, MeOH; iii, high dilution, $Et_3N$, PhMe, 60 °C, 6 days; iv, $LiAlH_4$, THF, 14 h, reflux

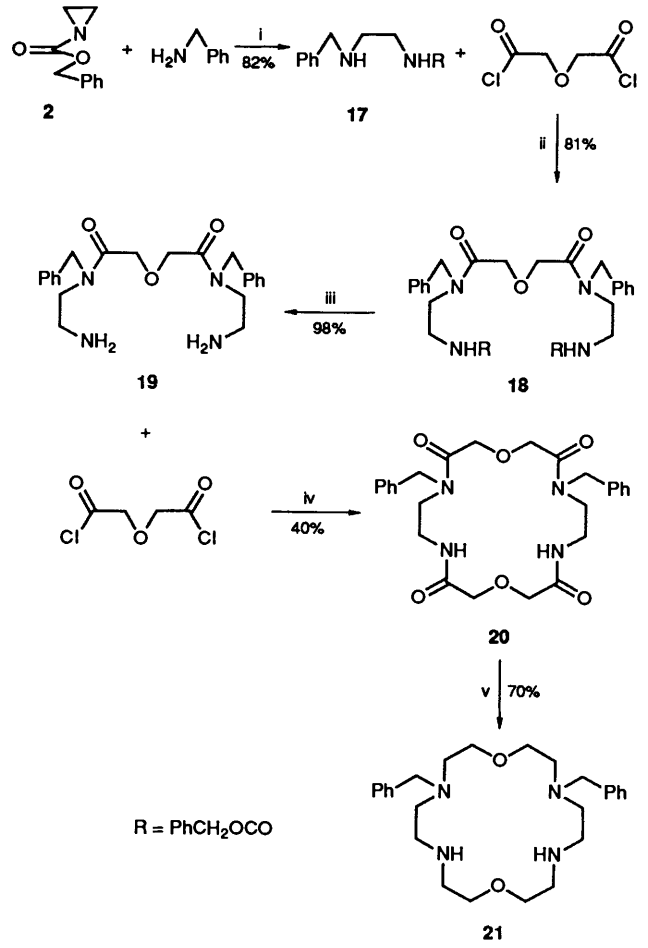
by $LiAlH_4$ or diborane giving tri- **12** and tetra-azamacrocycles **16**, **21** with selectively benzyl protected one or two macro-ring nitrogens.

The synthesis of 24-membered tetraaza-macrocycle **16** (Scheme 3B) started with ω,ω′-dibenzylamino-3,6-dioxaoctane which was prepared in high yield by Gokel's procedure[23] from ω,ω′-dichloro-3-oxapentane and benzylamine. For the synthesis of 18-membered tetraaza-macrocycle **21** by the same synthetic path, ω,ω′-dibenzylamino-3-oxapentane would be needed as the starting compound. However, it cannot be prepared in the same way since the reaction of ω,ω′-dichloro-3-oxapentane with benzylamine would give *N*-benzylmorpholine as the major product.[23] Thus for the synthesis of **21** a different path was used (Scheme 4). First, benzylamine was monoalkylated with aziridine **2** in the molar ratio of 5:1, respectively, giving **17** in 82% yield. Then, two molecules of **17** were bridged by reaction with diglycoloyl chloride giving **18** which was then transformed into **21** by hydrogenolysis, macrocyclization and reduction steps.

## Experimental

M.p.s were determined on Kofler block and are uncorrected. IR spectra were recorded on a Perkin-Elmer 197 spectrophotometer. UV spectra were measured on a Philips PU8700 UV–VIS spectrophotometer. $^1H$ NMR and $^{13}C$ NMR spectra were recorded at 100 and 25.2 MHz, respectively on a JEOL FX 100Q instrument. Tetramethylsilane was used as the internal reference. The mass spectra were recorded on a Shimadzu GCMS-QP 1000 spectrometer. Chromatographic columns were filled with Merck silica gel 60 (70–230 mesh), Kieselgel 60 (230–240 mesh) for flash chromatography or aluminium oxide active, basic. Merck Fertigplatten F-254 were used for TLC.

*N-Benzyloxycarbonylaziridine* **2**.—To a warm (45 °C) suspension of NaH (1.76 g, 36.0 mmol) in THF (50 $cm^3$) a solution of *N*-benzyloxycarbonylethanolamine toluene-*p*-sulfonate **1**[24] (10.7 g, 30.6 mmol) in THF (30 $cm^3$) was added dropwise during 2 h and stirred at the same temperature for additional 20 h. After removal of sodium toluene-*p*-sulfonate and solvent the oily residue was purified by column chromatography on silica gel (90 g, ether–light petroleum, 1:1) to give the oily product **2** (3.5 g, 64%), $R_f$ 0.54 (Found: C, 67.7; H, 6.35; N, 8.0. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.91%); $\nu_{max}$(film)/$cm^{-1}$ 3420 (NH), 3060, 3040, 3010 (aziridine $CH_2$), 1730 (C=O), 1500 (N–C=O), 900, 780 and 700 (Ph); $\delta_H(CDCl_3)$ 2.21 (4 H, s, aziridine $CH_2$), 5.12 (2 H, s, $OCH_2$) and 7.34 (5 H, s, Ph); $\delta_C$ 25.39 (t, aziridine $CH_2$), 67.72 (t, $OCH_2$), 127.71 (d, Ar),




**Scheme 4** *Reagents and conditions:* i, $CH_3CN$, 70 °C, 24 h; ii, PhMe 60 °C, 17 h; iii, $H_2$, 10% Pd/C, MeOH; iii, high dilution, $Et_3N$, PhMe, 60 °C, 6 days; iv, $B_2H_6$, THF, 50 °C, 24 h

127.88 (d, Ar), 128.16 (d, Ar), 135.44 (s, Ar) and 163.14 (s, C=O); *m/z* 177 ($M^+$, 6%), 148 (9), 134 (7), 108 (25), 107 (98), 105 (18), 92 (34), 91 (100), 79 (38), 77 (23), 70 (18), 65 (58), 43 (18), 42 (39) and 41 (12).

*General Procedure for Preparation of* N-*Benzyloxycarbonylaminoethylene Armed Lariats* **3**–**5**.—The parent mono- or diaza-crown (3 mmol) (Scheme 2) and aziridine **2** (50% stoichiometric excess) were dissolved in acetonitrile–toluene (1:1) (30 $cm^3$) and refluxed for 24 h under nitrogen. Removal of solvents under reduced pressure and flash chromatography of the oily residue (2% MeOH in $CH_2Cl_2$) gave 13-benzyloxycarbonylaminoethylene-1,4,7,10-tetraoxa-13-azacyclopentadecane **3** (heavy oil, 78%); $R_f$ 0.24 ($CH_2Cl_2$–MeOH, 9:1) (Found: C, 60.6; H, 8.4; N, 7.1. $C_{20}H_{32}N_2O_6$ requires C, 60.58; H, 8.14; N, 7.07%); $\nu_{max}$(film)/$cm^{-1}$ 3340 (NH), 1740 (C=O), 1520 (N–C=O), 1125 (C–O–C), 935, 740 and 700 (Ph); $\delta_H$($CDCl_3$) 2.68 (6 H, m, $CH_2N$), 3.25 (2 H, m, $CH_2NC$=O), 3.56 (16 H, m, $CH_2O$), 5.08 (2 H, s, $CH_2Ph$), 5.13 (1 H, br s, NH) and 7.33 (5 H, s, Ph); $\delta_C$ 39.10 ($HNCH_2$), 55.19 ($CH_2N$ + 2 $NCH_2$), 66.36 ($PhCH_2$), 69.35, 69.92, 70.14, 70.43 ($OCH_2$), 127.88, 128.10, 128.33, 136.85 (Ar) and 156.66 (C=O); *m/z* 396 ($M^+$, 1%), 276 (3), 236 (13), 232 (100), 144 (5), 100 (7), 91 (15) and 56 (12).

16-Benzyloxycarbonylaminoethylene-1,4,7,10-pentaoxa-16-azacyclooctadecane **4** (heavy oil, 77%); $R_f$ 0.21 ($CH_2Cl_2$–MeOH, 9:1) (Found: C, 60.1; H, 8.0; N, 6.2. $C_{22}H_{36}N_2O_7$ requires C, 59.98; H, 8.24; N, 6.36%); $\nu_{max}$(film)/$cm^{-1}$ 3340 (NH), 1720 (C=O), 1520 (N–C=O), 1115 (C–O–C), 950, 740 and 700 (Ph); $\delta_H$($CDCl_3$) 2.21 (6 H, m, $CH_2N$), 3.14 (2 H, m, $CH_2NC$=O), 3.15 (20 H, m, $CH_2O$), 5.09 (2 H, s, $CH_2Ph$), 5.92 (1 H, br s, NH) and 7.33 (5 H, s, Ph); $\delta_C$ 39.39 ($NHCH_2$), 54.45 ($NHCH_2CH_2N$), 54.74 ($NCH_2$), 66.36 ($PhCH_2$), 69.81, 70.31, 70.60, 70.71, 70.82 ($OCH_2$), 127.93, 128.10, 128.38, 136.96 (Ar) and 156.60 (C=O).

7,16-Bis(benzyloxycarbonylaminoethylene)-1,4,10,13-tetraoxa-7,16-diazacycloacetadecane **5** (heavy oil, 86%); $R_f$ 0.34 ($CH_2Cl_2$–MeOH, 9:1) (Found: C, 62.2; H, 7.8; N, 9.1. $C_{32}H_{48}N_4O_8$ requires C, 62.31; H, 7.85; N, 9.09%); $\nu_{max}$(film)/$cm^{-1}$ 3320, 3240 (NH), 1720 (C=O), 1520 (N–C=O), 1140 (C–O–C), 950, 740 and 700 (Ph); $\delta_H$($CDCl_3$) 2.63 (12 H, m, $CH_2N$), 3.17 (4 H, m, $CH_2NC$=O), 3.51 (16 H, m, $CH_2O$), 5.07 (4 H, s, $CH_2Ph$), 5.92 (2 H, br s, NH) and 7.32 (10 H, s, Ph); $\delta_C$ 39.10 ($NHCH_2$), 54.06 ($NHCH_2CH_2N$), 54.40 ($NCH_2$), 66.14 ($PhCH_2$), 69.52, 70.31 ($OCH_2$), 127.65, 127.82, 128.10, 136.62 (Ar) and 156.26 (C=O).

*General Procedure for Preparation of* N-*Aminoethylene Armed Lariats* **6**–**8**.—Lariat **3**, **4** or **5** (1.3 mmol) was dissolved in dry MeOH (25 $cm^3$), the catalyst 10% Pd/C (10% by weight) added and hydrogenated in Paar apparatus for 4 h. Removal of the catalyst by filtration and evaporation of MeOH gave the chromatographically pure product.

13-Aminoethylene-1,4,7,10-tetraoxa-13-azacyclopentadecane **6** (heavy oil, 98%); $\nu_{max}$(film)/$cm^{-1}$ 3400 ($NH_2$), 1600 (C–N–C), 1120 (C–O–C); $\delta_H$($CDCl_3$) 2.73 (10 H, m, $CH_2N$ and $NH_2$) and 3.64 (16 H, m, $CH_2O$); $\delta_C$ 39.95 ($NH_2CH_2$), 51.30 ($NH_2CH_2CH_2N$), 55.42 ($NCH_2$), 69.00, 69.22, 69.30 and 69.66 ($OCH_2$); *m/z* 262 ($M^+$, 1%), 232 (100), 188 (5), 144 (4), 112 (6), 100 (8) and 56 (15).

16-Aminoethylene-1,4,7,10,13-pentaoxa-16-azacyclooctadecane **7** (heavy oil, 98%); $\nu_{max}$(film)/$cm^{-1}$ 3410 ($NH_2$), 1600 (C–N–C) and 1150 (C–O–C); $\delta_H$($CDCl_3$) 2.75 (8 H, m, $CH_2N$) and 3.76 (22 H, m, $CH_2O$ and $NH_2$); $\delta_C$ 38.77 ($NH_2CH_2$), 54.68 ($NCH_2$), 54.96 ($NH_2CH_2CH_2N$), 69.13, 69.69 and 69.92 ($OCH_2$); *m/z* 306 ($M^+$, 1%), 277 (16), 276 (100), 264 (2), 246 (2), 188 (4), 144 (3), 112 (8), 100 (12), 70 (6) and 56 (17).

7,16-Bis(aminoethylene)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane **8** (92%), m.p. 126–127 °C (lit.,[10] m.p. 127 °C); $\delta_H$($CDCl_3$) 2.73 (16 H, m, $CH_2N$), 3.62 (16 H, m, $CH_2O$) and 3.90 (4 H, br, $NH_2$); $\delta_C$ 38.88 ($NH_2CH_2$), 54.51 ($NCH_2$), 56.91 ($NH_2CH_2CH_2N$), 69.08 and 70.37 ($OCH_2$).

3-*Benzyl*-1,5-*bis*(*benzyloxycarbonylamino*)-3-*azapentane* **9**.—Benzylamine (0.605 g, 5.6 mmol) and aziridine **2** (3.11 g, 16.9 mmol) were dissolved in acetonitrile–toluene (2:1; 60 $cm^3$) and stirred at 80 °C under $N_2$ for 3 days. After removal of solvents under reduced pressure the residue was subjected to column chromatography on silica gel (70 g). First, $CH_2Cl_2$ was used for elution to remove unreacted **2** and then $CH_2Cl_2$ containing MeOH (3%) gave **9** (heavy oil, 2.59 g, 99%); $R_f$ 0.4 ($CH_2Cl_2$–MeOH 49:1) (Found: C, 70.5; H, 6.8; N, 9.0. $C_{27}H_{31}N_3O_4$ requires C, 70.26; H, 6.77; N, 9.11%); $\nu_{max}$(film)/$cm^{-1}$ 3340 (NH), 1710 (C=O), 1520 (NC=O), 740 and 700 (Ph); $\delta_H$($CDCl_3$) 2.51 (4 H, t, *J* 5.2, $CH_2N$), 3.20 (4 H, m, $CH_2NH$), 3.52 (2 H, s, $CH_2Ph$), 5.03 (4 H, s, $OCH_2Ph$), 5.21 (2 H, br, NH), 7.20 (5 H, s, Ph), 7.27 (10 H, s, Ph); $\delta_C$ 38.43 ($CH_2NH$), 53.10 ($NCH_2$), 58.18 ($PhCH_2N$), 66.25 ($OCH_2Ph$), 126.86, 127.68, 128.10, 128.55, 136.45, 138.43 (Ar) and 156.43 (C=O).

3-*Benzyl*-3-*azapentane*-1,5-*diamine* **10**.—A stream of $H_2$ was bubbled slowly into a solution of **9** (2.51 g, 5.44 mmol) in dry MeOH (65 $cm^3$) containing 10% Pd/C (0.375 g). The reaction was stopped after TLC showed the disappearance of **9** ($R_f$ 0.4, $CH_2Cl_2$–MeOH, 49:1, 1.5–2 h). The removal of the catalyst and solvent under reduced pressure gave **10** (1.04 g; 98%), b.p. 156–158 °C/10 mmHg;[22] $\nu_{max}$(film)/$cm^{-1}$ 3280 (NH), 1580 (NHδ) and 1020 (C–N); $\delta_H$($CDCl_3$) 1.73 (4 H, s, $NH_2$), 2.63 (8 H, m, $CH_2N$), 3.58 (2 H, s, $CH_2Ph$), 5.03 (4 H, s, $OCH_2Ph$) and 7.28

(5 H, s, Ph); *m/z* 194 ($M^+ + 1$, 0.5%), 164 (3), 163 (21), 120 (8), 106 (3), 92 (9), 91 (100), 73 (8), 65 (18) and 58 (19); $\delta_C$ 39.67 ($NH_2CH_2$), 57.05 ($NCH_2$), 59.14 ($PhCH_2$), 126.97, 128.27, 128.83 and 139.44 (Ar).

10-*Benzyl*-1,4-*dioxa*-7,10,13-*triazacyclopentadecane*-5,13-*dione* **11**.—A solution of **10** (0.25 g, 1.32 mmol) and triethylamine (0.52 $cm^3$, 3.8 mmol) in dry toluene (12 $cm^3$) and DMF (8 $cm^3$) and a solution of ethylenedioxybis(acetyl chloride) (0.37 g, 1.70 mmol) in dry toluene (20 $cm^3$) were simultaneously added dropwise to dry toluene (25 $cm^3$) at 60 °C under vigorous stirring. After the addition was complete (8 h) the mixture was stirred at the same temperature for 6 days. The solvents were removed under reduced pressure, the residue dissolved in chloroform, washed with water and dried (sodium sulfate). After removal of chloroform the residue was subjected to preparative TLC (10% MeOH in $CH_2Cl_2$) to give **11** (0.14 g, 31%), m.p. 116–117 °C (from $CH_2Cl_2$–ether–hexane); $R_f$ 0.6 (Found: C, 60.9; H, 7.5; N, 12.5. $C_{17}H_{25}N_3O_4$ requires C, 60.88; H, 7.51; N, 12.40%); $\nu_{max}$(KBr)/$cm^{-1}$ 3410 (NH), 1680 (C=O), 1530 (NC=O), 1140, 1120 (C–O–C), 890, 740 and 700 (Ph); $\delta_H$($CDCl_3$) 2.63 (4 H, m, $NCH_2$), 3.36 (4 H, m, $CH_2NH$), 3.58 (2 H, s, $CH_2Ph$), 3.73 (4 H, s, $OCH_2$), 3.93 (4 H, s, $CH_2C$=O) and 7.27 (5 H, br s, Ph and 2 H, NH); $\delta_C$ 35.27 ($NHCH_2$), 52.03 ($NCH_2$), 57.05 ($PhCH_2$), 70.09 ($OCH_2$), 127.31, 128.33, 128.83, 137.92 (Ar) and 168.90 (C=O).

10-*Benzyl*-1,4-*dioxa*-7,10,13-*triazacyclopentadecane* **12**.—To a solution of **11** (0.10 g, 0.30 mmol) in dry THF (10 $cm^3$), $LiAlH_4$ (0.09 g, 2.36 mmol) was added in small portions and the reaction mixture refluxed for 18 h. After cooling (ice bath), the excess of $LiAlH_4$ was destroyed by the careful addition of ice cold water. The slurry was filtered through Celite and washed with the mixture of chloroform and EtOH (1:1; 20 $cm^3$). The filtrate was evaporated to dryness and the residue chromatographed on a column of basic alumina (10 g) using $CH_2Cl_2$ for elution to give **12** (47 mg, 51%, heavy oil); $\nu_{max}$(film)/$cm^{-1}$ 3430 (NH), 1590 (C=O), 1450 (Nδ), 1350 (C–N) 1130 (C–O), 740 and 700 (Ph); $\delta_H$($CDCl_3$) 2.62 (14 H, m, $NCH_2$ and NH), 3.57 (2 H, s, $CH_2Ph$), 3.66 (8 H, m, $OCH_2$) and 7.29 (5 H, s, Ph); $\delta_C$ 42.06 ($NHCH_2CH_2N$), 49.05 ($NHCH_2CH_2O$), 54.06 ($NCH_2CH_2NH$), 59.36 ($PhCH_2$), 69.64, 69.81 ($OCH_2$), 127.09, 128.33, 129.18 and 139.35 (Ar); *m/z* 307 ($M^+$, 4%), 251 (4), 202 (9), 201 (8), 187 (9), 175 (12), 173 (50), 161 (20), 147 (6), 135 (14), 134 (80), 91 (100), 71 (15) and 56 (30).

3,12-*Dibenzyl*-1,14-*bis*(*benzyloxycarbonylamino*)-6,9-*dioxa*-3,12-*diazatetradecane* **13**.— Following the procedure described for the preparation of **9**, 1,8-bis(benzylamino)-3,6-dioxaoctane[23] (2.10 g, 6.40 mmol) and aziridine **2** (3.45 g, 19.50 mmol) gave **13** (3.71 g, 85%, heavy oil); $R_f$ 0.31 ($CH_2Cl_2$–MeOH, 49:1) (Found: C, 70.3; H, 7.3; N, 8.1. $C_{40}H_{50}N_4O_6$ requires C, 70.36; H, 7.38; N, 8.21%); $\nu_{max}$(film)/$cm^{-1}$ 3320 (NH), 1720 (C=O), 1510 (NC=O), 1130 (C–O–C), 740 and 700 (Ph); $\delta_H$($CDCl_3$) 2.63 (8 H, m, $NCH_2$), 3.24 (4 H, m, $HNCH_2$), 3.48 (8 H, m, $OCH_2$), 3.61 (4 H, s, $CH_2Ph$), 5.06 (4 H, s, $OCH_2Ph$), 5.14 (2 H, br, NH), 7.25 (10 H, s, Ph) and 7.32 (10 H, s, Ph); $\delta_C$ 38.26 ($NHCH_2$), 52.82 ($NCH_2$), 58.91 ($PhCH_2N$), 66.08 ($PhCH_2O$), 68.79, 69.92 ($OCH_2$), 127.09, 127.65, 128.11, 128.95, 136.57, 137.25 (Ar) and 156.21 (C=O).

1,14-*Diamino*-3,12-*dibenzyl*-6,9-*dioxa*-3,12-*diazatetradecane* **14**.—As described for preparation of **10**, **13** (2.57 g, 3.76 mmol) and 10% Pd/C (0.35 g) in MeOH (70 $cm^3$) gave **14** (1.53 g, 98%, heavy oil); $\nu_{max}$(film)/$cm^{-1}$ 3380 (NH), 1130 (C–O–C), 740 and 700 (Ph); $\delta_H$($CDCl_3$) (1.82 (4 H, s, $NH_2$), 2.67 (12 H, m, $HNCH_2$), 3.60 (8 H, m, $OCH_2$), 3.62 (4 H, s, $CH_2Ph$), 7.27 (10 H, s, Ph); $\delta_C$ 39.39 ($NH_2CH_2$), 53.16 ($NH_2CH_2CH_2N$), 56.94 ($NCH_2$), 59.31 ($PhCH_2$), 69.98, 70.09 ($OCH_2$), 126.64, 127.93, 128.55 and 138.71 (Ar); *m/z* 414 ($M^+$, 1%), 385 (10), 384 (35), 355 (3), 341 (3), 294 (10), 263 (9), 239 (5), 208 (6), 184 (12), 163 (13), 134 (25), 120 (9), 92 (13), 91 (100) and 56 (5).

10,19-*Dibenzyl*-1,4,13,16-*tetraoxa*-7,10,19,22-*tetraazacyclotetracosane*-6,23-*dione* **15**.—As described for the preparation of **11**, **10** (1.61 g, 3.88 mmol) and ethylenedioxybis(acetyl chloride) (0.60 g, 4.02 mmol) gave **15** (0.60 g, 28%, heavy oil); $R_f$ 0.6 ($CH_2Cl_2$–MeOH, 9:1) (Found: C, 64.8; H, 8.0; N, 10.0. $C_{30}H_{44}N_4O_6$ requires C, 64.72; H, 7.97; N, 10.07%); $\nu_{max}$(film)/$cm^{-1}$ 3400 (NH), 1680 (C=O), 1530 (NC=O), 1110 (C–O–C), 740 and 700 (Ph); $\delta_H$($CDCl_3$) 2.64 (8 H, m, $NCH_2$), 3.38 (4 H, m, $HNCH_2$), 3.57 (8 H, m, $OCH_2$), 3.78 (4 H, s, $CH_2Ph$), 3.95 (4 H, s, $CH_2C$=O) and 7.27 (10 H, s, Ph and 2 H, br, NH); $\delta_C$ 36.06 ($NHCH_2$), 52.59 ($NHCH_2CH_2N$), 52.82 ($NCH_2CH_2O$), 59.31 ($PhCH_2$), 69.86, 69.91, 70.09, 70.26 ($OCH_2$), 126.69, 127.76, 128.38, 138.71 (Ar) and 169.68 (C=O); *m/z* 556 ($M^+$, 3%), 465 (7), 367 (4), 355 (5), 244 (26), 205 (8), 176 (7), 159 (9), 146 (3), 134 (14), 120 (9), 99 (9), 92 (11), 91 (100), 65 (5) and 56 (12).

10,19-*Dibenzyl*-1,4,13,16-*tetraoxa*-7,10,19,22-*tetraazacyclotetracosane* **16**.—Using the procedure described for preparation of **12**, **15** (0.55 g, 0.99 mmol) and $LiAlH_4$ (0.30 g, 7.80 mmol) gave **16** (0.48 g, 91%, heavy oil); $\nu_{max}$(film)/$cm^{-1}$ 3390 (NH), 1110 (C–O–C), 730 and 700 (Ph); $\delta_H$($CDCl_3$) 2.65 (18 H, m, $NCH_2$ and NH), 3.56–3.66 (20 H, m, $OCH_2$ and s, $CH_2Ph$) and 7.27 (10 H, s, Ph); $\delta_C$ 47.34 ($NHCH_2CH_2N$), 49.08 ($NHCH_2CH_2O$), 53.50 ($NHCH_2CH_2N$), 53.95 ($NCH_2CH_2O$), 60.10 ($PhCH_2$), 70.03, 70.26, 70.37, 70.48 ($OCH_2$), 126.97, 128.22, 128.95 and 139.56 (Ar); *m/z* 528 ($M^+$, 0.5%), 437 (20), 355 (16), 341 (8), 320 (5), 208 (19), 153 (7), 147 (10), 134 (23), 120 (12), 92 (10), 91 (100) and 56 (111).

N-*Benzyl*-N′-*benzyloxycarbonyl*-*ethylenediamine* **17**.—To a solution of benzylamine (3.01 g, 28.13 mmol) in dry acetonitrile (80 $cm^3$) at 75 °C, a solution of aziridine **2** (1.02 g, 5.76 mmol) in acetonitrile (20 $cm^3$) was added dropwise during 3 h. The mixture was stirred at 75 °C for 21 h. The solvent and the excess of benzylamine were removed under the reduced pressure. Column chromatography of the residue (silica gel, 3% MeOH in $CH_2Cl_2$) gave **17** (1.35 g, 82%, heavy oil which solidified upon cooling); $R_f$ 0.35 (10% MeOH in $CH_2Cl_2$) (Found: C, 71.8; H, 7.1; N, 10.0. $C_{17}H_{20}N_2O_2$ requires C, 71.81; H, 7.09; N, 9.81%); $\nu_{max}$(KBr)/$cm^{-1}$ 3330 (NH), 1730 (C=O), 1530 (NC=O), 730 and 700 (Ph); $\delta_H$($CDCl_3$) 2.16 (1 H, s, C–NH–C), 2.69 (2 H, t, *J* 5.6, $HNCH_2$), 3.21 (2 H, m, $HNCH_2$), 3.71 (2 H, s, $CH_2Ph$), 5.06 (2 H, s, $OCH_2Ph$), 5.53 (1 H, br, HNC=O), 7.25 (5 H, s, Ph) and 7.30 (5 H, s, Ph); $\delta_C$ 40.68 ($PhCH_2NHCH_2CH_2NH$), 48.30 ($PhCH_2NHCH_2CH_2NH$), 53.33 ($PhCH_2NH$), 66.48 ($PhCH_2O$), 126.92, 127.93, 128.33, 136.68, 140.07 (Ar) and 156.55 (C=O).

3,9-*Dibenzyl*-1,11-*bis*(*benzyloxycarbonylamino*)-6-*oxa*-3,9-*diazaundecane*-4,8-*dione* **18**.—A solution of oxybis(acetyl chloride) (0.24 g, 1.43 mmol) in dry toluene (10 $cm^3$) was added dropwise to the solution of **17** (0.76 g, 2.67 mmol) and triethylamine (0.47 $cm^3$, 3.40 mmol) in dry toluene (15 $cm^3$) at 60 °C. After stirring at 60 °C for 15 h the mixture was extracted with water. The aqueous layer was extracted with chloroform and the combined toluene and chloroform layers were dried ($Na_2SO_4$). The solvents were removed under reduced pressure and the residue chromatographed on the column of silica gel (2% MeOH in $CH_2Cl_2$) to give **18** (0.72 g, 81%, heavy oil); $R_f$ 0.71 ($CH_2Cl_2$–MeOH, 9:1) (Found: C, 68.2; H, 6.5; N, 8.25. $C_{38}H_{42}N_4O_7$ requires C, 68.45; H, 6.35; N, 8.40%); $\nu_{max}$(film)/$cm^{-1}$ 3310 (NH), 1720 (C=O), 1530 (NC=O), 1140

(C–O–C), 730 and 700 (Ph); $\delta_H(CDCl_3)$ 3.33 (8 H, m, $NCH_2$), 4.22 (4 H, m, $CH_2Ph$), 4.48 (4 H, m, $OCH_2C{=}O$), 5.05 (4 H, s, $OCH_2Ph$), 7.09 (2 H, br, NH), 7.25 (10 H, s, Ph) and 7.31 (10 H, s, Ph); $\delta_C$ 38.94 ($NHCH_2$), 45.71, 48.08 ($NCH_2$), 50.90 ($PhCH_2$), 66.59 ($PhCH_2O$), 69.47, 70.09 ($OCH_2$), 126.46, 127.82, 128.04, 128.50, 128.67, 129.01, 135.83, 136.06, 136.62, 136.91 (Ar), 156.60 (NHOC=O), 169.01 and 170.14 ($OCH_2C{=}O$).

1,11-*Diamino*-3,9-*dibenzyl*-6-*oxa*-3,9-*diazaundecane*-4,8-*dione* **19**.—Using the procedure described for preparation of **10**, **18** (0.68 g, 1.02 mmol) and 10% Pd/C (0.10 g) in dry MeOH (20 $cm^3$) gave **19** (1.53 g, 98%, heavy oil); $\nu_{max}$(film)/$cm^{-1}$ 3300 (NH), 1670 (C=O), 1540 (NC=O), 1130 (C–O–C), 740 and 700 (Ph); $\delta_H(CDCl_3)$ 2.23 (4 H, s, $NH_2$), 2.75 (4 H, m, $HNCH_2$), 3.36 (4 H, m, $NCH_2$), 3.72 (4 H, s, $CH_2Ph$), 4.01 (4 H, s, $OCH_2C{=}O$) and 7.25 (10 H, s, Ph); $\delta_C$ 38.03 ($NH_2CH_2$), 47.51 ($NCH_2$), 52.82 ($PhCH_2$), 70.37 ($OCH_2$), 126.35, 127.59, 127.93, 139.56 (Ar) and 168.33 (C=O).

4,16-*Dibenzyl*-1,10-*dioxa*-4,7,13,16-*tetraazacyclooctadecane*-3,8,12,17-*tetrone* **20**.—Using the procedure described for preparation of **15**, **19** (0.38 g, 0.95 mmol), triethylamine (0.41 $cm^3$, 3.03 mmol) and oxybis(acetyl chloride) (0.24 g, 1.25 mmol) gave **20** (0.19 g, 40%); m.p. 81–82 °C; $R_f$ 0.36 ($CH_2Cl_2$–MeOH, 9:1) (Found: C, 62.7; H, 6.8; N, 11.4. $C_{26}H_{32}N_4O_6$ requires C, 62.89; H, 6.50; N, 11.28%); $\nu_{max}$(KBr)/$cm^{-1}$ 3380 (NH), 1650 (C=O), 1550 (NC=O), 1140 (C–O–C), 730 and 700 (Ph); $\delta_H(CDCl_3)$ 3.61 (8 H, m, $NCH_2$), 3.97 (4 H, dAB, *J* 2.9, $CH_2Ph$), 4.24 (2 H, s, $OCH_2$), 4.31 (4 H, s, $OCH_2$), 4.44 (2 H, s, $OCH_2$), 4.61 (2 H, s, $OCH_2$), 7.26 (10 H, m, Ph) and 7.92 (2 H, br, NH); $\delta_C$ 37.24, 39.33 ($NHCH_2$), 45.31 ($NCH_2$), 48.02, 50.00 ($PhCH_2$), 67.94, 69.35, 72.34 ($OCH_2$), 125.62, 126.92, 127.48, 127.93, 128.10, 128.89, 133.97, 136.34 (Ar), 167.59, 167.60, 167.95 and 171.67 (C=O).

4,16-*Dibenzyl*-1,10-*dioxa*-4,7,13,16-*tetraazacyclooctadecane* **21**.—To the solution of **20** (0.10 g, 0.20 mmol) in THF (1.5 $cm^3$, distilled over $LiAlH_4$) under nitrogen, $B_2H_6$ in THF (1 mol $dm^{-3}$; 1.7 $cm^3$) was added and the mixture stirred for 24 h at 50 °C. The ice cooled mixture was treated with water (0.2 $cm^3$) and hydrochloric acid (7.0 mol $dm^{-3}$; 1.24 $cm^3$) and stirred at room temperature for 2 h. Evaporation under reduced pressure gave the residue which was dissolved in water (5 $cm^3$). After extraction with chloroform (2 × 5 $cm^3$) the aqueous solution was made alkaline (LiOH, pH > 11), re-extracted with chloroform (4 × 5 $cm^3$) and dried ($Na_2SO_4$). Evaporation of solvent gave **21** (0.062 g, 70%, oil); $\nu_{max}$(film)/$cm^{-1}$ 3350 (NH), 1140 (C–O–C), 740 and 700 (Ph); $\delta_C(CDCl_3)$ 2.68 (16 H, m, $NCH_2$), 3.22 (2 H, br, NH), 3.60 (12 H, m, $OCH_2$ and $CH_2Ph$) and 7.30 (10 H, m, Ph); $\delta_C$ 48.88 ($NHCH_2CH_2N$), 49.03 ($NHCH_2CH_2O$), 53.50 ($NHCH_2CH_2N$), 53.75 ($NCH_2CH_2O$), 59.53 ($PhCH_2$), 69.44, 69.61 ($OCH_2$), 129.96, 128.22, 129.03 and 139.04 (Ar); *m/z* 442 ($M^+$ + 2, 1.8%), 441 ($M^+$ + 1, 1.6), 440 ($M^+$, 1.6), 311 (23), 164 (42), 148 (62), 146 (63), 134 (88), 100 (66), 91 (95), 70 (43), 58 (57) and 56 (100).

*Extraction Experiments*.—To a solution of picric acid (4.0 mg, 0.0175 mmol, exactly weighed) in distilled water (20 $cm^3$) was added MOH (M = $Li^+$, $Na^+$ or $K^+$; 0.10 mmol) or $Cs_2CO_3$ (0.05 mmol), and the solution transferred to a 25 $cm^3$ volumetric flask and made up to the mark with distilled water. In each case the solution of M-picrate had pH 10.5–11.5. In the stoppered cuvettes the exact volume (10 $cm^3$) of each M-picrate solution (6.98 × $10^{-4}$ mol $dm^{-3}$) was shaken with chloroform solution (10 $cm^3$) containing 6.24 × $10^{-4}$ mmol of one of the lariats or their parent azacrown A15C5, A18C6 or $A_2$18C6. The cuvettes were agitated on a Koterman shaker for 1 h at constant speed. After standing for another hour, the exact volume (0.2 $cm^3$) of aqueous M-picrate solution was transferred into a 5 $cm^3$ volumetric flask and made up to the mark with distilled water. About 3 $cm^3$ of this solution was transferred to UV optical cell and absorbance determined at $\lambda_{max}$ 355 nm. The concentration of M-picrate remained in the aqueous layer after extraction was calculated using the molar extinction coefficient ($\varepsilon$) of 1.64 × $10^4$. The extraction efficiency was expressed in percentages of M-picrate transferred in chloroform layer with respect to the initial M-picrate concentration in the aqueous layer.

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