Novel Syntheses of *N*-Pivot Lariat Diaza-Crown Ethers from 4,13-Bis(benzotriazolylmethyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane

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4,13-Bis(benzotriazolylmethyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (**6**) was synthesized as a versatile intermediate in the preparation of bis(lariats) of diaza-18-crown-6. *N*,*N*-Bis(umbelliferon-8-ylmethyl) derivative **8**, bis(lariats) with terminal unsaturated groups (**11c**,**e**), ester functionalities (**11d**), *N*,*N*-di-β-aralkyl derivatives (**11a**,**b**), and γ-oxy-substituted (**13**, **14**) and γ-amino-substituted (**17**−**19**) propylene-side-armed derivatives were thus prepared in moderate to excellent yields. The X-ray structure of bis(lariat) **6** and stability constants for several of the complexes of bis(lariats), derivatives of **6**, with metal cations are discussed.

Introduction

Lariat diaza-crown ethers derived from 4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (diaza-18-crown-6) are the most studied and the most frequently reported side-arm-bearing N,O-containing macrocycles.[1−5] This popularity is based on the proven ability of such lariats to achieve a strong, selective, and dynamic three-dimensional binding of metal cations, imitating that of naturally occurring ionophores.[5]

Historically, diaza-18-crown-6 was first synthesized and employed as an intermediate in the preparation of cryptands ([2.2.2]cryptand).[6,7] However, numerous derivatives of diaza-18-crown-6 including both *C*- and *N*-pivot lariat crown ethers, were subsequently developed independently for many very successful applications. The strategical development of supramolecular chemistry has been to a considerable extent based on the structures derived from the diaza-18-crown-6 system.[8,9]

N,*N*-Bis(substituted) derivatives of 4,13-diaza-18-crown-6 have previously been prepared by (i) one-step reaction of aliphatic primary amines with tri(ethylene glycol) diiodide; (ii) macrocycle ring closures with the participation of secondary amines ("pre-formed side arm" method); (iii) *N*-alkylation or *N*-acylation of 4,13-diaza-18-crown-6; and (iv) transformations of *N*,*N*-bis(lariats) of 4,13-diaza-18-crown-6 containing replaceable leaving groups in the side arm (functionalized diaza-18-crown-6 ethers). Method i uses easily available primary amines that constitute incipient side arms; however, the range of substituents at the nitrogen atom of amines is somewhat restricted and the yields of isolated bis(lariats) are moderate.[1] Methods incorporated in the second and third group were comprehensively reviewed by Bradshaw *et al.*[5] and usually give from moderate to good yields. Bis(lariats) prepared by the second and third methods can be contaminated by difficult-to-remove inorganics,[10] which decrease their stability and/or hamper their purification.[5] Moreover, the aza-crowns formed can be contaminated by the formation of linear and larger and/or smaller cyclic byproducts, avoidance of which requires the use of special techniques (high dilution, scrupulous addition of reaction components, *etc.*). The third group of methods involving *N*-alkylation or *N*-acylation of the parent diaza-crown is apparently the most popular route to the side-arm elaboration, but if the side arm is of any complexity, the described examples have required multistep procedures and complex experimental manipulations.[11−13] Methods of the fourth group are quite rare and are mainly represented by a well-known adaptation of the Mannich reaction that uses the so-called "*pre-formed* aminomethylating reagents",[14] *i.e.*, reaction of aza-crown ethers with a pre-formed *N*-methylol unit in the form of a methoxymethyl ether. Bis-*N*,*N*-(methoxymethyl)-diaza-18-crown-6 was widely used in various *C*- and *N*-aminomethylation

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Table 1. New Preparations of Bibracchial Lariat Ethers Based on 4,13-Diaza-18-crown-6

side-arm structure	yield[a] (%)	side-arm structure	yield[a] (%)
$-CH_2Bt^b$ (**6**)	91	$-(CH_2)_2CH(Bt)OCH_2CH(CH_3)_2{}^b$ (**13a**)	71
$-$[(7-hydroxycoumarin-8-yl)methyl] (**8**)	31	$-(CH_2)_2CH(Bt)OCH_2CH_3{}^b$ (**13b**)	61
$-$[2-(2-nitrophenyl)ethyl] (**11a**)	62	$-(CH_2)_3OCH_2CH(CH_3)_2$ (**14a**)	84
$-$[2-(2-cyanophenyl)ethyl] (**11b**)	95	$-(CH_2)_3OCH_2CH_3$ (**14b**)	83
$-CH_2CH_2C{\equiv}CH$ (**11c**)	36	$-$[3-Bt-3-(2-oxopyrrolidin-1-yl)propyl]^b (**17**)	97
$-CH_2CH_2COOEt$ (**11d**)	69	$-$[3-Bt-3-(carbazol-9-yl)propyl]^b (**18**)	76
$-CH_2CH_2C{\equiv}CH_2$ (**11e**)	70	$-$[3-(pyrrolidin-1-yl)propyl] (**19**)	94

[a] Yields of isolated products. [b] Bt = *N*-benzotriazolyl.

reactions to give the corresponding bis(lariat) diaza-18-crown-6 derivatives.[15−17] Despite the good yields sometimes obtained and the mild reaction conditions employed, the use of this reagent is, by nature, limited to aminomethylation.
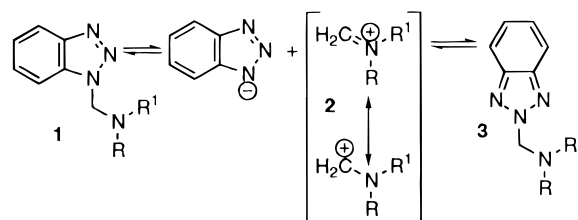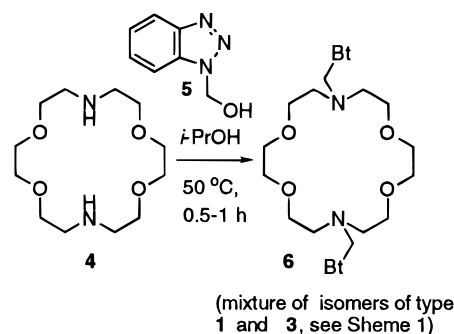
Although the methods mentioned above led to the successful preparations of certain bis(lariat) diaza-crowns, they are not particularly versatile. All chemical transformations reported to prepare bis(lariats) derived from 4,13-diaza-18-crown-6 and other diaza-crowns are based on a well-known limited set of reactions typical for *sec*-amino groups (acylation, alkylation, Michael addition, *etc.*). New reagents and reactions on their base that could expand the range of bis(lariats) prepared from diaza-crown ethers are therefore highly desirable.

We now report our synthesis of the new bis-side-armed functionalized diaza-crown ether, 4,13-bis(benzotriazolylmethyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane, and its synthetic transformations that have led to the preparation of a new series of lariat crowns with various side arms.

Results and Discussion

Our approach to the preparation of functionalized lariat aza-crown ethers originated from successful investigations carried out in our laboratory over the past several years, which involve the use of the adducts of *sec*-amines, aldehydes, and benzotriazole as key reagents for the preparation of a wide variety of variously substituted amines (for reviews, see refs 18 and 19). *N*-(*N*′-Benzotriazolylmethyl)-substituted amines **1** are reagents with high activity toward electrophilic substitution because of their formation of methyleneiminium salts **2** in equilibrium with parent (benzotriazolylmethyl)amines[20] (Scheme 1). In compounds **1** benzotriazole acts as a convenient leaving group in a variety of electrophilic substitution reactions.

The preparation of all the bis(lariats) using our new approach is summarized in Table 1. Reaction of 4,13-diaza-18-crown-6 (**4**) with *N*-(hydroxymethyl)benzotriazole (**5**) in warm 2-propanol gave 4,13-bis(benzotriazolylmethyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (**6**), which rapidly precipitated as yellow crystals from the reaction mixture in 91% yield (Scheme 2). The proton NMR spectrum of the crown **6** revealed that in solution it exists mainly in the $Bt^1CH_2CrCH_2Bt^1$

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Scheme 1

Scheme 2

(mixture of isomers of type **1** and **3**, see Scheme 1)

form (*ca.* 80%) together with some $Bt^1CH_2CrCH_2Bt^2$ isomer. However, as shown previously,[20] such isomer pairs exist in equilibrium with the corresponding methyleneiminium salt (*cf.* **1**, **2**, and **3**), and since both show the same reactivity, there is no need to separate them. Bis(lariat) **6** was also prepared in 87% yield by the reaction of benzotriazole, formaldehyde, and 4,13-diaza-18-crown-6 in warm ethanolic solution and was also precipitated during synthesis, thus simplifying its isolation.

We carried out an X-ray structure determination on the lariat **6**, which contains a crystallographic center of inversion.[48] Figure 1a shows a view, with atom labeling, of the major contributor to the structure, perpendicular to the plane of the ring. These results confirm the structure of compound **6** and show that the crystalline form of **6** has both benzotriazole groups attached through N(1) with the side arms positioned in the *anti* arrangement.[5] Futhermore, as shown in Figure 1b, there is disorder of some atoms within the crown macrocycle. In particular, O(7) and C(8) exist in two locations with relative populations of 67% for the major contributor (solid bonds), wherein the oxygen atom points in the same direction as the nearest benzotriazole substituent, and 33% for the minor contributor (open bonds), which has the opposite arrangement. This factor has important consequences for the design of lariats derived from **6**. Many X-ray crystal structures of metal-free derivatives of **4** have been reported, including the parent compound,[21] some molecular clathrates of both **4**[22,23] and of its diprotonated form,[24] as well as of *N,N*′-disubstituted

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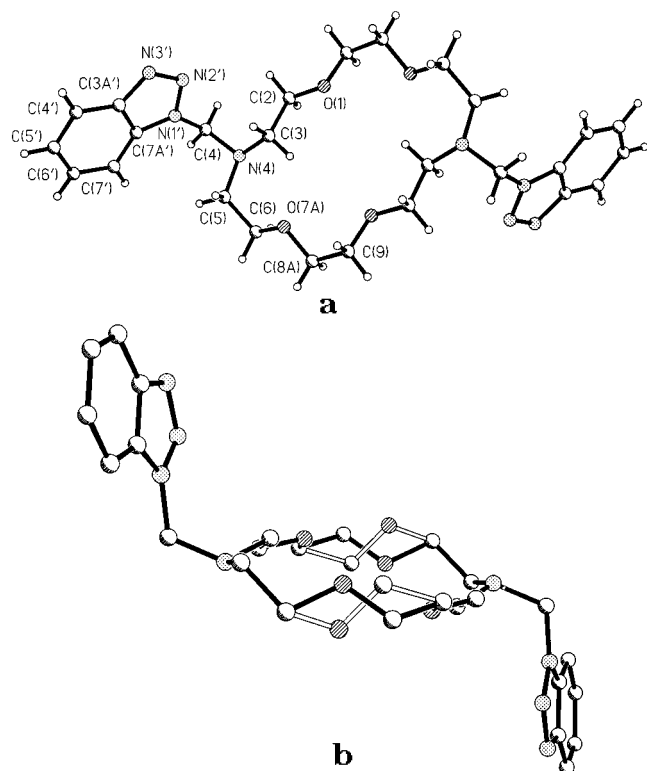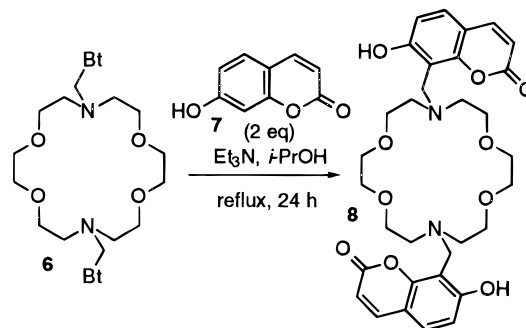
Figure 1. (a) Top view and atom labeling of the major contributor to the X-ray structure of **6**. (b) Side view of the structure of **6** showing the disordered major (solid bonds) and minor (open bonds) contributors.

derivatives.[25-28] These structures show various conformations for the 18-membered ring, which are controlled by a combination of intra- and intermolecular interactions. Whereas the minimum energy conformation of the parent macrocycle **4** has all torsional angles within the ring close to 180° (*i.e., anti*), this is not always the case in its derivatives. In the present case there are several gauche conformations within the ring, specifically those involving the following bonds: N(4)−C(5), C(5)−C(6), and C(8)−C(9). This has the effect of displacing the ring nitrogens further from the centroid of the crown macrocycle than is normally the case. In numerous structures of 18-membered crown, aza-crown, and diaza-crown compounds, the macrocyclic ring is not found to be in the "crown" conformation, but rather two methylene groups are turned inward to partially fill the molecular void. In the present structure, the C(3) and C(12) atoms occupy such internal positions, while the ring is nonplanar and disordered with the N−C bonds at positions 4 and 13 being somewhat flattened.

Subsequent chemical transformations of the new bis-(lariat) **6** now to be described represent the first in lariat aza-crowns, in which the reaction center is *remote* from

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Scheme 3

the macrocycle during the introduction of side arm and is located on the *carbon* atom adjacent to nitrogen. Our approach thus differs from the previously described methods for the assembling of side arms.

Reaction with 7-Hydroxycoumarin. We chose a derivatized phenol, 7-hydroxycoumarin (umbelliferone), as a model compound for a study of the reactions of crown **6** with phenols. Mannich reaction of 4-methylumbelliferone with formaldehyde and 4,13-diaza-18-crown-6 previously led to the formation of a proton-dissociable bis-side-armed chromogenic lariat crown ether (in unspecified yield), which was selective toward and recommended for the fluorimetric determination of Ca^{2+}.[29]

Bis(lariat) **6** was refluxed with umbelliferone (**7**) in 2-propanol in the presence of base for 24 h to give the new proton-dissociable bis(lariat) crown **8**, containing fluorescent labels on both sides of the macrocycle, in moderate yield (31%, Scheme 3). Bis(lariat) crown **8** was purified by column chromatography and additional recrystallization from EtOH/ether. The structure of **8** was confirmed by NMR spectroscopy and elemental analysis.

Reactions with Metalloorganic Reagents. Several new (**11a−c,e**) and one known (**11d**) bis(lariat) crowns were prepared by means of modified Reformatskii and Grignard reactions, starting from the same functionalized bis(lariat) **6**. An important advantage of lariat **6** is that it allows preparation of analogs of the previously described bis(lariats), which contain *one extra carbon atom* in the side arm, thus potentially increasing the effectiveness of cation binding. Theoretical examination of molecular models of different lariats led to the conclusion that "the best distance for the interaction between a ring-bound cation and an apical donor group is three, rather than two, carbons".[8] Moreover, the functionality at the end of the side arms of the newly formed lariats should alter drastically their selectivity and affinity, as shown by many previous examples: (i) Bis(lariats) of 4,13-diaza-18-crown-6 containing 2-nitrophenyl and 2-cyanophenyl substituents at the end of the side arm demonstrated a stronger affinity toward Ag^+ than toward alkali metal cations.[30] (ii) Lariats with terminal alkoxycarbonyl substituents showed high Ca^{2+} selectivity.[3] (iii) Derivatives of 4,13-diaza-18-crown-6 having π-donor side arms (ethenyl or ethynyl)[3,31] manifested extremely interesting affinities toward Na^+ or K^+: despite the absence of an oxygen or nitrogen donor in the side arm, they still have quite high stability constant values for Na^+ and (even

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Scheme 4

	10	11 , R
a		
b		
c		
d		
e		
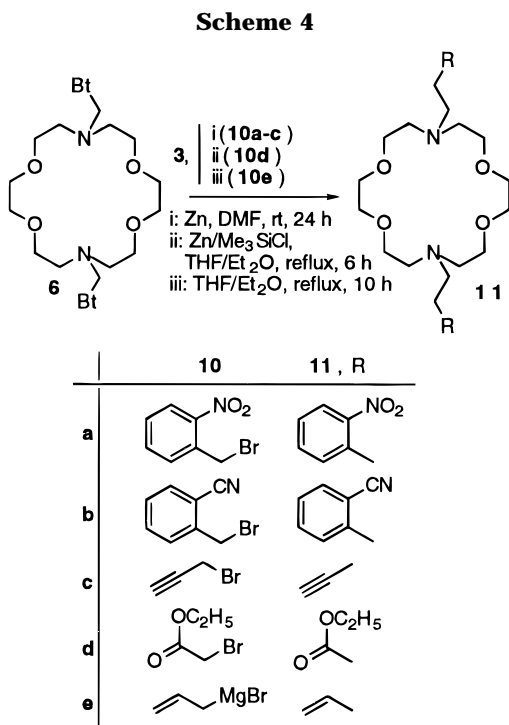
higher) for K$^+$ complexes, which could not be explained by the traditional "three-dimensional binding" approach (as confirmed by an X-ray study, in complexes of these lariats with KSCN, the π-bonds are directed away from the macrocycle).[31] The nature of this effect still awaits explanation, and thus relevant additional data, including elucidation of the influence of the variations in the distance between the π-system and the macrocycle, are of interest.

We synthesized different bis(lariats) **11a**−**e** from one starting crown ether **6** using appropriate metalloorganic reagents (Scheme 4). Modified Reformatskii reaction of crown **6** with 2-nitrobenzyl (**10a**) and 2-cyanobenzyl (**10b**) bromides (Zn powder, DMF as a solvent) afforded the corresponding bis(lariats) **11a,b** (yields are given for isolated products; crude reaction mixtures were separated by column chromatography). The lower yield in the case of **11a** is possibly due to partial reduction of the nitro group. Reaction of **6** with propargyl bromide **10c** under the same reaction conditions gave bis(lariat) **11c** containing two butynyl side arms, which was isolated after column chromatography in moderate yield. β-Bromoethyl acetate reacted with activated (Me$_3$SiCl) zinc in a mixture of THF and ether to give a organozinc reagent, which after reaction with crown **6** afforded bis(lariat) **11d** with ethoxycarbonyl groups at the end of the side arms. It was isolated by column chromatography in 69% yield. Lariat **11d** was reported to have been previously prepared by Michael addition of ethyl acrylate to 4,13-diaza-18-crown-6[10] in high yield; however, purification of the product was not performed, and its quality was described as "almost pure".[10] We also obtained the bis-butenyl side-armed crown ether **11e** by the Grignard reaction of functionalized crown ether **6** with allyl magnesium bromide **10e** in 70% yield (after column chromatography). Compounds **11a**−**e** were all fully characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

Reactions with Enol Ethers. An important theoretical question in the chemistry of lariat crown ethers concerns the length of the carbon chain connecting the macrocycle with the first donor heteroatom in the side

Scheme 5

For **12,13,14**:
a: R = *i*-Bu
b: R = Et
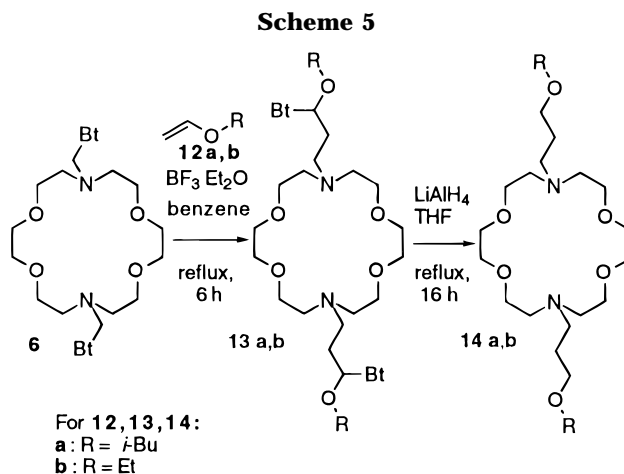
arm.[8] Since lariats with *N*-(propylenoxy)-substituted side arms are hard to access synthetically using traditional methods, we prepared such bis-armed crowns **13a,b** and **14a,b** (Scheme 5) on the basis of our recent results on the addition of *N*-(benzotriazolylmethyl)amines to enol ethers.[32]
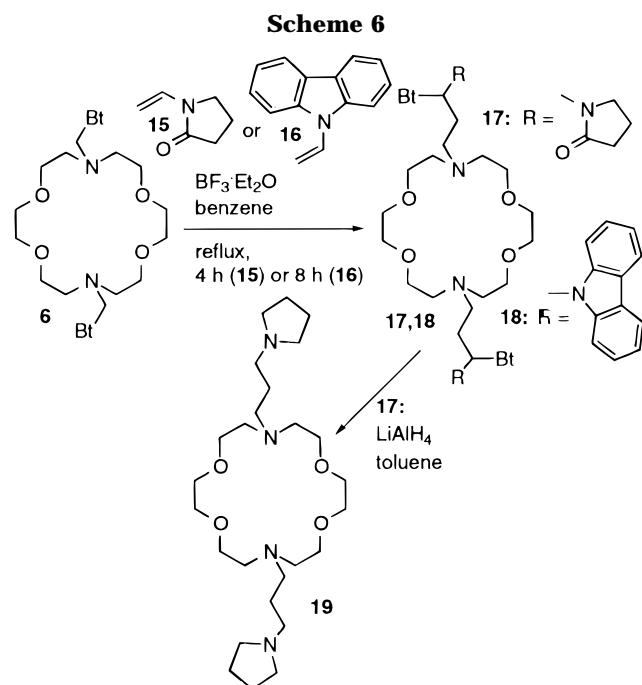
Crown **6** adds to isobutyl vinyl ether (**12a**) with Lewis acid catalysis to give bis(lariat) **13a**. Similarly, reaction of **6** and ethyl vinyl ether (**12b**) led to the formation of bis(lariat) **13b**. Both **13a** and **13b** were further reduced by lithium aluminum hydride to give the *N,N*-bis-(propylenoxy)-substituted 4,13-diaza-18-crowns-6 **14a,b**. Bis(lariats) **13a,b** and **14a,b** were purified by column chromatography and gave the expected ^{1}H and ^{13}C NMR data and elemental analyses. Crowns **13a,b** were isolated as mixtures of benzotriazol-1-yl (Bt^1) and benzotriazol-2-yl (Bt^2) isomers, whose ratio (in CDCl$_3$) differs depending on the bulkiness of the alkyl substituent at the oxygen: the bulkier the substituent is, the lower is the ratio of Bt^1:Bt^2 (1:8 for **13a** and 1:1.5 for **13b**). Since both Bt-isomers possess equivalent reactivity, their benzotriazole moieties were successfully replaced by hydrogen during reduction: in the ^{1}H NMR spectra of the reduced bis(lariats) **14a,b** the signals of all the Bt protons as well as of the *N,O*-acetal protons [−C*H*(Bt)O−] disappear. Corresponding changes were also observed in the ^{13}C NMR spectra of the reduced bis(lariats) **14a,b**.

Reactions with 1-Vinylpyrrolidin-2-one and 9-Vinylcarbazole. Bis(lariats) of diaza-crown ethers containing terminal amino groups are already compounds of considerable interest because of their extremely strong complexation toward alkali metal and ammonium cations.[13] In addition, the presence of easily modified amino groups facilitates the preparation of various derivatives of such crowns, including ferrocenyl-containing bis(lariats),[33] and compounds containing two distinct binding sites, like a "crowned" porphyrin.[34] Moreover, such diamines are prospective monomers for various polycondensation polymers.[13] A γ-amino-functionalized bis-(lariat) of 4,13-diaza-18-crown-6 was previously obtained by the Michael addition of acrylonitrile to the parent diaza-crown, followed by reduction of the resulting bis-*N,N*-(β-cyanoethyl) lariat either with diborane,[33] or catalytically (Raney Ni) in NH$_3$/MeOH solution.[34] Reaction of 4,13-diaza-18-crown-6 with *N*-(γ-bromopropyl)-

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(33) Beer, P. D.; Crowe, D. B.; Main, B. *J. Organomet. Chem.* **1989**, *375*, C39.
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Scheme 6

Table 2. Cation Complexation Constants for Bibrachial Lariat Ethers

compd structure	log K_S[a]	
	Na$^+$	K$^+$
18-crown-6 (this work)	4.32	6.03
18-crown-6 (previous work)[b]	4.35	6.08
<N18N>(CH$_2$CH$_2$COOEt)$_2$[c] (**11d**)	4.26	4.45
<N18N>[CH$_2$CH$_2$CH(Bt)OCH$_2$CH(CH$_3$)$_2$]$_2$[c] (**13a**)	3.58	3.75
<N18N>(CH$_2$CH$_2$CH$_3$)$_2$[c,d]	2.86	3.77
<N18N>[(CH$_2$)$_{11}$CH$_3$]$_2$[c,d]	2.99	3.80
<N18N>(CH$_2$C≡CH)$_2$[c,d]	3.61	4.99
<N18N>(CH$_2$CH$_2$OCH$_3$)$_2$[c,d]	4.75	5.46
<N18N>(CH$_2$COOEt)$_2$[c,d]	5.51	5.78
<N18N>(2-methoxybenzyl)$_2$[c,d]	3.65	4.94

[a] Measured in anhyd methanol at 25.0 ± 0.1 °C. [b] Data from ref 38. [c] <N18N> represents 4,13-diaza-18-crown-6. [d] Data from ref 39.

earlier described methods for [*N,N*-disubstituted 3-(carbazol-9-yl)-3-benzotriazolylamino]propanes,[36] led to the isolation of only the unchanged starting lariat **18**.

Complexation Studies. Cation binding by crown ethers has been assessed in a variety of ways over the past three decades. The most popular methods have been the picrate extraction technique and determination of K_S in homogeneous solution by using either calorimetric or ion-selective electrode (ISE) methods. Each of these approaches has advantages and disadvantages. The picrate extraction technique is convenient, and the only equipment required is a UV−vis spectrophotometer. A drawback of the method is that it lacks a standard, *i.e.*, solvent combinations, concentrations, ionic strengths, *etc.*, vary in different reports. Notwithstanding this variation, values contained under consistent conditions correlate reasonably well with homogeneous cation complexation constants.[37]

Homogeneous cation-binding constants have the advantage that their values in a specified solvent are consistent irrespective of the method by which they are determined. Solution calorimetry has been used extensively but requires an apparatus that is neither commonplace nor inexpensive. Ion-selective electrode methods require an apparatus less expensive than a calorimeter but less common than a UV spectrophotometer. We have used the ISE method for the present studies. In doing so, we first calibrated the system against the known cation-binding constants for Na$^+$ and K$^+$ with 18-crown-6 in anhyd methanol at 25 °C. The values obtained for log K_S with these two cations are shown in Table 2 along with previously determined values. The error for complexation determinations with either cation is 10%.

Sodium and potassium homogeneous complexation constants have been determined for two of the novel diaza-lariats and compared with several related compounds whose binding constants were previously determined. Specifically, 4,13-diaza-18-crown-6 having two side arms −(CH$_2$)$_2$COOEt (**11d**) or two −CH$_2$CH$_2$CH(Bt)-OCH$_2$CH(CH$_3$)$_2$ (**13a**) were studied. Sodium binding (log K_S) was found to be 4.26 and 3.58, while log K_S (K$^+$) was 4.45 and 3.75, respectively. These values do not compare favorably with K$^+$ binding by 18-crown-6, although Na$^+$ binding by **11d** is close to that observed for the simpler ligand.

phthalimide also gave the corresponding phthalimido derivative, which after hydrazinolysis yielded a γ-amino-functionalized bis(lariat) of 4,13-diaza-crown-6.[13]

We recently found that the reaction of *N*-(benzotriazolylmethyl)amines with enamides under Lewis acid catalysis gives addition products in accordance with the Markovnikov rule. Subsequent displacement of the benzotriazole moiety in these intermediates gives *N,N*-1,3-bis(unsymmetrically substituted)aminopropanes in good overall yields.[35] We also demonstrated that *N*-(benzotriazolylmethyl)amines react with 9-vinylcarbazole at elevated (130 °C) temperatures without solvents and catalysts to give [*N,N*-disubstituted 3-(carbazol-9-yl)-3-(benzotriazolyl)amino]propanes in moderate to good yields.[36] Following these synthetic pathways, we added functionalized lariat ether **6** to 1-vinylpyrrolidin-2-one (**15**) to obtain *N,N*-bis(propylenamido)-substituted lariat **17** in 97% yield (Scheme 6). Similarly, addition of **6** to 9-vinylcarbazole (**16**) afforded the corresponding γ-benzotriazolyl-γ-carbazolyl derivative **18**. Interestingly, the ^{1}H and ^{13}C NMR spectra of bis(lariats) **17** and **18** revealed that in each case *solely* the Bt^1-isomer was obtained. In the proton spectrum of **17** there are two doublets and two triplets corresponding to the Bt^1-isomer. The proton spectrum of **18**, though more complex than for **17**, also clearly shows only the presence of the Bt^1-isomer signals. In the carbon spectra of both **17** and **18** the set of six signals for the Bt^1-isomer was observed.

Reduction/displacement of benzotriazolyl substituent in **17**, carried out with LiAlH$_4$ in refluxing THF, afforded the corresponding γ,γ′-bis-(*N*-pyrrolidinyl)-substituted lariat **19** in excellent yield. However, the presence of a carbazolyl moiety in the structure of the lariat **18** made the molecule much less reactive, and several attempts to perform similar transformation with **18** were unsuccessful. Its reaction either with LiAlH$_4$ (both in refluxing toluene and in refluxing THF) or with Grignard reagent (EtMgBr) in refluxing toluene, in accordance with our

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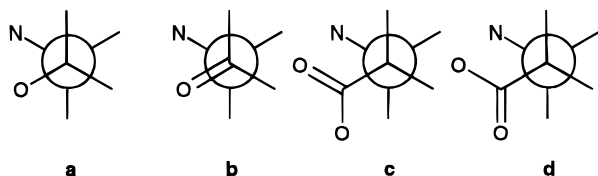
Figure 2.

Two important considerations in the binding of cations by diaza-lariat ether ligands deserve comment. First, the change from 18-crown-6 to a diaza-derivative costs the system two oxygen donor groups. Oxygen is a better donor for alkali metal cations than is nitrogen, and therefore, cation binding is expected to diminish. Addition of an oxygen atom in each side arm may compensate, but the donor group must be at an appropriate distance, must be able to adopt an appropriate orientation, and must be suitably hybridized to interact with the ring-bound cation. In **11d**, the side arm contains an ester carbonyl donor at a distance of three carbons from the ring. The ester carbonyl group is more polar than is an ether oxygen, and $EtOCOCH_2<N18N>CH_2COOEt$ binds both Na^+ and K^+ more strongly than does $MeOCH_2$-$CH_2<N18N>CH_2CH_2OMe$ (see Table 2).

In the early stage of the lariat ether studies, an examination of molecular models suggested that for the ether-side-armed compounds, three, rather than two, carbons separating macroring and donor group would provide more effective solvation of a ring-bound cation than would a two-carbon fragment. Studies with two-armed, diaza-18-crown-6 derivatives showed that the situation was considerably more complex than could be anticipated from these model studies. Sodium and potassium complexation was studied with diaza-18-crown-6 derivatives having two CH_2CH_2OH or two $CH_2CH_2OCH_3$ side arms.[40] Solid state structures were obtained[40] for each of these complexes. It was found that when the side arm was CH_2CH_2OH, complexation occurred with the side arm ether donors in a *syn*-arrangement whether the bound cation was Na^+ or K^+. When the side arms were $CH_2CH_2OCH_3$, a similar, cryptand-like conformation was observed for Na^+, but an *anti*-arrangement was apparent in the K^+ case. Subsequent work by others has shown variations on this pattern when the side arms differ.[41]

Both the $-NCCO-$ and $-NCCC-$ units may be considered as butane equivalents for purposes of conformational analysis. In the two-carbon case, the $C-X$ bonds may be in the normal, gauche arrangement (Figure 2a,b). Both donors are thus focused toward the cation. In the $-NCCCO-$ case, the gauche arrangement is less favorable since the $-C=O$ (or $-CO-$) bond is more remote (Figure 2c,d). This conformational difficulty makes improbable the *anti*-conformation in which both side arms interact with the cation along the axis. The cryptand-like conformation is also known to occur with bibrachial lariat ethers and is likewise compromised by the overall side-arm length.

An alternate interpretation of the conformational issue regards the potential complex as involving a 5- or 6-membered chelate ring. The smaller ring size is

"tighter," less sterically demanding, and less conformationally variable than the higher homolog. When two of the smaller rings are involved in binding on the same side of the complex, there is less unfavorable interaction than in the 6-membered, chairlike chelate.

Crown ether compounds having three or more carbons separating the donor atoms have been extensively investigated by Inoue, Hakushi, and their co-workers.[42] Although extraction constants rather than homogeneous binding constants were obtained for the interaction of these compounds with cations, it was found that increasing the ring size of 15-crown-5 by one carbon had little effect on Na^+ binding but K^+ complexation was diminished significantly. Although these results are not directly comparable with the present study, the trends are similar.

Compound **13a** presents more potential difficulties in binding cations because there are two possible donors (alkyl ether oxygen and aromatic nitrogen). In addition, however, there is considerably more steric hindrance in **13a** than in **11d** owing to the presence of the terminal isobutyl group, although it is clearly distal to the donor group sites. Both Na^+ and K^+ complexation strengths with **13a** are lower than with 18-crown-6. The loss of Na^+ binding strength is greater than observed for **11d** and similar to that observed with *N,N*-dipropargyl-4,13-diaza-18-crown-6 (see Table 2). Potassium cation binding with the latter ligand is superior to that observed with **13a**, but side-arm donor groups do not appear to be involved in the former case.[31]

In summary, a series of new bibrachial lariat diaza-crown ethers with chromophoric side arms (**8**), terminal unsaturated groups (**11c,e**), ester functionalities (**11d**), *N,N*-di-β-aralkyl derivatives (**11a,b**), and γ-oxy-substituted (**13**, **14**) and γ-amino-substituted (**17–19**) propylene-side-armed derivatives was prepared using the new versatile intermediate, 4,13-bis(benzotriazolylmethyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane. This series of bis(lariats) containing one extra carbon atom in the side arm was used to test experimentally a previous theoretical deduction[8] regarding the best distance for the interaction between a ring-bound cation and an apical donor group. This novel group of bibrachial lariat ethers binds both Na^+ and K^+ with substantial complexation constants, but neither binding strengths nor selectivities are superior to related structures having shorter, less sterically-hindered side arms.

Experimental Section

General Procedures. See refs 32, 43, and 44. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz in $CDCl_3$ (unless otherwise specified). Cation-binding constants were measured according to the method of Frensdorff[45] as described recently in details.[46] All the compounds containing the benzotriazole moiety described in the present paper consist of the mixture of Bt^1 and Bt^2 isomers in different ratios; both isomers readily undergo the transformations described here, therefore, their separation was not performed. Experimental Section contains NMR data of the mixtures of

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Bt[1] and Bt[2] isomers, without their complete assignments. 1-(Hydroxymethyl)-benzotriazole was prepared as previously described.[47]

4,13-Bis(benzotriazolylmethyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (6). A mixture of 1-(hydroxymethyl)-benzotriazole (5) (2.98 g, 20 mmol) and 4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (4) (2.62 g, 10 mmol) in 2-propanol (50 mL) was refluxed under stirring for 1 h. The reaction mixture was cooled to rt and allowed to stand overnight. The product was collected by filtration. An analytical sample was obtained by recrystallization from methanol: yellow needles; mp 126−127 °C; yield 91%; ^{1}H NMR δ 2.99 (t, $J = 5.2$ Hz, 8H), 3.05 (t, $J = 5.2$ Hz, 8H), 3.67 (s, 8H), 3.71 (t, $J = 5.2$ Hz, 8H), 5.66 (s, 4H), 5.68 (dd, $J = 2.5$ and 5.3 Hz, 4H), 7.30−7.42 (m, 4H + 2H), 7.48 (t, $J = 7.8$ Hz, 2H), 7.75 (t, $J = 7.8$ Hz, 2H), 7.88 (dd, $J = 2.6$ and 6.5 Hz, 4H), 8.03 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR δ 52.1, 52.2, 67.4, 69.6, 70.0, 70.5, 70.6, 70.7, 110.3, 118.2, 119.7, 123.7, 126.2, 127.2, 133.8, 144.1, 145.8. Anal. Calcd for $C_{26}H_{36}N_8O_4$: C, 59.52; H, 6.92; N, 21.36. Found: C, 59.80; H, 7.13; N, 21.45.

Alternatively, crown ether **6** has been prepared from benzotriazole (2.38 g, 20 mmol), formaldehyde (37% solution, 1.50 mL, 20 mmol), and 4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (4) (2.62 g, 10 mmol) under the same reaction conditions and solvent: yellow needles; mp 125−126 °C; yield 87%.

Crystal data of the crown ether 6, solution and refinement: $C_{26}H_{36}N_8O_4$, $M_r = 524.6$, monoclinic, space group $P2_1/c$, $a = 14.674(5)$ Å, $b = 8.138(3)$ Å, $c = 11.608(4)$ Å, $\beta = 103.64(3)°$, $V = 1347.1(8)$ Å^3, $T = 20$ °C, $F(000) = 560$, $Z = 2$, $D_c = 1.29$ g·cm^{-3}, μ(Mo Kα) = 0.90 cm^{-1}. Data were collected using the $\omega - 2\theta$ scan technique to a $2\theta_{max}$ of 45°. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedures. Non-hydrogen atoms were made anisotropic, and hydrogen atoms were included in calculated positions. In the final least-squares cycles 192 parameters were adjusted; the final R index was 0.038 for data with $I > 2\sigma(I)$ and wR 0.072 for all 1765 data.[48]

4,13-Bis[(7-hydroxycoumarin-8-yl)methyl]-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (8). Bis(lariat) crown **6** (0.524 g, 1 mmol) was added portionwise within a 30 min period to a stirred mixture of 7-hydroxycoumarin (0.34 g, 2.1 mmol) and triethylamine (1.39 mL, 10 mmol) in 2-propanol (30 mL) while a mixture was heated to reflux. The stirring and refluxing was continued under nitrogen for 24 h. The solvent was evaporated under reduced pressure, and the crude product was subjected to column chromatography (eluent, CHCl$_3$). The first (colored) portion was collected, the solvent was evaporated and the residue was recrystallized from DMSO/water: yellow prisms; mp 217−218 °C; yield 31%; ^{1}H NMR δ (DMSO-d_6) 2.85 (t, $J = 4.7$ Hz, 8H), 3.55 (s, 8H), 3.65 (t, $J = 4.6$ Hz, 8H), 4.07 (s, 4H), 6.21 (d, $J = 9.2$ Hz, 2H), 6.75 (d, $J = 9.2$ Hz, 2H), 7.48 (d, $J = 9.2$ Hz, 2H), 7.94 (d, $J = 9.2$ Hz, 2H); ^{13}C NMR δ 49.6, 53.2, 67.9, 69.9, 108.9, 110.6, 110.8, 113.3, 128.2, 145.0, 152.9, 160.2, 162.3. Anal. Calcd for $C_{32}H_{38}N_2O_{10}$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.28; H, 6.64; N, 4.70.

General Procedure for the Preparation of Lariat Crown Ethers 11a−c. To a stirred mixture of bis(lariat) **6** (0.20 g, 0.38 mmol) and Zn powder (0.10 g, 1.50 mmol) in DMF (1.5 mL) was added the corresponding bromide **10a−c** (1.50 mmol) at rt. The mixture was stirred for 24 h at rt, poured into a mixture of concd NH$_4$OH (2 mL) and ice (1 g), and stirred until solids were dissolved. The product was extracted with CH$_2$Cl$_2$ (3 × 5 mL). The organic layer was washed with water (10 mL), separated, dried over anhyd Na$_2$SO$_4$ and concentrated under reduced pressure. The oily residue was purified by column chromatography using the eluents specified. The solvents were evaporated to give pure bis(lariats) **11a−c**.

4,13-Bis[2-(2-nitrophenyl)ethyl]-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (11a): eluent CHCl$_3$:methanol 50:1, then CHCl$_3$:methanol 20:1; yellow oil; yield 62%; ^{1}H NMR δ 2.28−2.88 (m, 12H), 3.02−3.07 (m, 4H), 3.58−3.61 (m, 16H), 7.30−7.38 (m, 4H), 7.49−7.55 (m, 2H), 7.89 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR δ 30.7, 53.8, 56.3, 69.9, 70.7, 124.6, 127.0, 132.6, 132.8, 135.5, 149.5; HRMS calcd for $C_{28}H_{41}N_4O_8$ 561.2924 (M$^+$ + 1), found 561.2941.

4,13-Bis[2-(2-cyanophenyl)ethyl]-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (11b): mp 97−98 °C (ethyl acetate); yield 95%; ^{1}H NMR δ 2.81−2.89 (m, 12H), 2.95−3.00 (m, 4H), 3.58−3.62 (m, 16H), 7.26−7.32 (m, 2H), 7.35 (d, $J = 7.4$ Hz, 2H), 7.48−7.51 (m, 2H) 7.60 (d, $J = 7.7$ Hz, 2H); ^{13}C NMR δ 32.3, 53.7, 56.4, 69.9, 70.6, 112.4, 118.0, 126.4, 130.0, 132.5 (2C), 144.5. Anal. Calcd for $C_{30}H_{40}N_4O_4$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.27; H, 8.04; N, 10.76.

4,13-Di(1-butyn-3-yl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (11c): eluent ethyl acetate, then CHCl$_3$:methanol 20:1; yellow oil; yield 36%; ^{1}H NMR δ 1.95 (t, $J = 2.6$ Hz, 2H), 2.33 (dt, $J = 2.6$, 7.4 Hz, 4H), 2.78−2.85 (m, 12H), 3.59−3.63 (m, 16H); ^{13}C NMR δ 16.8, 53.7, 54.2, 69.0, 69.8, 70.6, 82.9; HRMS calcd for $C_{20}H_{35}N_2O_4$ 367.2597 (M$^+$ + 1), found 367.2593.

4,13-Bis[2-(ethoxycarbonyl)ethyl]-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (11d). To a stirred suspension of dry Zn powder (0.12 g, 1.90 mmol) in dry diethyl ether (4 mL) was added trimethylchlorosilane (0.05 mL, 0.4 mmol), and the mixture was stirred for 15 min at rt. A solution of bis(lariat) **6** (0.21 g, 0.40 mmol) in dry THF (4 mL) was added, the mixture was heated to reflux, the bromide **10d** (0.20 g, 1.20 mmol) was added in one portion, and the mixture was stirred at reflux under nitrogen for 6 h, cooled to rt, and worked up as described above for bis(lariats) **10a−c**. Column chromatography: eluent ethyl acetate, then CHCl$_3$:methanol 20:1; yellow oil; yield 70%; ^{1}H NMR δ 1.25 (t, $J = 7.2$ Hz, 6H), 2.45 (t, $J = 7.2$ Hz, 4H), 2.78 (t, $J = 5.8$ Hz, 8H), 2.87 (t, $J = 7.2$ Hz, 4H), 3.57−3.60 (m, 16H), 4.12 (q, $J = 7.2$ Hz, 4H); ^{13}C NMR δ 14.2, 32.7, 51.0, 53.8, 60.3, 69.9, 70.7, 172.6.

4,13-Di(1-buten-3-yl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (11e). To a stirred solution of bis(lariat) **6** (0.32 g, 0.60 mmol) in dry THF (8 mL) was added a Grignard reagent, prepared from allyl bromide (**10e**) (0.37 g, 3.03 mmol) and magnesium turnings (0.18 g, 7.37 mmol) in ether (4 mL), dropwise. The mixture was stirred at reflux under nitrogen for 10 h and poured into a saturated solution of NH$_4$Cl. The product was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic layer was washed with concd NH$_4$OH (10 mL) and water (2 × 10 mL), separated, dried over anhyd Na$_2$SO$_4$, and concentrated under reduced pressure. The oily residue was purified by column chromatography (eluent ethyl acetate, then CHCl$_3$:methanol 20:1). Organic solvents were evaporated to give bis(lariat) **11e** as a yellow oil: yield 70%; ^{1}H NMR δ 2.22 (dt, $J = 7.0$, 7.8 Hz, 4H), 2.58−2.63 (m, 4H), 2.80 (t, $J = 5.9$ Hz, 8H), 3.59−3.63 (m, 16H), 4.96−5.07 (m, 4H), 5.74−5.88 (m, 2H); ^{13}C NMR δ 31.6, 53.8, 55.2, 69.9, 70.7, 115.4, 136.7. Anal. Calcd for $C_{20}H_{38}N_2O_4$: C, 64.84; H, 10.37. Found: C, 64.77; H, 10.61.

General Procedure for the Addition of Bis(lariat) Crown Ether 6 to Vinyl Ethers 12a,b. To a solution of bis(lariat) **6** (0.21 g, 0.40 mmol) were added the corresponding vinyl ether **12a,b** (0.88 mmol) and BF$_3$·Et$_2$O (1 drop) in dry benzene (5 mL) at reflux for 6 h. After being cooled to rt, the reaction mixture was dissolved in CH$_2$Cl$_2$ (20 mL) and washed with a mixture of concd NH$_4$OH (10 mL) and water (10 mL) and then with water (20 mL). The organic layer was separated, dried over anhyd Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent ethyl acetate, then CHCl$_3$:methanol 20:1). Organic solvents were evaporated to give the corresponding bis(lariat) **13a** or **13b**.

4,13-Bis[3-(benzotriazol-2-yl)-4-oxa-6-methylheptyl]-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (13a): yellow oil; yield 71%; ^{1}H NMR δ 0.80 (d, $J = 6.7$ Hz, 6H), 0.87 (d, $J = 6.7$ Hz, 6H), 1.76−1.89 (m, 2H), 2.32−2.54 (m, 4H), 2.59−2.63 (m, 4H), 2.76 (d, $J = 5.8$ Hz, 8H), 3.08 (dd, $J = 6.5$, 9.0 Hz, 2H), 3.28 (dd, $J = 7.1$, 9.0 Hz, 2H), 3.52−3.57 (m, 16H),

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(48) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

6.02 (t, J = 6.3 Hz, 2H), 7.38−7.41 (m, 4H), 7.89−7.92 (m, 4H); ^{13}C NMR δ 19.0, 19.2, 28.1, 33.2, 50.6, 54.0, 69.9, 70.6, 76.3, 93.7, 118.5, 126.5, 144.1. Anal. Calcd for $C_{38}H_{60}N_8O_6$: C, 62.96; H, 8.34; N, 15.46. Found: C, 63.31; H, 8.64; N, 15.28.

4,13-Bis(3-benzotriazolyl-4-oxahexyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (13b): yellow oil; yield 61%; ^{1}H NMR δ 1.13 (t, J = 7.0 Hz, 6H), 1.16 (t, J = 7.2 Hz, 6H), 2.20−2.62 (m, 8H), 2.72−2.78 (m, 8H), 3.24−3.60 (m, 20H), 6.07 (t, J = 6.3 Hz, 2H), 6.24 (t, J = 6.5 Hz, 2H), 7.35−7.50 (m, 4H + 2H + 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.87−7.93 (m, 4H), 8.07 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 14.6, 14.7, 32.8, 33.2, 50.4, 50.7, 54.0, 64.5, 65.2, 69.8, 69.9, 70.6, 88.5, 93.2, 111.1, 118.5, 119.9, 124.0, 126.5, 127.3, 131.6, 144.1, 146.6. Anal. Calcd for $C_{34}H_{52}N_8O_6$: C, 61.05; H, 7.84. Found: C, 61.13; H, 8.13.

General Procedure for the Reduction of Bis(Lariat) Crown Ethers 13a,b. A mixture of LiAlH$_4$ (0.03 g, 0,79 mmol) and the corresponding bis(lariat) **13a,b** (0.28 mmol) in toluene (5 mL) was stirred and refluxed under nitrogen for 8 h. After the mixture was cooled to rt, methanol (0.5 mL) was added dropwise to decompose the excess LiAlH$_4$. A solution of NaOH (1M, 5 mL) was added, and the precipitate formed was filtered and washed with CH$_2$Cl$_2$ (5 mL). The filtrate was extracted with CH$_2$Cl$_2$ (2 × 10 mL), and combined organic layers were washed with H$_2$O (10 mL), dried over anhyd Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent ethyl acetate, then CHCl$_3$:methanol 20:1). Organic solvents were evaporated to give the corresponding bis(lariat) **14a** or **14b**.

4,13-Bis(4-oxa-6-methylheptyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (14a): yellow oil; yield 84%; ^{1}H NMR δ 0.89 (d, J = 6.8 Hz, 12H), 1.69−1.90 (m, 6H), 2.64 (t, J = 7.4 Hz, 4H), 2.82 (t, J = 5.5 Hz, 8H), 3.15 (d, J = 8.5 Hz, 4H), 3.42 (t, J = 6.2 Hz, 8H), 3.60−3.64 (m, 16H); ^{13}C NMR δ 19.4, 27.2, 28.4, 52.5, 54.0, 68.9, 69.9, 70.7, 77.8; HRMS calcd for $C_{26}H_{55}N_2O_6$ 491.4060 (M$^+$ + 1), found 491.4075.

4,13-Bis(4-oxahexyl)-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (14b): yellow oil; yield 83%; ^{1}H NMR δ 1.19 (t, J = 7.0 Hz, 6H), 1.71 (tt, J = 6.5, 7.2 Hz, 4H), 2.58 (t, J = 7.2 Hz, 4H), 2.77 (t, J = 5.9 Hz, 8H), 3.43 (t, J = 6.5 Hz, 4H), 3.46 (q, J = 7.0 Hz, 4H), 3.58−3.62 (m, 16H); ^{13}C NMR δ 15.2, 27.6, 52.5, 54.0, 66.0, 68.7, 70.0, 70.7; HRMS calcd for $C_{22}H_{47}N_2O_6$ 435.3434 (M$^+$ + 1), found 435.3434.

General Procedure for Addition of Bis(Lariat) Crown Ether 6 to 1-Vinylpyrrolidin-2-one (15) and 9-Vinylcarbazole (16). The procedure is identical to that described for the preparation of bis(lariats) **13a,b**, with the only difference in reaction time: reaction with 1-vinylpyrrolidin-2-one (**15**) was carried out for 4 h, while reaction with 9-vinylcarbazole was completed after 8 h. The crude products were worked up

in the same way as bis(lariats) **13a,b** (see above) to afford bis-(lariats) **17** and **18**.

4,13-Bis[3-(benzotriazol-1-yl)-3-(2-oxopyrrolidin-1-yl)-propyl]-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (17): yellow oil; yield 97%; ^{1}H NMR δ 1.83−2.05 (m, 4H), 2.21−2.93 (m, 20H), 3.19−3.27 (m, 2H), 3.34−3.59 (m, 16H), 3.61−3.67 (m, 2H), 7.02 (dd, J = 5.4, 7.8 Hz, 2H), 7.36−7.41 (m, 2H), 7.48−7.53 (m, 2H), 7.87 (d, J = 9.3 Hz, 2H), 8.04 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 17.7, 28.8, 30.8, 42.4, 50.9, 53.9, 61.1, 69.8, 70.5, 110.7, 119.4, 124.3, 127.7, 132.9, 145.5, 175.1; HRMS calcd for $C_{38}H_{55}N_{10}O_6$ 747.4306 (M$^+$ + 1), found 747.4355.

4,13-Bis[3-(benzotriazol-1-yl)-3-(carbazol-9-yl)propyl]-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (18): yellow microcrystals, upon trituration with ether, mp 169−171 °C; yield 76%; ^{1}H NMR δ 2.41−2.76 (m, 12H), 3.04−3.15 (m, 2H), 3.24−3.42 (m, 16H), 3.52−3.67 (m, 2H), 7.16−7.26 (m, 10H), 7.39−7.44 (m, 4H), 7.73 (dt, J = 2.5 and 7.0 Hz, 2H), 7.81 (d, J = 8.2 Hz, 4H), 7.97−8.05 (m, 6H); ^{13}C NMR δ 29.4, 51.0, 53.8, 65.3, 69.6, 69.7, 70.5, 109.8, 110.3, 119.9, 120.1, 120.4, 123.6, 124.2, 126.2, 127.6, 133.1, 139.0, 146.1. Anal. Calcd for $C_{54}H_{58}N_{10}O_4$: N, 15.38. Found: N, 15.29.

4,13-Bis[3-(pyrrolidin-1-yl)propyl]-4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (19). To a suspension of LiAlH$_4$ (0.11 g, 2.8 mmol) in dry THF (5 mL) was added a solution of bis(lariat) **17** (0.28 mmol) in dry THF (2 mL) at rt, and the mixture was stirred and refluxed under nitrogen for 12 h. After the mixture was cooled to rt, a mixture of THF and water (1: 1, 2 mL) was added dropwise to decompose the excess LiAlH$_4$. A solution of NaOH (1 M, 5 mL) was added, and the precipitate formed was filtered and washed with CH$_2$Cl$_2$ (5 mL). The filtrate was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic layers were then washed with H$_2$O (10 mL), dried over anhyd Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent ethyl acetate, then CHCl$_3$:methanol 20:1). Organic solvents were evaporated to give the corresponding bis(lariat) **19**: yellow oil; yield 94%; ^{1}H NMR δ 1.62−1.80 (m, 12H), 2.40−2.56 (m, 16H), 2.76 (t, J = 5.8 Hz, 8H), 3.57−3.63 (m, 16H); ^{13}C NMR δ 23.1, 26.5, 53.6, 53.8 (2C), 54.2, 69.6, 70.3. Anal. Calcd for $C_{26}H_{52}N_4O_4$: C, 64.42; H, 10.81. Found: C, 64.09; H, 11.21.