Synthesis of New *N*-Pivot Lariat Crown Ethers Containing a Propylene Linkage in the Side Arm

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A series of new 15- and 18-membered *N*-pivot lariat aza-crown ethers having a propylene linkage in the side arm was prepared starting from functionalized diethanolamines and functionalized lariat aza-crown ethers containing the easily modified benzotriazole moiety. Addition reactions of such derivatives to electron-rich vinyl ethers or vinylamides followed by displacement of the benzotriazolyl group in the addition products by hydrogen (by reduction with $LiAlH_4$) gives a variety of *N*-(3-oxo-3-substituted)- and *N*-(3-aza-3-substituted)propylene side-armed derivatives of aza-crown ethers. Stability constants for the complexes of several synthesized lariats with metal cations are discussed.

Introduction

The intensive development of the lariat crown ether concept[1] led to the synthesis of hundreds of side-armed crown ethers, designed for uses ranging from routine (polymer-supported PTC catalysts, separation/extraction reagents, *etc.*) to sophisticated (applications as redox switches for membrane transport, synthetic cation-conducting channels, nucleotide-based molecular boxes, *etc.*).[2] The concept of mimicking the cation-binding behavior of naturally occurring ionophores, such as valinomycin, spurred efforts culminating in the syntheses of both *C*- and *N*-pivot lariat ethers.[3] The former proved to be the more rigid; inversion of the nitrogen atom at the *N*-pivot ethers allows more freedom for the side arm to effectively participate in coordination and leads to higher cation-binding affinities.[4] Another advantage of the *N*-pivot lariats is their easier synthetic accessibility, frequently based on chemical modification of the parent NH-containing azacrowns.[5] Investigations in the area of the synthesis and especially of applications of *N*-pivot lariat crown ethers are now expanding dramatically, as reflected by the continuously growing number of publications.

Several trends in the design of *N*-containing lariat ethers are based on structural and synthetic considerations. For example, for a side arm attached to a *N*-atom, molecular modeling predicted that an optimal distance for the interaction between a cation bound to the macrocyclic ring and a donor group covering a cation from the apical direction is three carbon atoms.[2] Indeed, various *N*-pivot aza-crown lariats containing benzyl side arms substituted by donor groups in the *o*-position of the phenyl ring have demonstrated improved complexing ability and selectivity[3,6−11] compared to the unsubstituted (benzyl) side arm. This phenomenon in the case of phenolic side-armed *N*-pivot crowns is satisfactorily explained by the "loose/normal/rigid ligand" approach,[7,8] based on CPK space-filling models: when an ideal 6-membered chelate ring is formed, the cation trapped in the crown cavity is effectively capped apically by the oxygen anion from the *o*-hydroxybenzyl side arm. In this most successful case, a "normal" 6-membered chelate is formed by the metal cation, one nitrogen, three carbon atoms (one of the methylene group and two of the phenyl ring), and one oxygen, while in two other cases, "loose" (7-membered ring) and "rigid" (5-membered ring), chelates have less than optimal geometries and correspondingly poorer selectivity and stability of their complexes. In the case when an ammonium cation is accommodated by the lariat *N*-pivot crown [*N*-(2-methoxyethyl)aza-18-crown-6], NH_4^+ binds to donor atoms of the ring by means of three discrete hydrogen bonds in a tetrahedral manner, but it is not capped from the apical direction by the side arm: the chain of two carbons and one oxygen is too short to allow such an interaction of the last N−H bond in the perpendicular direction.[3] Complete hydrogen bonding of the NH_4^+ cation was attained only when an extra oxyethylene unit was introduced into the side arm; with the 2′-(2-methoxyethoxy)ethyl substituent only the remote oxygen was involved in binding. These factors prompted us to design and synthesize a new series of *N*-pivot lariat crown ethers containing a *propylene* unit between the nitrogen atom of the ring and the side-arm donor.

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1996.

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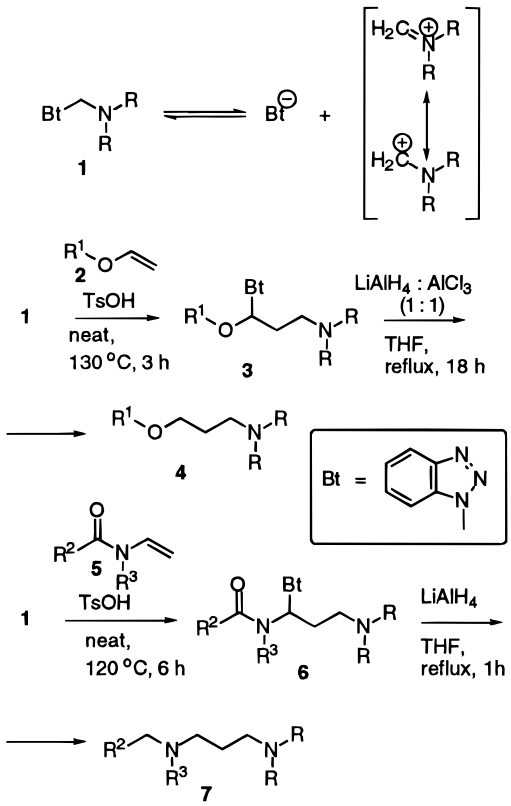
Results and Discussion

Surprisingly enough, this type of lariat crown ethers is not well-known from the literature: in the most complete recent reference[12] only a few such lariats are listed, mostly containing a hydroxy group at the central carbon atom of propylene bridge derived from epoxy-containing azacrowns.[13−15]

Methods for the preparation of *N*-pivot lariat aza-crowns can be divided into three main categories: (i) attachment of the side arm by chemical modification of an amino group of an aza-crown ether (*N*-alkylation, *N*-acylation, or Michael addition of olefins); (ii) cyclization of an *N*-substituted diethanolamine or *N*-substituted primary amine with α,ω-oligo(ethylene glycol) ditosylate, dimesylate, or dihalide, and (iii) Electrophilic substitution reactions of *N*-CH_2-A-containing azacrowns (where A stands for an activating group that leaves after the formation of a new bond). Method i seems to be more effective and simpler than the other two: from it, the yields of the lariat crowns are usually high and the reaction is not complicated by the formation of polymers or products of alternative cyclizations. However, method i is not universal because of the restricted availability of reagents used for modification. Method ii also requires the modification of diethanolamine at an early stage by the same procedures used for method i, *i.e.*, alkylation, acylation, or Michael addition need to be used to prepare the *N*-substituted diethanolamine, which then is reacted with an oligo(ethylene glycol) derivative to form a macrocycle; alternatively, a primary amine could be cyclized with an oligo(ethylene glycol) derivative to give a cyclic product by double alkylation of the amino group. As mentioned above, the choice of reagents for the alkylation of diethanolamine is limited, and such reactions usually require high-dilution techniques to avoid the formation of polycondensation products. Furthermore, the alkylation of diethanolamine required the use of inorganic bases, e.g., sodium carbonate, and it was difficult to remove residual salts, therefore making purification of *N*-alkylated diethanolamines difficult.[3] Cyclizations involving primary amines (method of Calverley and Dale[16]) are generally suitable only for small-sized macrocycles.[3] Method iii is mostly represented by the reactions of *N*-(methoxymethyl) derivatives of azacrowns with various CH or NH active compounds and can be considered a variation of the Mannich reaction; this method was developed by Luk'yanenko *et al.*[17,18]

Examination of the above methods demonstrates that they are not convenient for the preparation of *N*-pivot lariats with three carbon atoms between the ring and the side arm donor. Firstly, the analogs of 2-(halogen-substituted)ethyl alkyl ethers previously used for the preparation of *N*-pivot lariat azacrowns[3] by the methods

Scheme 1



i or ii, 3-(halogen-substituted)propyl alkyl ethers, are not readily available. 3-Aminopropanol was utilized[3] as a starting material in the synthesis of *N*-(3-hydroxypropyl)-aza-12-crown-4 according to the method of Calverley and Dale but was not used for the syntheses of larger macrocycles (15- or 18-membered rings). Finally, although Mannich reactions of *N*-(methoxymethyl) derivatives of azacrowns with phenols[10,11] lead to the formation of the above-mentioned three-carbon atom chain, this now includes two sp^2 aromatic ring carbon atoms, which diminishes the side-arm mobility.

We recently found that an addition of *N*-(benzotriazolylmethyl)-substituted secondary amines to electron-rich olefins (vinyl ethers[19] or vinyl amides[20]), catalyzed by Lewis acids, gives the corresponding Markovnikov-type products of addition of Bt^- and $R_2N^+{=}CH_2$ in almost quantitative yields. Furthermore, these products were successfully reduced in order to remove the benzotriazole moiety, forming 3-(amino-substituted)propyl alkyl ethers or variously substituted 1,3-diaminopropanes (Scheme 1) in quite high yields (65−94%).[19,20] We have now employed this synthetic pathway in the preparation of *N*-pivot lariat crowns containing propylene-bridging units in the side arm.

We anticipated that reactions of the Mannich-type adduct **1**, prepared directly from diethanolamine (**1a**, R = R^1 = CH_2CH_2OH), with ethers **2** or amides **5**, followed by reduction of the intermediate addition products, should access the desired building blocks with propylene linkages (**4**, **7**). We isolated the adduct **1a** as a solid in fair yield when 1-(hydroxymethyl)benzotriazole was reacted with diethanolamine in refluxing benzene for an

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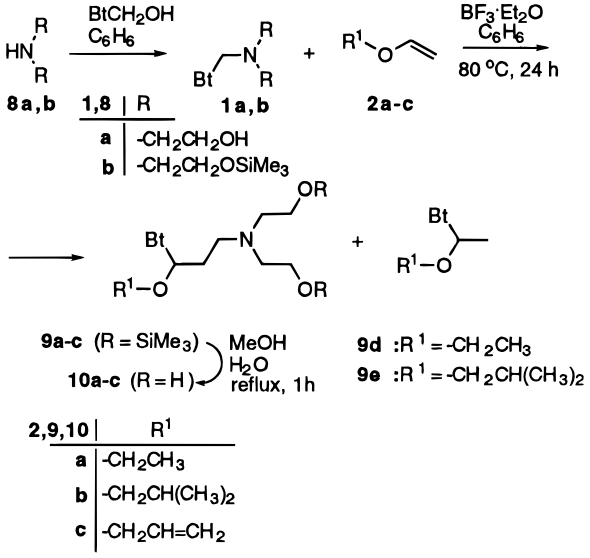
Scheme 2



extended reaction time. However, reaction of **1a** with vinyl ethers **2** (**2a**, R^2 = Et; **2b**, R^2 = *i*-Bu) failed because a competing side reaction prevailed—formation of 2-benzotriazolyl-3-oxa-5-methylhexane (**9d**) and 2-benzotriazolyl-3-oxapentane (**9e**), respectively (Scheme 2). This type of side product is generally formed in such reactions, as the NMR spectra of crude reaction products showed. Presumably, the presence of hydroxy groups in the structure of **1a** that easily release protons makes the side reaction dominant; *i.e.*, the more acidic the protons in the reaction components are, the more the side product is formed. We avoided the formation of such undesirable side products by preparing bis(*O*-silylated) diethanolamine **8b** in 91% yield from diethanolamine and hexamethyldisilazane, according to the general silylation method.[21] Subsequently, **8b** was condensed with 1-(hydroxymethyl)benzotriazole in benzene yielding the adduct **1b**, which after removal of solvent and without further purification reacted with vinyl ethers **2a**−**c** to afford α-benzotriazolyl-substituted *O*-silylated ethers **9a**−**c**. The crude addition products **9a**−**c** were conveniently hydrolyzed by methanol−water to the diols **10a**−**c** (Scheme 2).

Taking into account Scheme 1, two possible pathways to prepare *N*-pivot azacrowns were considered: first, reduction of diols **10a**−**c** (removal of benzotriazole moiety) followed by cyclization with oligo(ethylene glycol) ditosylates, and second, cyclization of derivatives **10a**−**c** followed by reduction of the preformed macrocycles. Reduction of the ether **10b** with $LiAlH_4$ was performed in refluxing THF for 2 days. However, we were unable to separate the amino ether thus formed from inorganics by extraction even after careful adjustment of pH of the reaction mixture. Therefore, we utilized the second pathway, *i.e.*, cyclization of the ethers **10a**−**c** with ditosylates **11a,b** by refluxing in THF containing a small excess of sodium hydride for 2 days (Scheme 3). We used ethers **10a**−**c** directly after isolation, without additional purification; their structures were confirmed by NMR spectra and by following transformations into macrocycles **12a**−**e**. Benzotriazole-containing macrocycles **12a**−**e**, which have alkyl propyl ethers as side arms, were isolated after column chromatography in yields of 50% and higher. The reaction rate is very slow: attempted

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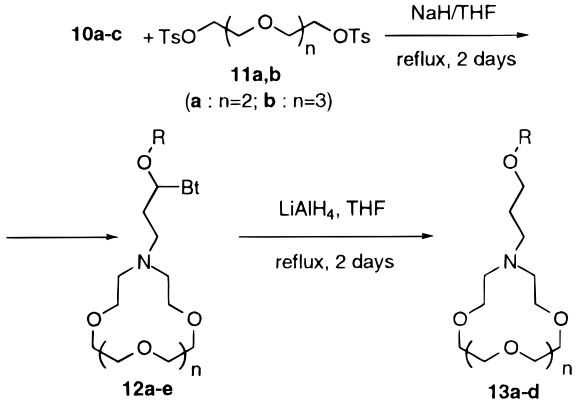
Scheme 3



12	n	R
a	2	-CH_2CH_3
b	3	-CH_2CH_3
c	2	-$CH_2CH(CH_3)_2$
d	3	-$CH_2CH(CH_3)_2$
e	2	-$CH_2CH{=}CH_2$

13	n	R
a	2	-CH_2CH_3
b	3	-CH_2CH_3
c	2	-$CH_2CH(CH_3)_2$
d	3	-$CH_2CH(CH_3)_2$

isolation of the macrocycles **12a**−**e** after 1 day of reflux led to the yields of target compounds of 28% (**12b**) to 40% (**12c**). Lariat ether **12e** was isolated only in 28% yield, presumably because of polymerization of allyl diol **10c** during cyclization upon action of high temperature. The conditions both in this reaction and in the following reduction could be optimized, and the yields improved. Our new preparation of these and the following lariat azacrowns is briefly summarized in Table 1.

Lariats **13a**−**d** were obtained after reduction of their precursors **12a**−**d** with $LiAlH_4$ in refluxing THF after 2 days. In contrast to reduction of **10b** (see above), the final crowns were easy to isolate after simple workup; they were purified by column chromatography followed by Kugelrohr distillation (100−150 °C/0.09 Torr).

Considering the growing interest in the biological activity of aza-crown ethers,[12] and also the fact that many 1,3-disubstituted diaminopropane derivatives possess well-known therapeutic properties,[22] we elaborated a new synthesis of *N*-pivot lariats containing a tertiary amino group at the end of the propylene side arm (Scheme 4). Addition of the protected diol **1b** to enamides **5a,b** led to the formation of benzotriazolyl-substituted amides **14a,b**; again, these were easily hydrolyzed to give deprotected products **15a,b** in excellent yields (90% and 98%, respectively). However, their attempted cyclization with ditosylates **11a,b** to afford macrocyclic lariat-amides **16a,b** failed: no appreciable amount of macrocycles **16a,b** was detected after 2 days of reflux of equimolar amounts of **15a,b** with either **11a** or **11b** in THF in the presence of NaH. Therefore, we considered another route for preparation of the macrocycles **16a,b** (Scheme 4). Modification of the method of Calverley and Dale,[16] which consisted of the replacement of acetonitrile used as a solvent in the previous method by much less polar toluene, gave the protected macrocycle **18a** in 86% yield. This modification may be useful in the preparation of the other lariat azacrowns, since it employs more accessible tosylates instead of iodides and toluene instead of acetonitrile. Subsequent removal of the protecting group by hydro-

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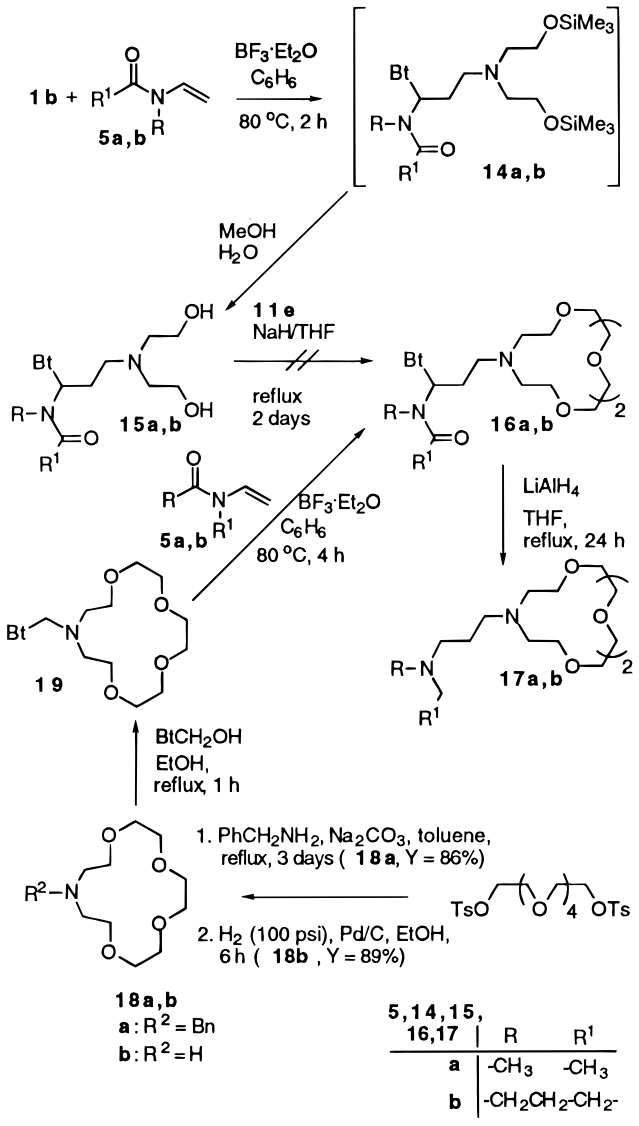
Table 1. New Preparations of Bracchial Lariat Ethers: Derivatives of 1-Aza-15-crown-5 (A) and 1-Aza-18-crown-6 (B)

side-arm structure	crown/yield[a] (%)	side-arm structure	crown/yield[a] (%)
$-(CH_2)_2CH(Bt)OCH_2CH_3$[b] (**12a**)	A/54	$-(CH_2)_3OCH_2CH(CH_3)_2$ (**13d**)	A/45
$-(CH_2)_2CH(Bt)OCH_2CH_3$[b] (**12b**)	B/50	$-CH_2Bt$[b] (**19**)	A/97
$-(CH_2)_2CH(Bt)OCH_2CH(CH_3)_2$[b] (**12c**)	A/56	$-(CH_2)_2CH(Bt)N(CH_3)COCH_3$[b] (**16a**)	A/75
$-(CH_2)_2CH(Bt)OCH_2CH(CH_3)_2$[b] (**12d**)	B/62	$-$[3-Bt-3-(2-oxopyrrolidin-1-yl)propyl][b] (**16b**)	A/81
$-(CH_2)_2CH(Bt)OCH_2CH{=}CH_2$[b] (**12e**)	A/28	$-(CH_2)_3N(CH_3)CH_2CH_3$ (**17a**)	A/52
$-(CH_2)_3OCH_2CH_3$ (**13a**)	A/40	$-$[3-(pyrrolidin-1-yl)propyl] (**17b**)	A/59
$-(CH_2)_3OCH_2CH_3$ (**13b**)	B/38		
$-(CH_2)_3OCH_2CH(CH_3)_2$ (**13c**)	A/45		

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

Scheme 4



genation, according to the procedure described earlier,[3] afforded aza-15-crown-5 **18b** in 89% yield (after column chromatography). 1-(Benzotriazolylmethyl)aza-15-crown-5 (**19**) was readily prepared in excellent yield from 1-(hydroxymethyl)benzotriazole and aza-15-crown-5 in EtOH; it was further reacted with enamides **5a,b** in the presence of $BF_3{\cdot}Et_2O$ in refluxing dry benzene. The corresponding macrocyclic amides **16a,b** were isolated and purified by column chromatography to give 75% and 81% of pure products, respectively. Their structures were confirmed by NMR and C,H,N analysis data. Reduction of the amides **16a,b** was completed in much shorter reaction time compared to the reduction of the benzotriazole-containing ethers **12a,b,d,e** and afforded the corresponding *N,N′*-bridged unsymmetrical diamines **17a,b** in good yields.

Table 2. Cation Complexation Constants for Bracchial Lariat Ethers

compd structure	log K_S[a] Na^+	log K_S[a] K^+	ref
18-crown-6	4.32	6.03	this work
18-crown-6	4.35	6.08	24
⟨18N⟩$CH_2CH_2CH_3$[b]	3.50	4.92	25
⟨18N⟩$CH_2CH{=}CH_2$	3.58	5.02	25
⟨18N⟩$CH_2CH_2OCH_3$	4.58	5.67	26
⟨18N⟩$CH_2CH_2CH_2OCH_2CH_3$ (**13b**)	3.67	4.56	this work
⟨18N⟩$CH_2CH_2CH(Bt)OCH_2CH_3$ (**12b**)	3.84	4.53	this work
⟨18N⟩$CH_2CH_2CH(Bt)OCH_2CH(CH_3)_2$ (**12d**)	3.59	4.57	this work
⟨18N⟩$CH_2CONHCH(s\text{-}Bu)COOCH_3$	4.03	5.10	27

[a] Measured in anhyd methanol at 25.0 ± 0.1 °C. [b] ⟨18N⟩ represents 1-aza-18-crown-6.

Complexation Study. Homogeneous sodium, potassium, calcium, and ammonium cation-binding constants (log K_S) have been reported for nearly 100 *N*-pivot lariat ethers having ring sizes that vary from 12- to 18-members. Cation-binding data (in anhyd methanol at 25.0 ± 0.1 °C) for several of the novel lariats reported herein are recorded in Table 2. Crown ethers are designated using an abbreviated form of the macroring.[23] The symbol ⟨00⟩ represents a crown ether having 00 members. Thus, 18-crown-6 can be abbreviated as ⟨18⟩. Azalariats having 18-membered rings and having side arms attached at nitrogen can be represented as R⟨N18⟩. In all cases recorded in Table 2, the lariat ether side arms are attached to nitrogen.

Sodium and potassium cation binding by macrocycles is favored by oxygen over nitrogen donors. Thus, replacement of O in 18-crown-6 by $NCH_2CH_2CH_3$ leads to a loss of binding strength of approximately 10-fold for both cations. This is true whether the side chain is saturated (*n*-propyl) or unsaturated (allyl). When the terminal methyl group of propyl is replaced by a methoxy group, the additional donor group boosts the Na^+ binding strength by 10-fold (3.58−4.58). The increase in K^+-binding was smaller (4.92−5.67) but still substantial.

When the oxygen donor atom is moved away from the ring by a single carbon, both Na^+ and K^+ binding

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(27) White, B. D.; Arnold, K. A.; Gokel, G. W. *Tetrahedron Lett.* **1987**, *28*, 1749.

decrease by essentially 10-fold. This is almost certainly a conformational effect since the *gauche* conformation of *XCCX* is lower in energy than the *gauche* conformation of *XCCCX*. Indeed, it is likely that the *X*−*C* and *C*−*C*−*X* bonds will prefer to be *trans* (*anti*). In the *anti* conformation, the heteroatoms do not organize into the required chelate. There may also be some steric hindrance associated with the ethoxy group compared to methoxy substituent in ⟨18N⟩CH_2CH_2OMe, although in the series ⟨18N⟩CH_2COOR, in which R = ethyl, *n*-decyl, or *n*-octadecyl, log K_S values for either Na^+ or K^+ vary by less than 0.1 log unit.

Steric hindrance almost certainly is a problem for the two novel lariats ⟨18N⟩CH_2CH_2CH(Bt)OEt (**12b**) and ⟨18N⟩CH_2CH_2CH(Bt)$OCH_2CH(CH_3)_2$ (**12e**), but only for the smaller Na^+ cation. Potassium binding strengths for these to compounds are essentially identical, suggesting that when the larger cation is ring-bound, the side arm and the associated ethyl or isobutyl group is too remote to affect the binding conformation. The steric crowding appears to exact a 2-fold price in the Na^+-binding case. These new compounds are also compared to the previously reported ⟨18N⟩$CH_2CONHCH$(*s*-Bu)$COOCH_3$, which possesses a *sec*-butyl group. This isoleucine (gly-ile) derivative probably uses the proximal carbonyl donor for binding, as found in the solid state structures of the two-armed gly-gly esters.[28]

An important difference between ⟨18N⟩$CH_2CONHCH$(*s*-Bu)$COOCH_3$ and **12e** is that the donor group in the former case is known to be an amide carbonyl, whereas in the present case either the ether oxygen or one of the benzotriazole nitrogen atoms may interact with the ring-bound cation. On the basis of donicities, it is presumed that *O* rather than *N* served as ligand, but this is not known with certainty. A weaker donor in a more favorable position may lead to a more stable complex than a stronger donor inappropriately positioned for interaction.

In conclusion, we have elaborated a new synthetic approach to the preparation of *N*-pivot lariat aza-crown ethers containing 3-oxo- and 3-azapropylene units in the side arm, which involves the addition reactions of Mannich-type benzotriazole derivatives of diethanolamine or of aza-crown ethers to vinyl ethers or vinylamides, with subsequent reduction of the benzotriazolyl substituent in the addition products.

Experimental Section

General. See refs 29 and 30. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz in $CDCl_3$. Cation-binding constants were measured according to the method of Frensdorff[31] as described recently in detail.[32] All the compounds containing a benzotriazole moiety that are described in the present paper consist of the mixture of benzotriazol-1-yl (Bt^1) and benzotriazol-2-yl (Bt^2) isomers in different ratios; both isomers readily undergo the transformations described here, and therefore, their isolation was not performed. The Experimental Section contains NMR data of the mixtures of Bt^1 and Bt^2 isomers, without their complete assignments. 1-(Hydroxymethyl)benzotriazole was prepared as previously described.[33]

Bis[2-(trimethylsiloxy)ethyl]amine (8b). The protected diethanolamine was prepared according to the general literature procedure[21] and was used without further purification. Colorless low-density liquid, yield 91%; ^{1}H NMR δ 3.65 (t, J = 5.4 Hz, 4H), 2.69 (t, J = 5.4 Hz, 4H), 0.07 (s, 18H); ^{13}C NMR δ 61.8, 51.5, −0.6. Anal. Calcd for $C_{10}H_{27}NO_2Si_2$: C, 48.13; H, 10.91; N, 5.62. Found: C, 47.83; H, 11.15; N, 5.53.

(Benzotriazolylmethyl)bis[2-(trimethylsiloxy)ethyl]amine (1b). A mixture of bis-[2-(trimethylsiloxy)ethyl]amine (**8b**) (2.5 g, 10.0 mmol) and 1-(hydroxymethyl)benzotriazole (1.59 g, 10.7 mmol) in benzene (50 mL) was refluxed for 24 h. The solvent was evaporated *in vacuo* to give 3.7 g (97%) of a colorless viscous oil: ^{1}H NMR δ 8.15 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.7, 6.2 Hz, 2H), 7.88 (d, J = 8.0 Hz, 1H), 7.59−7.42 (m, 2H + 1H), 5.74 (s, 2H), 3.80 (t, J = 5.6 Hz, 4H), 3.78 (t, J = 5.6 Hz, 4H), 3.07 (t, J = 5.6 Hz, 4H), 3.00 (t, J = 5.6 Hz, 4H), 0.21 (s, 18H); ^{13}C NMR δ 145.9, 144.2, 133.6, 127.1, 123.6, 119.6, 118.2, 110.5, 75.3, 68.2, 61.4, 61.0, 54.8, 54.6, −0.6. Anal. Calcd for $C_{17}H_{32}N_4O_2Si_2$: C, 53.64; H, 8.47. Found: C, 53.43; H, 8.45.

General Procedure for the Preparation of *N*-[3-Benzotriazolyl-4-oxa-4-(substituted)]-*N*,*N*-diethanolamines 10a−c. A mixture of amine **1b** (6 mmol), the corresponding vinyl ether **2a**−**c** (9 mmol), boron trifluoride etherate (2 drops), and dry benzene (50 mL) was stirred and heated at 80 °C for 24 h (a sealed tube was used in the case of **2a**). After cooling, benzene and unreacted vinyl ether **2** were removed under reduced pressure, the residue was dissolved in methanol (50 mL), and water was added until the solution became milky (approximately 3−5 mL). The obtained mixture was refluxed for 1.5 h, and then methanol was evaporated *in vacuo*. Water (50 mL) was added to the residue, which was extracted with ether (100 mL) and then with CH_2Cl_2 (100 mL). The combined organic extracts were washed with water and dried over anhyd $MgSO_4$. After solvent removal the diol **10** was obtained as a yellow viscous oil, which was used without further purification in the next step. The analytical samples of **10a**−**c** were obtained using column chromatography (eluent $CHCl_3$:methanol 20:1).

***N*-(3-Benzotriazolyl-4-oxahexyl)-*N*,*N*-diethanolamine (10a):** yellow oil; yield quantitative; ^{1}H NMR δ 8.08 (d, J = 8.3 Hz, 1H), 7.91 (dd, J = 3.1, 6.7 Hz, 2H), 7.80 (d, J = 8.3 Hz, 1H), 7.52−7.38 (m, 2H + 2H), 6.33 (t, J = 6.3 Hz, 1H), 6.17 (t, J = 6.3 Hz, 1H), 3.62−3.44 (m, 7H), 3.38−3.22 (m, 1H), 2.78−2.66 (m, 2H), 2.62−2.37 (m, 6H), 1.17 (t, J = 7.0 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 144.0, 127.6, 126.9, 124.3, 120.1, 118.5, 118.4, 111.1, 93.2, 88.7, 65.3, 64.6, 59.5, 59.4, 56.1, 55.9, 49.2, 32.9, 14.6.

***N*-(3-Benzotriazolyl-4-oxa-6-methylheptyl)-*N*,*N*-diethanolamine (10b):** dense yellow oil; yield quantitative; ^{1}H NMR δ 8.09 (d, J = 8.3 Hz, 1H), 7.92 (dd, J = 3.14, 6.7 Hz, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.52−7.38 (m, 2H + 2H), 6.28 (t, J = 6.4 Hz, 1H), 6.13 (dd, J = 5.3, 6.7 Hz, 1H), 3.60−3.43 (m, 6H), 3.32−3.25 (m, 1H), 3.03 (dd, J = 6.6, 9.1 Hz, 1H), 2.92 (dd, J = 6.9, 8.9 Hz, 1H), 2.80−2.60 (m, 2H), 2.60−2.38 (m, 4H + 2H), 1.90−1.75 (m, 1H), 0.92−0.77 (m, 6H); ^{13}C NMR δ 144.0, 127.6, 126.9, 125.6, 124.4, 120.1, 118.4, 115.0, 111.2, 93.7, 89.1, 76.5, 75.8, 59.6, 59.5, 56.1, 56.0, 50.1, 50.0, 49.4, 32.9, 32.5, 28.2, 28.1, 19.4, 19.2, 19.1, 19.0.

***N*-(3-Benzotriazolyl-4-oxahept-6-enyl)-*N*,*N*-diethanolamine (10c):** dense yellow oil; yield quantitative; ^{1}H NMR δ 8.07 (d, J = 8.3 Hz, 1H), 7.90 (dd, J = 3.1, 6.7 Hz, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.49 (t, J = 7.1 Hz, 1H), 7.47−7.37 (m, 1H + 2H), 6.37 (t, J = 6.4 Hz, 1H), 6.21 (t, J = 6.3 Hz, 1H), 5.86−5.72 (m, 1H), 5.32−5.13 (m, 2H), 4.01−3.78 (m, 2H), 3.70−3.45 (m, 6H), 2.78−2.48 (m, 6H), 2.36−2.24 (m, 1H); ^{13}C NMR δ 146.6, 144.0, 134.6, 132.6, 131.4, 127.7, 126.9, 124.4, 120.0, 118.5, 118.4, 111.1, 92.3, 87.8, 70.3, 69.7, 67.9, 61.4, 59.6, 59.5, 59.4, 58.8, 58.0, 57.4, 56.2, 56.0, 50.0, 35.0, 32.8, 32.4.

General Procedure for the Preparation of *N*-[3-(Benzotriazolyl)-4-oxa-4-(substituted)]aza-Crown Ethers 12a−

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e. A mixture of substituted diethanolamine **10a**−**c** (12 mmol) and the corresponding oligo(ethylene glycol)ditosylate **11a,b** (12 mmol) in dry THF (100 mL) was added dropwise to the refluxing and stirring suspension of NaH (0.8 g, 33 mmol) in dry THF (200 mL) under nitrogen. The reaction mixture was stirred and refluxed under nitrogen for 2 days, cooled, and quenched with water. The organic layer was separated, and the water fraction was extracted with ether (50 mL) and CH_2Cl_2 (50 mL). The combined organic layers were dried over anhyd $MgSO_4$. The solvents were evaporated *in vacuo*, and the oily residue was purified by column chromatography (eluent ethyl acetate:hexanes 1:3, followed by gradual replacement of hexanes with ethyl acetate).

13-(3-Benzotriazolyl-4-oxahexyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (12a): heavy yellow oil; yield 54%; ^{1}H NMR δ 8.07 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.48 (t, J = 7.1 Hz, 1H), 7.38 (t, J = 7.1 Hz, 1H), 6.26 (dd, J = 1.1, 6.0 Hz, 1H), 3.70−3.46 (m, 17H), 3.27 (dq, J = 7.0, 9.4 Hz, 1H), 2.71 (t, J = 6.0 Hz, 4H), 2.62−2.55 (m, 2H), 2.50−2.38 (m, 1H), 2.28−2.16 (m, 1H), 1.13 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 146.6, 131.6, 127.3, 124.0, 119.9, 111.2, 88.4, 71.0, 70.5, 70.1, 70.0, 64.5, 54.8, 51.8, 33.1, 14.7. Anal. Calcd for $C_{21}H_{34}N_4O_5$: N, 13.26. Found: N, 13.68.

16-(3-Benzotriazolyl-4-oxahexyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (12b): dense yellow oil; yield 50%; ^{1}H NMR δ 8.07 (d, J = 8.3 Hz, 1H), 7.90 (dd, J = 3.1, 6.7 Hz, 2H), 7.80 (d, J = 8.3 Hz, 1H), 7.48 (t, J = 7.1 Hz, 1H), 7.43−7.35 (m, 2H + 1H), 6.25 (d, J = 6.4 Hz, 1H), 6.08 (t, J = 6.4 Hz, 1H), 3.70−3.50 (m, 20H), 3.40−3.24 (m, 2H), 2.80−2.70 (m, 4H), 2.64−2.56 (m, 2H), 2.52−2.20 (m, 2H), 1.15 (dt, J = 7.0, 8.8 Hz, 3H); ^{13}C NMR δ 146.5, 144.0, 131.5, 127.2, 126.5, 124.0, 119.9, 118.5, 111.2, 93.3, 88.5, 70.7, 70.6, 70.2, 69.7, 69.6, 65.1, 64.4, 54.1, 50.8, 33.1, 32.7, 14.7, 14.6. Anal. Calcd for $C_{23}H_{38}N_4O_6$: N, 12.01. Found: N, 12.31.

13-(3-Benzotriazolyl-4-oxa-6-methylheptyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (12c): heavy yellow oil; yield 56%; ^{1}H NMR δ 8.07 (d, J = 8.3 Hz, 1H), 7.90 (dd, J = 3.1, 6.7 Hz, 2H), 7.78 (d, J = 8.3 Hz, 1H), 7.47 (dt, J = 1.0, 7.0 Hz, 1H); 7.42−7.35 (m, 1H), 6.22 (dd, J = 1.6, 5.8 Hz, 1H), 6.04 (m, 1H), 3.70−3.56 (m, 16H), 3.26 (dd, J = 6.4, 9.0 Hz, 1H), 2.94 (dd, J = 6.4, 9.0 Hz, 1H), 2.72 (t, J = 6.0 Hz, 4H), 2.60 (t, J = 6.7 Hz, 2H), 2.50−2.40 (m, 1H), 2.30−2.15 (m, 1H), 1.87−1.73 (m, 1H), 0.83 (d, J = 6.7 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 146.7, 131.5, 127.2, 124.0, 119.9, 111.3, 88.9, 75.6, 71.0, 70.5, 70.1, 70.0, 54.8, 51.9, 33.1, 28.2, 19.2. Anal. Calcd for $C_{23}H_{38}N_4O_5$: N, 12.44. Found: 12.45.

16-(3-Benzotriazolyl-4-oxa-6-methylheptyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (12d): dense yellow oil; yield 62%; ^{1}H NMR δ 8.07 (d, J = 8.3 Hz, 1H), 7.90 (dd, J = 3.1, 6.7 Hz, 2H), 7.78 (d, J = 8.3 Hz, 1H), 7.50−7.35 (m, 4H), 6.20 (dd, J = 1.1, 6.0 Hz, 1H), 6.02 (t, J = 6.4 Hz, 1H), 3.70−3.54 (m, 20H), 3.31−3.23 (m, 2H), 3.08 (dd, J = 2.7, 6.4 Hz, 1H), 2.93 (dd, J = 2.2, 6.7 Hz, 1H), 2.77−2.71 (m, 4H), 2.62−2.57 (m, 2H), 2.50−2.20 (m, 2H), 1.85−1.78 (m, 1H), 0.89−0.77 (m, 6H); ^{13}C NMR δ 144.1, 127.2, 126.5, 124.1, 120.0, 118.5, 111.3, 93.7, 89.0, 70.8, 70.7, 70.4, 69.9, 69.8, 54.1, 51.1, 50.8, 33.3, 28.2, 19.2, 19.1, 19.0; HRMS calcd for $C_{25}H_{43}N_4O_6$ 495.3182 (M^+ + 1), found 495.3180.

13-[3-(Benzotriazol-2-yl)-4-oxa-hept-6-enyl]-1,4,7,10-tetraoxa-13-azacyclopentadecane (12e): yellow oil; yield 28%; ^{1}H NMR δ 7.90 (dd, J = 3.1, 6.7 Hz, 2H), 7.40 (dd, J = 3.1, 6.7 Hz, 2H), 6.13 (t, J = 6.4 Hz, 1H), 5.89−5.75 (m, 1H), 5.25 (ddd, J = 1.5, 2.8, 17.2 Hz, 1H, *cis*-CH_2=CH−), 5.15 (ddd, J = 1.5, 2.8, 10.3 Hz, 1H, *trans*-CH_2=CH−), 4.03−3.89 (m, 2H), 3.69−3.56 (m, 16H), 2.73 (t, J = 5.8 Hz, 4H), 2.65−2.35 (m, 4H); ^{13}C NMR δ 144.1, 132.9, 126.6, 118.5, 118.1, 92.5, 71.0, 70.5, 70.3, 70.1, 70.0, 54.7, 51.5, 33.4. Anal. Calcd for $C_{22}H_{34}N_4O_5$: C, 60.81; H, 7.89; N, 12.89. Found: C, 60.46; H, 8.14; N, 13.31.

General Procedure for the Reduction of Benzotriazole-Containing Lariat Aza-Crowns 12. A solution of $LiAlH_4$ in THF (5 mmol, 5 mL of a 1 M solution) was added in one portion to the solution of the corresponding benzotriazole-containing lariat aza-crown **12** (2.5 mmol) in dry THF (100 mL) under nitrogen at room temperature, and the resulting solution was refluxed for 2 days. The reaction mixture was cooled, and the excess $LiAlH_4$ was carefully quenched with water. The suspension obtained was treated with 5 mL of a 1 N aqueous solution of NaOH and then with 5 mL of water. The white sticky precipitate was filtered off and washed with water (10 mL) and THF (10 mL). The filtrate was extracted with ether (2 × 30 mL) and CH_2Cl_2 (30 mL), and the organic layers were separated and dried over anhyd. $MgSO_4$. The solvents were removed *in vacuo*, and the residual oily reaction products were purified by column chromatography (eluent ethyl acetate:hexanes 1:3, followed by gradual replacement of hexanes with ethyl acetate) and then by distillation (Kugelrohr apparatus, 100−150 °C/0.09 Torr) to give lariats **13a,b** as viscous pale-yellow liquids.

13-(4-Oxahexyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (13a): viscous yellow oil; yield 40%; ^{1}H NMR δ 3.70−3.62 (m, 16H), 3.45 (q, J = 7.0 Hz, 2H), 3.44 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 6.1 Hz, 4H), 2.59 (t, J = 7.4 Hz, 2H), 1.73 (quintet, J = 7.5 Hz, 2H), 1.19 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 70.9, 70.4, 70.1, 70.0, 68.7, 66.0, 54.6, 53.6, 27.7, 15.2; HRMS calcd for $C_{15}H_{31}NO_5$ 305.2202 (M^+), found 305.2196.

16-(4-Oxahexyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (13b): viscous yellow oil; yield 38%; ^{1}H NMR δ 3.70−3.59 (m, 20H), 3.45 (q, J = 7.0 Hz, 2H), 3.44 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 6.0 Hz, 4H), 2.59 (t, J = 7.4 Hz, 2H), 1.72 (quintet, J = 7.5 Hz, 2H), 1.19 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 70.8, 70.7 (2C), 70.3, 69.9, 68.6, 65.9, 54.0, 52.6, 27.5, 15.1; HRMS calcd for $C_{17}H_{36}NO_6$ 350.2542 (M^+ + 1), found 350.2540.

13-(4-Oxa-6-methylheptyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (13c): viscous yellow oil; yield 45%; ^{1}H NMR δ 3.69−3.61 (m, 16H), 3.42 (t, J = 6.5 Hz, 2H), 3.15 (d, J = 6.7 Hz, 2H), 2.75 (t, J = 6.0 Hz, 4H), 2.60 (t, J = 7.3 Hz, 2H), 1.92−1.78 (m, 1H), 1.78−1.67 (m, 2H), 0.89 (d, J = 6.7 Hz, 6H); ^{13}C NMR δ 77.7, 70.9, 70.4, 70.0, 68.9, 54.5, 53.5, 28.3, 27.6, 19.3. Anal. Calcd for $C_{17}H_{35}NO_5$: N, 4.20. Found: N, 4.60.

16-(4-Oxa-6-methylheptyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (13d): viscous yellow oil; yield 45%; ^{1}H NMR δ 3.98−3.59 (m, 20H), 3.43 (t, J = 6.4 Hz, 2H), 3.15 (d, J = 6.7 Hz, 2H), 2.76 (t, J = 6.0 Hz, 4H), 2.59 (t, J = 7.1 Hz, 2H), 1.92−1.78 (m, 1H), 1.78−1.67 (m, 2H), 0.89 (d, J = 6.7 Hz, 6H); ^{13}C NMR δ 77.7, 70.8, 70.7, 70.3, 69.9, 68.9, 54.0, 52.6, 28.3, 27.4, 19.3; HRMS calcd for $C_{19}H_{39}NO_6$ 377.2777 (M^+), found 377.2781.

13-Benzyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (18a). A solution of penta(ethylene glycol)ditosylate (5.00 g, 9 mmol) in toluene (75 mL) and a solution of benzylamine (0.98 g, 9 mmol) in toluene (75 mL) were slowly and simultaneously added from two dropping funnels to the vigorously stirred suspension of anhyd sodium carbonate (4.80 g, 45 mmol) in toluene (250 mL). The mixture was refluxed and stirred for 3 days. The suspension formed was cooled, solids were filtered off, and methanol (35 mL) was added to the filtrate. A solution was heated at 50 °C for 30 min, cooled, and then concentrated *in vacuo* to give the light yellow oil, which was purified by column chromatography (eluent ethyl acetate:hexanes 1:1). Yield of *N*-benzyl-protected crown **18a**: 86%. The ^{1}H NMR spectrum of the isolated crown was consistent with previously published data.[3]

1,4,7,10-Tetraoxa-13-azacyclopentadecane (18b). Hydrogenation and purification of 13-benzyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (**18a**) was carried out in accordance with the method described in literature.[3] Yield of aza-crown **18b**: 89%. The ^{1}H NMR spectrum of the isolated crown was consistent with previously published data.[3]

13-(Benzotriazolylmethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (19). A solution of the aza-crown **18b** (0.50 g, 2.3 mmol) and 1-(hydroxymethyl)benzotriazole (0.34 g, 2.3 mmol) in ethanol (25mL) was stirred under reflux for 1 h. The solvent was evaporated *in vacuo*, and the resulting colorless oil was dried on a vacuum line for 48 h: viscous oil; yield 97%; ^{1}H NMR δ 8.03 (d, J = 7.8 Hz, 1H), 7.84 (dd, J = 2.6 and 6.5 Hz, 2H), 7.70 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.42−7.32 (m, 2H + 1H), 5.66 (s, 1H), 5.61 (s, 1H), 3.72−3.62 (m, 16H), 3.04 (t, J = 5.1 Hz, 4H), 2.98 (t, J = 5.1 Hz, 4H); ^{13}C NMR δ 145.7, 144.1, 133.5, 127.2, 126.0, 123.6, 119.6, 118.1,

110.1, 75.7, 70.8, 70.2, 70.1, 69.6, 69.5, 68.2, 52.7, 52.4; HRMS calcd for $C_{17}H_{37}N_4O_4$ 351.2032 ($M^+ + 1$), found 351.2033.

General Procedure for the Preparation of Benzotriazole-Containing Lariat Aza-Crowns 16. To a stirred solution of 13-(benzotriazolylmethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**19**) (0.62 g, 1.77 mmol) and the corresponding vinylamide **5a** or **5b** (3 mmol) in dry benzene (50 mL) was added BF_3−etherate (1 drop) at rt, and the reaction mixture was refluxed for 4 h. After cooling, the solvent was removed *in vacuo*, and the residue was triturated with MeOH (10 mL) for 30 min. Methanol was evaporated under reduced pressure, and the resulting yellow oil was dissolved in CH_2Cl_2, washed with water, and dried over anhyd $MgSO_4$. The solvent was evaporated, and the crude product was purified by column chromatography (eluent ethyl acetate:hexanes 1:1, then $CHCl_3$:MeOH 20:1) to give amide **16** as a yellow oil.

13-(3-Benzotriazolyl-4-aza-4-methyl-5-oxohexyl)-1,4,7,-10-tetraoxa-13-azacyclopentadecane (16a): yield 75%; ^{1}H NMR δ 8.04 (d, J = 8.3 Hz, 1H), 7.85 (t, J = 3.0 Hz, 2H), 7.83 (d, J = 8.3 Hz, 1H), 7.60−7.53 (dd, J = 6.0, 8.6 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.45−7.35 (m, 1H + 2H), 3.70−3.46 (m, 16H), 3.01 (s, 3H), 2.95 (s, 3H), 2.80−2.40 (m, 8H), 2.14 (s, 3H), 2.10 (s, 3H); ^{13}C NMR 171.2, 145.5, 143.9, 133.0, 127.6, 126.6, 126.5, 124.2, 119.4, 118.3, 110.9, 71.0, 70.8, 70.6, 70.4, 70.2, 70.0, 69.9, 62.4, 55.1, 54.7, 52.2, 30.0, 28.9, 22.1, 22.0; HRMS calcd for $C_{22}H_{36}N_5O_5$ 450.2716 ($M^+ + 1$), found 450.2725.

13-[3-Benzotriazolyl-3-(2-oxopyrrolidin-1-yl)propyl]-1,4,7,10-tetraoxa-13-azacyclopentadecane (16b): yield 81%; ^{1}H NMR δ 8.04 (d, J = 8.3 Hz, 1H), 7.91−7.85 (m, 1H + 2H), 7.50 (t, J = 7.1 Hz, 1H), 7.40−7.35 (m, 1H + 2H), 7.09−7.03 (m, 1H), 3.70−3.42 (m, 16H + 2H), 3.30−3.20 (m, 1H), 2.96−2.82 (m, 1H), 2.80−2.58 (m, 5H), 2.56−2.38 (m, 3H), 2.36−2.20 (m, 1H), 2.10−1.96 (m, 1H), 1.96−1.80 (m, 1H); ^{13}C NMR δ 175.1, 145.5, 132.9, 127.6, 126.5, 124.2, 119.3, 118.4, 110.7, 70.9, 70.3, 70.0, 69.95, 69.9, 61.1, 54.7, 52.0, 42.4, 30.7, 29.1, 17.7; HRMS calcd for $C_{23}H_{36}N_5O_5$ 462.2716 ($M^+ + 1$), found 462.2723.

Reduction of Benzotriazole-Containing Lariat Aza-Crowns 16. Reduction of the lariats **16a,b** and isolation of the reaction products were carried out according to the above procedure for the lariats **12**. However, amido-lariats **16** were reduced completely after 24 h of reflux with $LiAlH_4$ in THF to give amino-substituted lariat azacrowns **17a,b**.

13-(4-Methyl-4-azahexyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (17a): yellow oil; yield 52%; ^{1}H NMR δ 3.70−3.60 (m, 16H), 2.75 (t, J = 6.1 Hz, 4 H), 2.52 (t, J = 7.4 Hz, 2H), 2.52 (t, J = 7.4 Hz, 2H), 2.41 (q, J = 7.2 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.21 (s, 3H), 1.70−1.62 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 70.9, 70.6, 70.3, 70.0, 69.9, 55.1, 54.9, 54.5, 51.3, 41.5, 25.1, 12.1. Anal. Calcd for $C_{16}H_{34}N_2O_4$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.36; H, 10.94; N, 8.72.

13-[3-(Pyrrolidin-1-yl)propyl]-1,4,7,10-tetraoxa-13-azacyclopentadecane (17b): yellow oil; yield 59%; ^{1}H NMR δ 3.69−3.62 (m, 16H), 2.76 (t, J = 6.1 Hz, 4H), 2.58−2.40 (m, 8H), 1.80−1.68 (m, 6H). ^{13}C NMR δ 70.9, 70.4, 70.1 (2C), 55.1, 54.5 (2C), 54.2, 27.0, 23.4. Anal. Calcd for $C_{17}H_{34}N_2O_4$: C, 61.79; H, 10.37; N, 8.48. Found: C, 61.51; H, 10.49; N, 8.76.

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