Synthesis and *N*-Alkylation of 5-Bromomethyl-5-methyl-1,4,7,10-tetraoxa-13-azacyclopentadecane

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5-Bromomethyl-5-methyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (monoaza-15-crown-5) was prepared by the reaction of 4-bromomethyl-4-methyl-1,8-ditosyloxy-3,6-dioxaoctane, prepared from the corresponding dihydroxy compound, by reaction with bis(2-hydroxyethyl)amine under basic conditions in 37% yield, without protection of the reactive bromomethyl and amino groups. The product, monoaza-15-crown-5, can be *N*-alkylated in 42–70% with alkyl halide/sodium carbonate in dioxane.

Lariat ethers, crown ether derivatives with an electron-donating side arm, show interesting complexation properties for a variety of guest compounds based on the secondary coordination of the side arm.[1–5] The introduction of an electron-donating side arm to monoazacrown ethers (*N*-pivot lariat ethers) remarkably increased their complexing ability toward alkali metal cations.[6,7] In the molecular design of *C*-pivot lariat ethers, a methyl group at the pivot position was found to play an important role in regulating their selectivity toward sodium and potassium cations.[8–10] The complexation properties toward cations were remarkably improved by attaching plural electron-donating side arms to crown ethers[11] and diazacrown ethers.[12] Accordingly, monoazacrown ethers having two side arms on the nitrogen and carbon atoms, which participate in coordination, are expected to have excellent complexation properties. We now describe a facile synthetic method for the preparation of 5-bromomethyl-5-methyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (**4**), a key reactive intermediate, and its modification to new host compounds. Compound **4** is also a potentially important intermediate in the design of highly functionalized crown ethers such as cryptands,[13] synthetic ionophores,[14,15] and crown polymers.[16]

The synthesis starts with the preparation of 1,8-dihydroxy-4-bromomethyl-4-methyl-3,6-dioxaoctane (**2**) by bromoalkoxylation of ethylene glycol mono-2-methylallyl ether (**1**) with *N*-bromosuccinimide (NBS) and ethylene glycol in 40% yield. Compound **2** was easily converted to the corresponding di-*p*-toluenesulfonate **3** in 92% yield by a conventional procedure.[17] The key step of our synthetic strategy is the cyclization process, which was reported by us earlier for the preparation of unsubstituted monoazacrown ethers.[18,19] The reaction of **3** with bis(2-hydroxyethyl)amine under basic conditions gave **4** in 37% yield without the use of protecting groups for both the reactive amino and bromo groups. The presence of a methyl group at the quaternary carbon prevents an undesirable elimination reaction which may occur under basic conditions. The low reactivity of the bromomethyl group of **4** makes possible the selective alkylation at the nitrogen atom if proper reaction conditions are chosen. For example, the reaction of **4** with

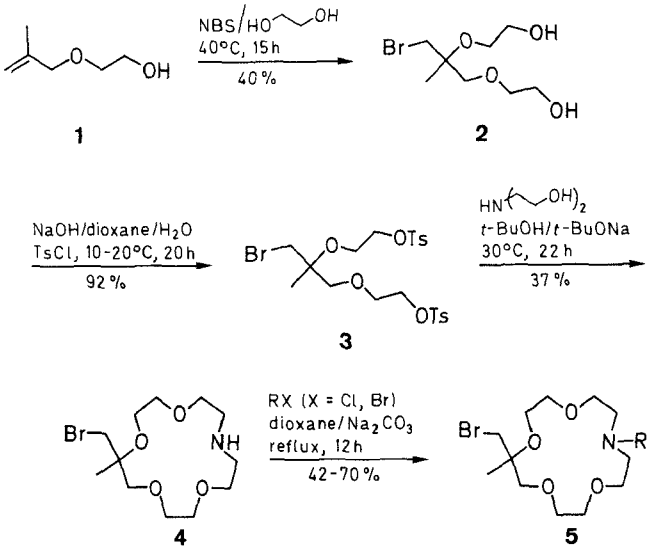

Table. Monoaza-15-crown-5 Derivatives **5** Prepared

Product	R	Yield[a] (%)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS (70 eV) *m/z* (%)
5a	CH_3	30[c]	$C_{13}H_{26}BrNO_4$ (340.3)	1.26 (s, 3H), 2.33 (s, 3H), 2.62–2.73 (m, 4H), 3.50–3.73 (m, 16H)	339 (M^+, 3), 260 (73), 44 (100)
5b	n-C_8H_{17}	70[d]	$C_{20}H_{40}BrNO_4$ (438.5)	0.88 (t, 3H, J = 6.8), 1.19–1.48 (m, 15H), 2.42–2.58 (m, 2H), 2.62–2.78 (m, 4H), 3.36–3.76 (m, 16H)	438 (M^+ + 1, 100)[e]
5c	n-$C_8H_{17}OCH_2CH_2$	67	$C_{22}H_{44}BrNO_5$ (482.5)	0.88 (t, 3H, J = 6.8), 1.19–1.56 (m, 15H), 2.72–2.92 (m, 6H), 3.48–3.71 (m, 20H)	481 (M^+, 1.5), 338 (100)
5d	n-$C_8H_{17}(OCH_2CH_2)_2$	47	$C_{24}H_{48}BrNO_6$ (526.6)	0.88 (t, 3H, J = 6.8), 1.19–1.62 (m, 15H), 2.72–2.92 (m, 6H), 3.42–3.71 (m, 24H)	526 (M^+ + 1, 100)[e]
5e	n-$C_8H_{17}(OCH_2CH_2)_3$	42	$C_{26}H_{52}BrNO_7$ (570.6)	0.88 (t, 3H, J = 6.8), 1.24–1.61 (m, 15H), 2.76–2.86 (m, 6H), 3.40–3.83 (m, 28H)	570 (M^+ + 1, 100)[e]

[a] Yield of pure isolated product.

[b] Satisfactory microanalyses obtained C ±0.40, H ±0.18, N ±0.25.

[c] Cyclization yield from **3** and methylbis(2-hydroxyethyl)amine.

[d] Octyl bromide was used.

[e] FAB-MS.

alkyl chloride was carried out in dioxane in the presence of sodium carbonate to give **5** having a reactive bromomethyl group (Table). Compound **5** can be easily modified under the basic conditions successfully used for the synthesis of methyl-substituted lariat ethers.[10]

^{1}H-NMR spectra were recorded on a JEOL JNM-GSX 400 spectrometer and mass spectra were obtained on a JEOL JMS-DX 303 HF spectrometer.

4-Bromomethyl-4-methyl-1,8-ditosyloxy-3,6-dioxaoctane (3):
To a stirred suspension of ethylene glycol (186.21 g, 3 mol) and NBS (53.40 g, 0.3 mol) is added ethylene glycol mono-2-methylallyl ether (**1**; 34.85 g, 0.3 mol) over a period of 40 min and the mixture is stirred for another 15 h at 40 °C. Excess ethylene glycol is removed and the residue is then dissolved in Et_2O. The precipitated succinimide is removed by filtration and the filtrate is purified on a silica gel column (acetone/CH_2Cl_2, 15:85) to give compound **2** as a colorless viscous oil; yield: 32.87 g (40%). This compound is used without further purification in the next step. To a stirred solution of **2** (16.33 g, 0.06 mol) and NaOH (8.40 g, 0.21 mol) in a mixture of dioxane (40 mL) and water (40 mL) is added tosyl chloride (34.32 g, 0.18 mol) in dioxane (40 mL) over a period of 2.5 h keeping the temperature below 10 °C by occasional cooling. The mixture is stirred for another 17 h at r.t. Water (50 mL) is added to the mixture and the product is extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers are dried ($MgSO_4$), and concentrated. The crude product is purified on a silica gel column (dioxane/benzene, 10:90) to give **3** as a colorless viscous oil; yield: 31.15 g (92%).

$C_{22}H_{29}BrO_8S_2$	calc.	C 46.73	H 5.17	
(566.5)	found	47.00	5.22	

IR (neat): ν = 2900, 1600, 1450, 1360, 1180, 1100, 1020, 920, 820, 780 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.17 (s, 3 H), 2.44 (s, 6 H), 3.50–4.22 (m, 12 H), 7.31–7.83 (m, 8 H).

5-Bromomethyl-5-methyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (4):
Bis(2-hydroxyethyl)amine (8.41 g, 0.04 mol) and sodium metal (3.86 g, 0.168 mol) is dissolved in *tert*-butyl alcohol (1000 mL). To this solution is added **3** (22.62 g, 0.04 mol) in a mixture of *tert*-butyl alcohol (45 mL) and dioxane (20 mL) over a period of 4 h at 30 °C. The mixture is then stirred for another 14 h at that temperature. After the solvent is evaporated, water (50 mL) is added to the residue. The mixture is washed with hexane (20 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The organic layer is concentrated and distilled in a Kugelrohr apparatus to give **4** as a slightly yellow oil; yield: 4.84 g (37%); boiling range 110–120 °C/0.07 Torr.

$C_{12}H_{24}BrNO_4$	calc.	C 44.18	H 7.42	N 4.29
(326.4)	found	44.46	7.42	4.54

IR (neat): ν = 2900, 1650, 1460, 1350, 1300, 1250, 1100, 960 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.28 (s, 3 H), 2.78–2.85 (m, 5 H), 3.44–3.74 (m, 16 H).

MS (DEI) m/z = 325 (M^+, 2), 100 (100).

5-Bromomethyl-5-methyl-13-[2-(octyloxy)ethyl]-1,4,7,10-tetraoxa-13-azacyclopentadecane (5c); Typical Procedure:
A mixture of 1-chloro-3-oxaundecane (0.93 g, 4.8 mmol), **4** (1.31 g, 4.0 mmol), and Na_2CO_3 (0.64 g, 6.0 mmol) in dioxane (3 mL) is stirred at 100 °C for 12 h. Insoluble matter is removed by filtration. Water (30 mL) is added to the mixture and the product is extracted with CH_2Cl_2 (2 × 30 mL). The organic layer is concentrated and distilled in a Kugelrohr apparatus to give **5c** as a slightly yellow oil; yield 1.29 g (67%); boiling range 140–150 °C/0.07 Torr (Table).

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