Synthesis of formyl derivatives of benzocrown ethers containing N, S, and O heteroatoms in the macrocycle

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A method for the synthesis of 4′-bromobenzodithia-15(18)-crown-5(6) and 4′-bromobenzodiaza-15(18)-crown-5(6) by condensation of 3,4-di(2′-haloethoxy)bromobenzene with polyoxaalkanes containing terminal SH or NHMe groups was suggested. The method for the synthesis of formyl derivatives of benzocrowns containing N, S, and O heteroatoms in the macrocycle based on the metallation of appropriate bromo derivatives with Bu^nLi followed by treatment of the resulting organolithium intermediates with DMF was developed. Oximes and semicarbazones of benzaldehydes containing a crown ether fragment were obtained, and their transformation into the original aldehydes by treatment with KNO_2 in an acid medium was studied.

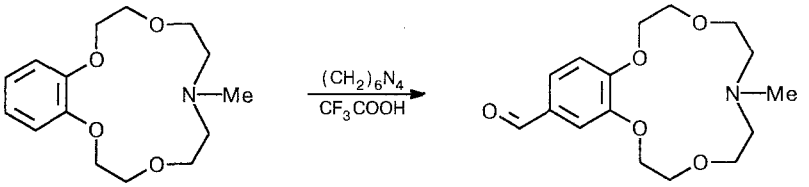
Key words: 4′-bromobenzocrowns, synthesis, metallation; 4′-formylbenzocrown ethers; semicarbazones and oximes of 4′-formylbenzocrown ethers.

The formyl derivatives of benzocrown ethers are widely used in syntheses of various crown-containing compounds,[1,2] including crown-containing styryl dyes.[3] The oximes of formyl derivatives of benzocrown ethers possess pharmacological activity.[4] Two approaches to the synthesis of crown-containing benzaldehydes are known. The first one, which is based on electrophilic formylation of crown ethers, has been used for obtaining formyl derivatives of oxygen-containing benzocrown ethers under the conditions of the Vilsmeier reaction.[5] Another method is a formylation according to Duff.[1,2,6] The second approach based on the reaction of organolithium derivatives of crown ethers with DMF,[7] has been implemented only in the synthesis of the formyl derivative of 1,3-xylyl-18-crown-5.

However, attempts to use the Vilsmeier or Duff reactions for obtaining formyl derivatives of benzodithia-15(18)-crown-5(6) and *N,N′*-dimethylbenzodiaza-15(18)-crown-5(6) failed. Probably due to interaction with electrophiles, two electron-donating N or S atoms in the crown ether macrocycle form cationic centers. As a result, deactivation of the aromatic ring toward electrophilic substitution occurs. In addition, strong resinification occurs in the case of benzodithiacrown ethers, which is probably related to destruction of the macrocycle. Preliminary transformation of these compounds into sulfoxides also does not provide the desired result.

If the macrocycle contains an N atom remote from the aromatic ring, formylation is not hindered. For example, we managed to introduce a formyl group into *N*-methylbenzoaza-15-crown-5 (**1**) in 30 % yield using the Duff reaction by a procedure proposed previously[2] for the formylation of compounds of similar structure (Scheme 1).

Scheme 1



1 **2**

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Table 1. Characteristics of the synthesized compounds **2, 5, 6, 8, 10, 12, 14—16**

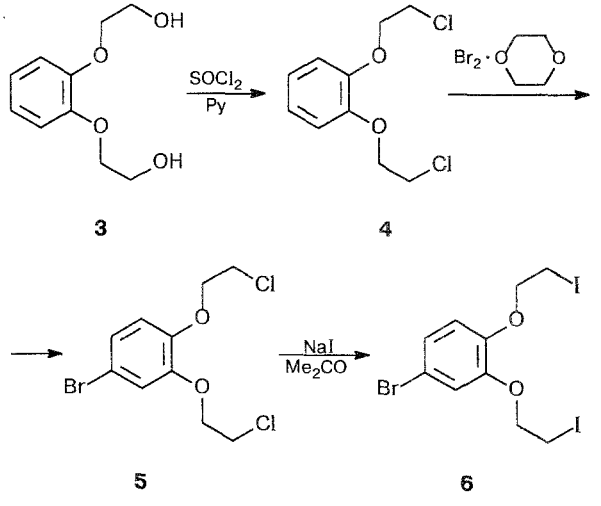
Compound[a]	M.p./°C (from a benzene—MeOH mixture)	Yield (%)[b]	Found / Calculated (%) C	H	N	Molecular formula
2	84—85[c]	30	62.28 62.12	7.65 7.49	4.34 4.53	$C_{16}H_{23}NO_5$
5	61—62	96	38.39 38.25	3.47 3.53	—	$C_{10}H_{11}BrCl_2O_2$
6	79—80	89	24.02 24.17	2.17 2.23	—	$C_{10}H_{11}BrI_2O_2$
8a	81—82	56	44.29 44.33	5.03 5.05	—	$C_{14}H_{19}BrO_3S_2$
8b	118—119	75	45.20 45.39	5.58 5.48	—	$C_{16}H_{23}BrO_4S_2$
10a	Oil	64				$C_{16}H_{25}BrN_2O_3$
10b	Oil	50				$C_{18}H_{29}BrN_2O_4$
12	104—108	9	45.13 45.39	5.60 5.48	—	$C_{32}H_{46}Br_2O_8S_4$
14c	121—122	74	55.20 54.85	6.13 6.14	—	$C_{15}H_{20}O_4S_2$
14d	131—132	70	54.89 54.82	6.54 6.49	—	$C_{17}H_{24}O_5S_2$
14f	Oil	95[f]				$C_{19}H_{30}N_2O_5$
16a	142—143	92	54.43 54.38	6.55 6.56	11.38 11.89	$C_{16}H_{23}N_3O_6$
16b	147—148	93	54.39 54.40	6.92 6.85	10.40 10.57	$C_{18}H_{27}N_3O_7$
16c	100—102	89	56.88 56.72	8.00 7.85	16.78 16.54	$C_{20}H_{33}N_5O_5$
16d	78—81[d]	95				$C_{15}H_{21}NO_6 \cdot 0.5H_2O$
16e	137—138[e]	95				$C_{17}H_{25}NO_7$

[a] Compounds **15a—f** were identified based on ^{1}H NMR spectra (see Refs. 16—20). [b] Calculations for compounds **16a—e** were performed using ^{1}H NMR spectral data. [c] From heptane. [d] From benzene (*cf.* Ref. 15). [e] From AcOEt (*cf.* Ref. 4). [f] From semicarbazone.

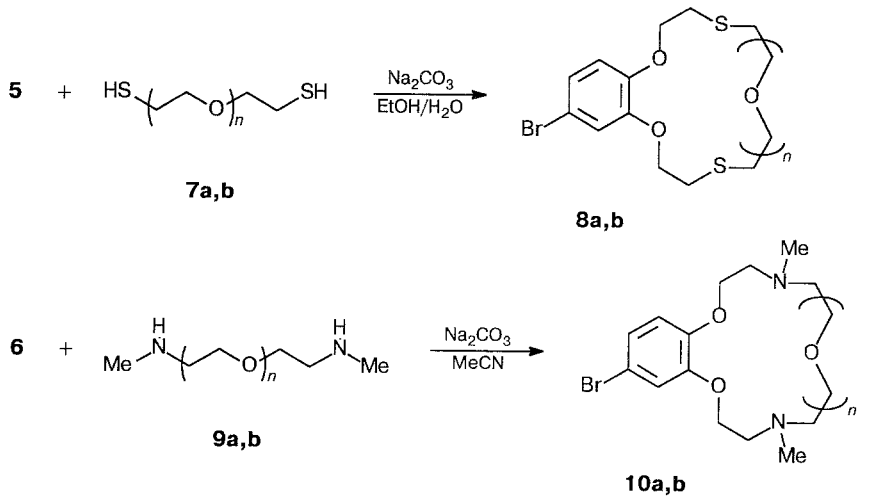
It is well known that oxygen-containing benzocrown ethers[8] and 1,3-xylylcrown ethers[7] containing a Br atom linked to the benzene ring can be metallated with *n*-butyllithium. The resulting organolithium compounds readily react with various electrophiles. It could therefore be expected that organolithium derivatives of benzocrown ethers with such heteroatoms as N, S, and O would undergo formylation when treated with DMF.

The 4′-bromobenzo-15(18)-crown-5(6) (**13a,b**) required for studying this reaction were obtained by treatment of benzo-15(18)-crown-5(6) (**15a,b**) with *N*-bromosuccinimide.[9,10] The schemes for the synthesis of bromo-derivatives of benzodithia-15(18)-crown-5(6) (**8a,b**) and *N,N*′-dimethylbenzodiaza-15(18)-crown-5(6) (**10a,b**) have been suggested by us for the first time. As is evident from Scheme 2, dichloride **4** was obtained by a known procedure[19] from diol **3** and $SOCl_2$. However, we managed to increase its yield from 68 % to 88 %. Compound **4** was brominated in high yield with dioxane dibromide. Subsequently, we treated the bromo-derivative **5** with NaI to give diiodide **6** (Scheme 2, Table 1).

Scheme 2

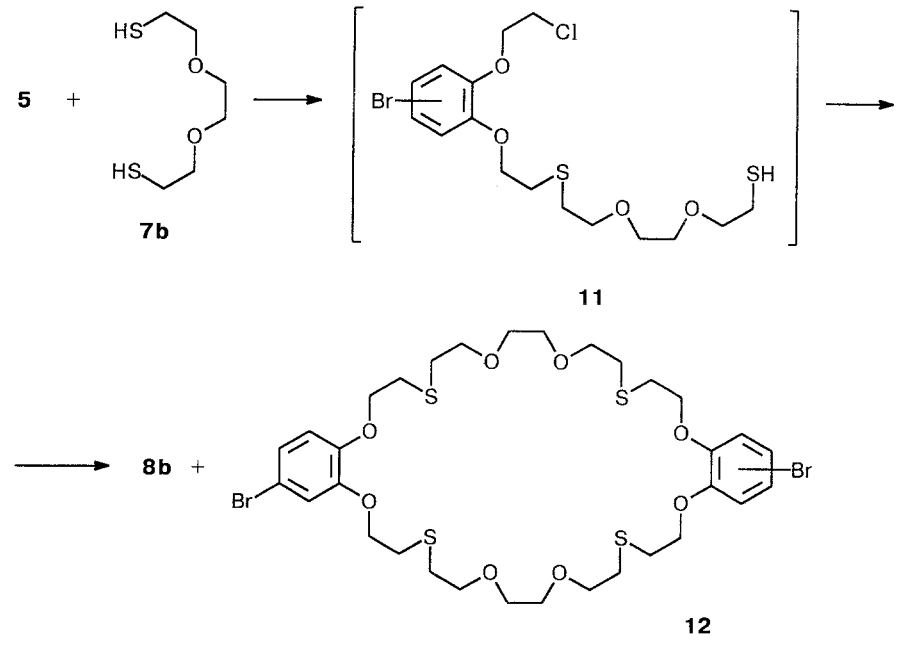


Scheme 3



7—10: n = 1 (**a**), 2 (**b**)

Scheme 4

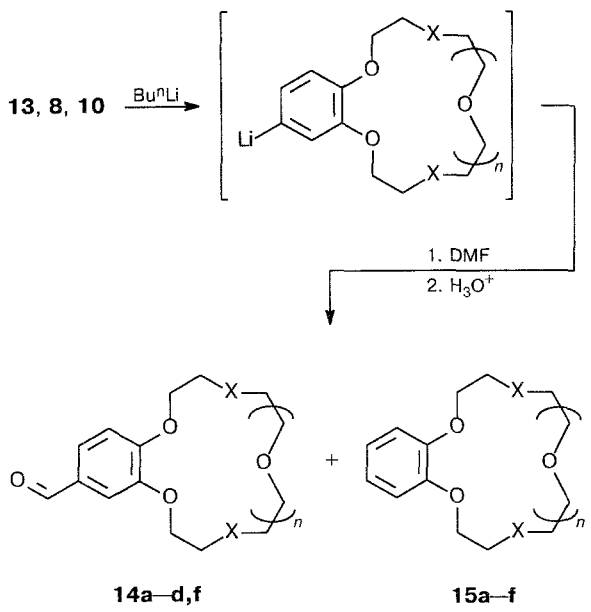


The reaction of dichloride **4** with dithiol **7b** has been reported previously.[12] This simplified our search for the optimum conditions of the synthesis of bromo-derivatives **8a,b** from compounds **5** and **7a,b** (Scheme 3). Diiodide **6** and *N,N'*-dimethyldiamines **9a,b** were transformed into benzodiaza-15(18)-crown-5(6) ethers **10a,b** (see Scheme 3) according to procedures similar to those used to obtain aliphatic diazacrown ethers.[13]

The condensation of bromo-derivative **5** with dithiols **7a,b** to give compounds **8a,b** occurs in high yields. However, in the case of 3,6-dioxa-1,8-octanedithiol (**7b**) we managed to isolate (in 9 % yield) a dibromo-derivative of dibenzotetrathia-36-crown-12 (Scheme 4) and establish its structure. The presence of compound **12** among the reaction products suggests that condensation of bromo-derivative **5** with **7b** is a two-step process. Probably, nucleophilic substitution of one Cl atom occurs initially to give the linear intermediate **11** (see Scheme 4). Subsequently, **11** can undergo either intramolecular cyclization into **8b** or intermolecular dimerization into dibromo-derivative **12**.

We studied how the temperature of metallation of bromobenzocrown ethers (**13**, **8**, and **10**) with *n*-butyllithium and the duration of its subsequent reaction with

Scheme 5



13—15: n = 1 (**a**, **c**, **e**), 2 (**b**, **d**, **f**);
X = O (**a**, **b**), S (**c**, **d**), NMe (**e**, **f**)

DMF affect the yields of formyl derivatives of benzocrown ethers **14a—d,f** (Scheme 5).

We chose the degree of completion of side processes and the recovery of the starting compounds as criteria for estimating the efficiency of the reaction. The basic side compounds are debromination products (**15a—f**, see Scheme 5) and products of macrocycle destruction formed in small yields. We did not analyze in detail the structures of the latter products. The formation of debromination products can be explained either by hydrolysis of the organolithium derivative (the fraction not reacting with DMF) after the reaction mixture is quenched with dilute HCl or by protonation of the carboanion during metallation due to abstraction of a proton from a solvent molecule.

It was found that organolithium derivatives of benzocrown ethers are formed only at definite temperatures. For example, metallation of 4′-bromobenzo-18-crown-6 (**13b**) at −40 °C results in significant amounts of debromination product **15b** (65 %), which suggests that the corresponding organolithium derivative is unstable under these conditions. On the other hand, after metallation of **13b** at −100 °C and formylation with DMF, we recovered 42 % of the starting compound **13b**, which suggests that incomplete metallation occurs at this low temperature. It can also be concluded from the data presented in Table 2 that complete metallation of **13b** occurs at −60 °C and −80 °C. In addition, the yield of the formyl derivative depends only slightly on the metallation time and on the time of reaction with DMF, *i.e.*, to successfully perform the first stage of the synthesis, 2 h is sufficient, while the second stage requires 1.2 h. However, the organolithium derivative obtained from compound **13a** probably has lower reactivity than its analog synthesized from **13b**, since an increase in the time of its reaction with DMF to 4 h significantly affects the yield of product **14a**. We used the data obtained for optimizing the conditions for the synthesis of formyl derivatives of benzocrown ethers **14c,d,f**.

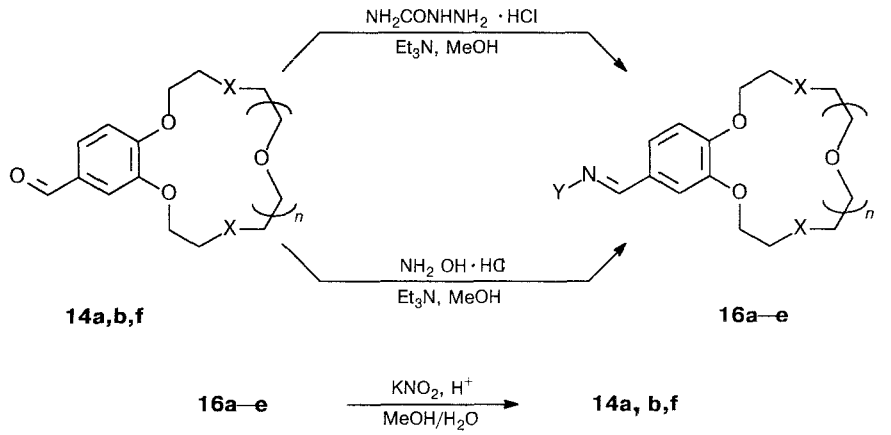
It turned out that organolithium compounds can be obtained from benzocrown ethers **8** and **10** only at −100 °C. These are also the optimum conditions for formylation with DMF in the syntheses of aldehydes **14c,d,f**. It was also found that this reaction produces

Table 2. Conditions of metallation of benzocrown ethers **13**, **8**, and **10** and the reactions of their organolithium derivatives with DMF; yields of products

Starting compound	T/°C	Duration/h		Recovery of the starting compound (%)	Products (yield (%))
		metallation	reaction with DMF		
13a*	−60	2.0	2.5	0	**15a** (61), **14a** (36)
	−60	2.0	4.0	0	**15a** (14), **14a** (80)
13b*	−40	4.0	2.0	0	**15b** (65), **14b** (30)
	−60	4.0	1.2	0	**15b** (38), **14b** (59)
	−60	2.0	3.5	0	**15b** (42), **14b** (55)
	−80	2.0	1.2	0	**15b** (39), **14b** (55)
	−100	4.0	2.5	42	**15b** (64), **14b** (29)
8a	−100	3.0	4.0	0	**15c** (23), **14c** (74)
8b	−100	2.5	5.0	0	**15d** (26), **14d** (58)
10a*	−100	4.0	4.0	40	**15e** (67), **14e** (0)
	−70	3.0	3.0	0	**15e** (75), **14e** (0)
10b*	−100	4.0	3.0	0	**15f** (27), **14f** (63)

* The ratio of the reaction products was found from ^{1}H NMR spectra.

Scheme 6



16: n = 1 (**a**, **d**), 2 (**b**, **c**, **e**);
X = O (**a**, **b**, **d**, **e**), NMe (**c**);
Y = $NHCONH_2$ (**a—c**), OH (**d**, **e**)

aldehydes **14b,d,f** containing a 18-crown-6 moiety in almost equal yields (~60 %) that are, however, somewhat lower than those of the formyl derivatives of benzo-15-crown-5 **14a,c** (up to 80 %). This is probably due to the lower ability of the Li^+ cation, which has a small ionic radius, to form complexes with the larger cavity of the 18-crown-6 moiety (see Ref. 3). Probably, formation of the complex containing Li^+ favors the formation of an organolithium derivative of the benzocrown ether and simultaneously decreases its reactivity toward DMF.

In this connection we should note the anomalous behavior of *N,N'*-dimethyl-(4'-bromobenzo)diaza-15-crown-5 (**10a**) in this reaction. Based on the published data,[15] this compound is assumed to possess the highest ability to bind a Li^+ cation. This probably results in a sharp decrease in the reactivity of the organolithium derivative of benzocrown ether **10a** toward DMF, since the electron density is moved away from the Li—C bond towards the second Li^+ cation that is located in the crown ether cavity. Indeed, experiments show (see Table 1) that metallation of compound **8a** occurs rather successfully (the yield of the debromination product reaches 75 %), but subsequent treatment of the reaction mixture with DMF does not give the corresponding aldehyde.

Isolation of the 4'-formylbenzodithia-15(18)-crown-5(6) **14c,d** from the reaction mixtures was performed chromatographically. However, this method did not allow us to purify the formyl derivatives of oxygen-containing benzocrown ethers **14a,b** and benzodiazacrown ether **14f**. To isolate these compounds, we transformed aldehydes **14a,b** and **14f** into semicarbazones **16a—c** by treating them with semicarbazide hydrochloride in the presence of triethylamine (Scheme 6). The compounds obtained were easily isolated by chromatography. The reverse transformation of semicarbazones **16a—c** into aldehydes **14a,b** and **14f** occurs quantitatively by treatment with KNO_2 in an acid medium (see Scheme 6).

It was also suggested that the components of the reaction mixtures be separated by treatment with hydroxylamine hydrochloride in the presence of triethylamine. The conditions for the formation of oximes **16d,e** have been reported previously.[4,15]

The transformation of oximes **16d,e** into aldehydes **14a,b** after chromatographic separation of the compounds followed the same procedure as in the case of semicarbazones **16a—c**.

The structures of the compounds obtained were established by ^1H NMR and IR spectroscopy and mass spectrometry and confirmed by data of elemental analyses (see Tables 1, 3, and 4).

Thus, we have synthesized bromine-containing benzocrown ethers and elaborated a new method for synthesizing formyl derivatives of benzocrown ethers from these compounds. The method makes it possible to obtain the previously inaccessible formyl derivatives of benzocrown ethers containing S, N, and O heteroatoms in the macrocycle.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Bruker AC-200p and Bruker WM-250 spectrometers using $SiMe_4$ as the internal standard. Mass spectra were obtained on Kratos MS-30 and Varian MAT 311A mass spectrometers at an ionization energy of 70 eV with direct insertion of samples into the ionization chamber. IR spectra were recorded in KBr pellets on a Shimadzu IR-470 spectrophotometer. The reactions were monitored by TLC on DC-Alufolien Kieselgel-60 F_{254} plates.

***N*-Methyl-10-aza-1,4,7,13-tetraoxa-2,3-(4′-formylbenzo)-cyclopentadecene-2 (2).** CF_3COOH (5.1 mL) and hexamethylenetetramine (1 g, 7.14 mmol) were added to *N*-methylbenzoaza-15-crown-5 (**1**). The mixture was heated for 12 h at 90 °C in an Ar atmosphere. After cooling, an aqueous solution of K_2CO_3 was added to pH 10, and the mixture was extracted with chloroform. The extract was concentrated *in vacuo*, and the residue was chromatographed on a column with Al_2O_3 using benzene—MeOH (7 : 1) as the eluent to give 0.64 g of compound **2**.

1,2-Di(2′-chloroethoxy)benzene (4) was synthesized from 1,2-di(2′-hydroxyethoxy)benzene (**3**) and $SOCl_2$ in benzene with the addition of pyridine. Yield 88 %, m.p. 53—55 °C (*cf.* Ref. 11).

3,4-Di(2′-chloroethoxy)bromobenzene (5). Freshly prepared dioxane dibromide (23.5 g, 95 mmol) was quickly added to compound **4** (22.1 g, 94 mmol) in Et_2O (120 mL). The mixture was stirred for 1 h at 20 °C, then water (100 mL) was added. The ethereal layer was separated, and the aqueous layer was extracted with Et_2O. The extract was washed with a dilute Na_2SO_3 solution, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on a column with silica gel (Silica gel 60, 70—230 mesh ASTM) using benzene as the eluent to give 4.4 g of unreacted compound **4** and 22.7 g of compound **5**.

3,4-Di(2′-iodoethoxy)bromobenzene (6). A solution of dichloride **5** (1.53 g, 4.87 mmol) and NaI (4.58 g, 30.5 mmol) in dry Me_2CO (20 mL) and dry EtOH (2.5 mL) was refluxed

Table 3. IR and ^1H NMR spectra of compounds **2**, **5**, **6**, **8**, **10**, **12**, **14**, and **16**

Compound	IR (KBr), ν/cm^{-1}	^1H NMR ($CDCl_3$), δ (J/Hz)
2	1677 (C=O)	2.34 (s, 3 H, NMe); 2.73 (t, 4 H, 2 CH_2N); 3.75 (m, 4 H, 2 CH_2O); 3.90 (m, 4 H, 2 CH_2O); 4.19 (m, 4 H, 2 CH_2O); 6.92 (d, 1 H, H-6, J = 8.2); 7.37 (s, 1 H, H-3); 7.43 (d, 1 H, H-5, J = 8.2); 9.82 (s, 1 H, CH=O)
5		3.86 (m, 4 H, 2 CH_2Cl); 4.29 (m, 4 H, 2 CH_2O); 6.83 (d, 1 H, H-5, J = 8.2); 7.06 (s, 1 H, H-2); 7.09 (d, 1 H, H-6, J = 8.2)
6		3.43 (m, 4 H, 2 CH_2I); 4.28 (m, 4 H, 2 CH_2O); 6.82 (d, 1 H, H-5, J = 8.4); 7.05 (s, 1 H, H-2); 7.08 (d, 1 H, H-6, J = 8.4)
8a		2.96 (m, 4 H, 2 CH_2S); 3.08 (m, 4 H, 2 CH_2S); 3.82 (m, 4 H, 2 CH_2O); 4.22 (m, 4 H, 2 CH_2O); 6.74 (d, 1 H, H-6, J = 8.4); 6.98 (s, 1 H, H-3); 7.04 (d, 1 H, H-5, J = 8.4)
8b		2.96 (m, 4 H, 2 CH_2S); 3.12 (m, 4 H, 2 CH_2S); 3.63 (s, 4 H, 2 CH_2O); 3.76 (m, 4 H, 2 CH_2O); 4.18 (m, 4 H, 2 CH_2O); 6.71 (d, 1 H, H-6, J = 8.5); 6.95 (s, 1 H, H-3); 7.01 (d, 1 H, H-5, J = 8.5)
10a		2.29 (s, 6 H, 2 NMe); 2.69 (m, 4 H, 2 CH_2N); 2.83 (m, 4 H, 2 CH_2N); 3.64 (m, 4 H, 2 CH_2O); 3.96 (m, 4 H, 2 CH_2O); 6.64 (d, 1 H, H-6, J = 8.5); 6.89 (s, 1 H, H-3); 6.93 (d, 1 H, H-5, J = 8.5)
10b		2.38 (s, 6 H, 2 NMe); 2.81 (m, 4 H, 2 CH_2N); 3.00 (m, 4 H, 2 CH_2N); 3.57 (s, 4 H, 2 CH_2O); 3.63 (m, 4 H, 2 CH_2O); 4.04 (m, 4 H, 2 CH_2O); 6.69 (d, 1 H, H-6, J = 8.5); 6.93 (s, 1 H, H-3); 6.95 (d, 1 H, H-5, J = 8.5)
12		2.87 (m, 8 H, 4 CH_2S); 2.97 (m, 8 H, 4 CH_2S); 3.63 (s, 8 H, 4 CH_2O); 3.70 (m, 8 H, 4 CH_2O); 4.13 (m, 8 H, 4 CH_2O); 6.73 (d, 2 H, H-6, H-6′, J = 8.4); 6.99 (s, 2 H, H-3, H-3′); 7.01 (d, 2 H, H-5, H-5′, J = 8.4)
14c	1676 (C=O)	2.96 (m, 4 H, 2 CH_2S); 3.10 (m, 4 H, 2 CH_2S); 3.82 (m, 4 H, 2 CH_2O); 4.30 (m, 4 H, 2 CH_2O); 6.93 (d, 1 H, H-6, J = 8.3); 7.36 (s, 1 H, H-3); 7.43 (d, 1 H, H-5, J = 8.3); 9.83 (s, 1 H, CH=O)
14d	1683 (C=O)	2.97 (m, 4 H, 2 CH_2S); 3.15 (m, 4 H, 2 CH_2S); 3.62 (s, 4 H, 2 CH_2O); 3.75 (m, 4 H, 2 CH_2O); 4.27 (m, 4 H, 2 CH_2O); 6.95 (d, 1 H, H-6, J = 8.2); 7.38 (s, 1 H, H-3); 7.45 (d, 1 H, H-5, J = 8.2); 9.84 (s, 1 H, CH=O)
14f	1692 (C=O)**	2.29 (s, 6 H, 2 NMe); 2.74 (m, 4 H, 2 CH_2N); 2.92 (m, 4 H, 2 CH_2N); 3.53 (s, 4 H, 2 CH_2O); 3.58 (m, 4 H, 2 CH_2O); 4.07 (m, 4 H, 2 CH_2O); 6.89 (d, 1 H, H-6, J = 8.3); 7.32 (s, 1 H, H-3); 7.34 (d, 1 H, H-5, J = 8.3); 9.73 (s, 1 H, CH=O)
16a*	3440 (N—H); 1676 (C=O)	3.62 (s, 8 H, 4 CH_2O); 3.75 (m, 4 H, 2 CH_2O); 4.09 (m, 4 H, 2 CH_2O); 6.50 (s, 2 H, NH_2); 6.91 (d, 1 H, H-6, J = 8.3); 7.07 (d, 1 H, H-5, J = 8.3); 7.42 (s, 1 H, H-3); 7.73 (s, 1 H, CH=N); 10.10 (s, 1 H, NH)
16b	3456 (N—H); 1676 (C=O)	3.67 (s, 4 H, 2 CH_2O); 3.70 (m, 4 H, 2 CH_2O); 3.74 (m, 4 H, 2 CH_2O); 3.90 (m, 4 H, 2 CH_2O); 4.14 (t, 4 H, 2 CH_2O); 5.86 (br.s, 2 H, NH_2); 6.77 (d, 1 H, H-6, J = 8.3); 7.02 (d, 1 H, H-5, J = 8.3); 7.18 (s, 1 H, H-3); 7.69 (s, 1 H, CH=N); 10.04 (s, 1 H, NH)
16c*	3456, 3312, 3200 (N—H); 1680 (C=O)	2.31 (2 s, 6 H, 2 NMe); 2.71 (m, 4 H, 2 NCH_2); 2.88 (m, 4 H, 2 NCH_2); 3.52 (s, 4 H, 2 CH_2O); 3.57 (m, 4 H, 2 CH_2O); 4.09 (m, 4 H, 2 CH_2O); 6.18 (br.s, 2 H, NH_2); 6.96 (d, 1 H, H-6, J = 8.3); 7.10 (d, 1 H, H-5, J = 8.3); 7.36 (s, 1 H, H-3); 7.79 (s, 1 H, CH=N); 9.81 (s, 1 H, NH)

* The ^1H NMR spectrum was recorded in DMSO-d_6. ** In vaseline oil.

Table 4. Mass spectra of compounds **2**, **6**, **8**, **10**, **12**, and **14**

Compound	m/z (I_{rel} (%))*
2	309 (13), 252 (18), 164 (8), 114 (100), 87 (13), 86 (13), 84 (10), 83 (12), 71 (13), 70 (16), 57 (61)
6	498 (3), 496 (4), 343 (8), 341 (7), 216 (12), 214 (16), 155 (100), 127 (4), 79 (19), 63 (6), 51 (22)
8a	380 (11), 378 (12), 216 (77), 214 (100), 131 (27), 105 (74), 87 (44), 79 (34), 61 (95), 60 (60), 59 (27)
8b	424 (16), 422 (16), 216 (31), 214 (27), 149 (29), 89 (39), 87 (61), 79 (27), 61 (62), 60 (100), 59 (21)
10a	374 (3), 372 (3), 273 (49), 185 (59), 102 (51), 100 (56), 88 (92), 85 (98), 83 (61), 72 (88), 71 (100) Found: $[M]^+$ = 372.1029. Calculated: M = 372.1048.
10b	418 (1), 416 (1), 229 (51), 146 (33), 100 (48), 84 (22), 72 (27), 71 (53), 70 (65), 58 (100), 57 (57) Found: $[M]^+$ = 416.13216. Calculated: M = 416.13100.
12	848 (2), 846 (4), 844 (2), 235 (40), 216 (62), 214 (64), 207 (46), 175 (46), 149 (100), 118 (35), 105 (37)
14c	328 (42), 191 (54), 164 (91), 163 (77), 136 (32), 131 (28), 105 (100), 87 (49), 61 (61), 60 (39), 59 (28)
14d	372 (49), 175 (24), 164 (47), 163 (27), 149 (98), 105 (43), 89 (37), 87 (88), 61 (84), 60 (100), 59 (51)
14f	366 (7), 229 (72), 221 (52), 208 (69), 100 (59), 85 (27), 84 (38), 72 (62), 71 (74), 70 (100), 56 (34) Found: $[M]^+$ = 366.2175. Calculated: M = 366.2154.

* The molecular ion peak and ten most intense peaks are given.

for 40 h. The solvent was evaporated, benzene was added to the residue, and the insoluble compounds were filtered off. The solution in benzene was concentrated *in vacuo*, and the residue was chromatographed on a column with silica gel using benzene as the eluent to give 2.16 g of compound **6**.

1,10-Dithia-4,7,13-trioxa-5,6-(4′-bromobenzo)cyclopentadecene-5 (8a). A solution of 3-oxa-1,5-pentanedithiol **7a** (3.75 g, 27 mmol) and dichloroethoxybromobenzene **5** (8.4 g, 27 mmol) in dry EtOH (50 mL) was added with stirring over a period of 1 h to a boiling solution of Na_2CO_3 (15 g, 142 mmol) in 50 % aqueous EtOH (1 L), and the mixture was refluxed for 48 h. The crystalline precipitate that formed on cooling was filtered off, the filtrate was concentrated *in vacuo*, and the residue was combined with the precipitate. The mixture was extracted with hot AcOEt, and the extracts were concentrated *in vacuo*. The residue was recrystallized from dry EtOH to give 5.7 g of compound **8a**.

1,10-Dithia-4,7,13,16-tetraoxa-5,6-(4′-bromobenzo)cyclooctadecene-5 (8b) and 1,10,19,28-tetrathia-4,7,13,16,22,25,31,34-octaoxa-5,6-(4′-bromobenzo)-23,24-[4″(5″)-bromobenzo]cyclohexatriaconta-5,23-diene (12). A solution of compound **5** (6.69 g, 21.3 mmol) and 3,6-dioxa-1,8-octanedithiol **7b** (3.88 g, 21.3 mmol) in a mixture of EtOH (75 mL) and benzene (10 mL) was added over a period of 1 h to a boiling solution of $Na_2CO_3 \cdot 10H_2O$ (30.5 g, 107 mmol) in a mixture of EtOH (420 mL) with water (380 mL). The reaction mixture was refluxed for 14 h, then EtOH was distilled off. The aqueous phase was extracted with a benzene—$CHCl_3$ mixture (10 : 1), dried with K_2CO_3, and concentrated *in vacuo*. The residue was chromatographed on a small column with silica gel using benzene—AcOEt (5 : 1) as the eluent. Recrystallization from benzene gave 5.17 g of compound **8b**. The filtrate was repeatedly chromatographed to give an additional 1.63 g of compound **8b** (R_f 0.67) and 0.78 g of compound **12** (R_f 0.36).

***N,N′*-Dimethyl-7,13-diaza-1,4,10-trioxa-2,3-(4′-bromobenzo)cyclopentadecene-2 (10a).** Na_2CO_3 (21.6 g, 0.2 mol) and dry MeCN (0.9 L) were placed into a three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. The reaction mixture was heated to boiling, then a solution of diiodide **6** (9.94 g, 0.02 mol) and *N,N′*-dimethyl-3-oxa-1,5-pentanediamine **9a** (2.64 g, 0.02 g) in dry MeCN (100 mL) was added dropwise with stirring over a period of 2 h. The mixture was refluxed for 24 h with stirring and then cooled, and the inorganic precipitate was filtered off. The MeCN was distilled off, and the reaction product was dissolved in chloroform, washed with water, and concentrated *in vacuo*. The residue was chromatographed on a column with Al_2O_3 (L 40/250) using $CHCl_3$—MeOH as the eluent to give 3.8 g of compound **10a** as a viscous yellow oil.

***N,N′*-Dimethyl-7,16-diaza-1,4,10,13-tetraoxa-2,3-(4′-bromobenzo)cyclooctadecene-2 (10b)** was synthesized similarly to compound **10a** by heating diiodide **6** with *N,N′*-dimethyl-3,6-dioxa-1,8-octanediamine (**9b**) in MeCN in the presence of Na_2CO_3 for 48 h.

Synthesis of the formyl derivatives of benzo-15(18)-crown-5(6) (14a—d,f) (general procedure). 4′-Bromobenzo-15(18)-crown-5(6) (**13**, **8**, or **10**) was dissolved in a mixture of dry Et_2O (25 mL) with dry THF (15 mL), placed into a three-neck flask with a mechanic stirrer, a thermometer, and a source of dry Ar. Using vapor from liquid N_2, the solution was cooled to −60 °C (in the case of benzocrown ether **13**) or to −100 °C (in the case of compounds **8** and **10**). A solution of *n*-butyllithium (3 mmol) in hexane was quickly added from a pipette, and the reaction mixture was stirred for 2—4 h at one of the temperatures specified above. Then, dry DMF (3.3 mmol) was added in a similar way, and the mixture was stirred for 1.5—5 h. The temperature of the reaction mixture was slowly increased to ~20 °C, and 40 mL of an HCl solution (7 : 1) (in the case of benzocrown ethers **8** and **13**) or 20 mL of water (in the case of benzocrown ether **10**) were added. The organic layer was separated, and the aqueous layer was extracted with chloroform. The extracts were combined and concentrated *in vacuo*. The reaction products containing compounds **14c,d** were chromatographed on a column with silica gel using benzene—AcOEt (5 : 1) as the eluent. To isolate the formyl derivatives **14a,b,f**, the mixtures of reaction products were worked up according to one of the following procedures.

A. The mixture of reaction products was dissolved in MeOH (25 mL), $NH_2CONHNH_2 \cdot HCl$ (3.6 mmol) and Et_3N (7.2 mmol) were added, and the mixture was refluxed for 30 h and concentrated *in vacuo*. To obtain compounds **16a,b**, the residue was dissolved in water (20 mL) and extracted with chloroform. The extract was concentrated *in vacuo*, and the residue was chromatographed on a column with Al_2O_3 (L40/250) using $CHCl_3$ and then $CHCl_3$—MeOH (4 : 1) as eluents. To obtain compound **16c**, the residue was chromatographed on a column with Silochrom S-80 silica gel using benzene—MeOH—Et_3N (50 : 5 : 1) as the eluent. The resulting solution of semicarbazones **16a—c** (0.3 mmol, see Tables 2 and 3) in MeOH (15 mL) was treated with concentrated HBr (2.5 mL) and a solution of KNO_2 (1.2 mmol) in

water (10 mL). After 24 h, the methanol was evaporated *in vacuo*, and the aqueous solution was extracted with benzene. The benzene was distilled off, and the resulting 4′-formylbenzo-15(18)-crown-5(6) (**14a,b**) were recrystallized from heptane. Yield of 4′-formylbenzo-15-crown-5 (**14a**) 93 %, m.p. 83—84 °C (*cf.* Ref. 1). Yield of 4′-formylbenzo-18-crown-6 (**14b**) 88 %, m.p. 62—65 °C (*cf.* Ref. 1). To obtain compound **14f**, the aqueous solution left after removal of methanol was treated with 1 *M* KOH to pH 10 and extracted with benzene. The extract was concentrated *in vacuo*, and the residue was chromatographed on a column with Al_2O_3 using benzene—MeOH (7 : 1) as the eluent.

B. Similarly to method ***A***, a mixture of reaction products containing compounds **14a,b** was treated with $NH_2OH \cdot HCl$. The MeOH was distilled off, the residue was dissolved in water (20 mL) and extracted with chloroform, and the extract was concentrated *in vacuo*. To obtain oximes **16d** and **16e**, the residues were recrystallized from benzene and AcOEt, respectively. Then, the resulting solution of oxime **16d,e** (0.3 mmol) in MeOH (15 mL) was treated with concentrated HBr (2.5 mL) and a solution of KNO_2 (1.2 mmol) in water (10 mL). After 24 h, the methanol was evaporated *in vacuo*, and the aqueous solution was extracted with chloroform. The $CHCl_3$ was distilled off, and the residue was recrystallized from heptane. Yield of 4′-formylbenzo-15-crown-5 (**14a**) 86 %, m.p. 83—84 °C (*cf.* Ref. 1). Yield of 4′-formylbenzo-18-crown-6 (**14b**) 81 %, m.p. 62—65 °C (*cf.* Ref. 1).

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