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Intraannular functionalization of the 1,3-phenylene-19-crown-6 system via bromine–lithium exchange[1]

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Abstract

In contrast to the behavior of its lower homologue 1,3-phenylene-16-crown-5 (**1**), the direct lithiation of 1,3-phenylene-19-crown-6 (**2**) with *n*-BuLi at the intruannular position-2 was found to be slow and not quantitative. Therefore, (2-bromo-1,3-phenylene)-19-crown-6 (**8**) was synthesized by the reaction of the dicesium salt of 2-bromo-resorcinol (**7**) with pentaethylene glycol dibromide. The crystal structure of **8** revealed the existence of three chemically identical residues in the unit cell; in all cases, the bromine atom sticks out of the crown ether ring. The bromine–lithium exchange reaction of **8** with *n*-BuLi to furnish the desired (2-lithio-1,3-phenylene)-19-crown-6 (**4**) was quantitative after 2 h at −65°C in THF. Derivatization of **4** with deuterium oxide, dimethyl disulfide, iodine, carbon dioxide, mercuric bromide (1 or 0.5 molar equivalents), and magnesium bromide yielded (2-deuterio-1,3-phenylene)-19-crown-6 (**2a**), (2methylthio-1,3-phenylene)-19-crown-6 (**10**), (2-iodo-1,3-phenylene)-19-crown-6 (**11**), (2-carboxy-1,3-phenylene)-19-crown-6 (**12**), (2-bromomercurio-1,3-phenylene)-19-crown-6 (**13**), bis[(1,3-phenylene-19-crown-6)-2-yl]mercury (**14**), and (2-bromomagnesio-1,3-phenylene)-19-crown-6 (**15**), respectively. The synthesis of the Grignard reagent **15** was also carried out by the direct reaction of **8** with magnesium; contrary to the corresponding 1,3-xylylene crown ethers, cleavage of the crown ether ring during the formation of **15** was not observed. At room temperature, the solution of crude **4** (prepared from **8**) gave rise to ether cleavage and to the formation of (2-*n*-butyl-1,3-phenylene)-19-crown 6 (**16**). © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Crown ethers; Lithium; Mercury; Magnesium; Crystal structure

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1. Introduction

Recently, we reported the intraannular functionalization of 1,3-phenylene-16-crown-5 (**1**) via direct lithiation with *n*-BuLi [1]. It was selective and quantitative; a deuterium oxide quench of the organolithium **3** yielded the deuterated crown ether **5** (98% deuterium incorporation) (Scheme 1).

Unfortunately, it turned out that the analogous lithiation of the larger crown ether 1,3-phenylene-19-crown-6 (**2**) with *n*-BuLi was not quantitative; a deuterium oxide quench of the intermediate (2-lithio-1,3-

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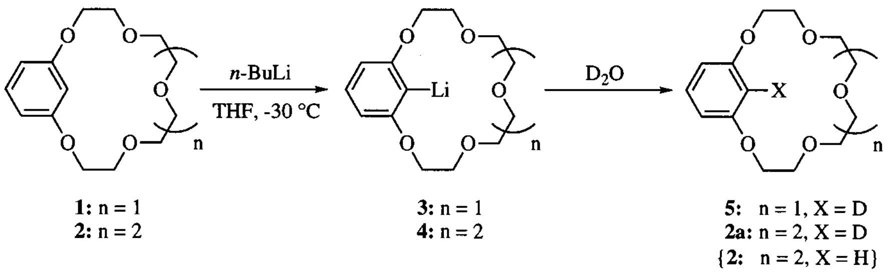


Scheme 1.

phenylene)-19-crown-6 (**4**) yielded a mixture of **2**/**2a** (Scheme 1). For that reason, we investigated the synthesis of **4** by bromine–lithium exchange, a reaction which had been applied successfully to (2-bromo-1,3-xylylene)-crown ethers [2]. The synthesis and the crystal structure of (2-bromo-1,3-phenylene)-19-crown-6 (**8**) will be presented also. The bromine–lithium exchange of **8** led to functional derivatives of the title compound **2** via the organolithium precursor **4**.

Previously, we had reported the reaction of the (2-bromo-1,3-xylylene)-crown ethers with magnesium metal to prepare the (2-bromomagnesio-1,3-xylylene)-crown ethers; however, the formation of these Grignard reagents was accompanied by (sometimes) extensive crown ether cleavage [3]. Therefore, the synthesis of these Grignard reagents by the reaction of the organolithium analogue with magnesium bromide was more convenient [4]; this was also the case in the synthesis of (2-bromomagnesio-1,3-phenylene)-16-crown-5 [1]. Surprisingly, and in contrast to (2-bromo-1,3-xylylene)-crown ether analogues, the reaction of **8** with magnesium metal led to the corresponding Grignard reagent **15** without cleavage of the crown ether ring.

2. Results and discussion

2.1. Lithiation of 1,3-phenylene-19-crown-6 (2)

In contrast to the previously reported quantitative lithiation of **1** [1], lithiation of **2** with *n*-BuLi was found to be slow and not quantitative. The reaction was performed at −30°C for 7 h, after which the reaction mixture was quenched with deuterium oxide. Two compounds were detected by GC/MS and ^{1}H-NMR spectroscopy: **2** and **2a** (ratio 56:44, according to ^{1}H-NMR spectroscopy) (Scheme 1). The metallation reaction was also attempted with *n*-BuLi/TMEDA, *n*-BuLi/*t*-BuOK, *t*-BuLi; however, in all cases, hydrogen–lithium exchange was not complete. When the reaction mixtures were allowed to warm above −30°C, cleavage of the crown ether ring occurred.

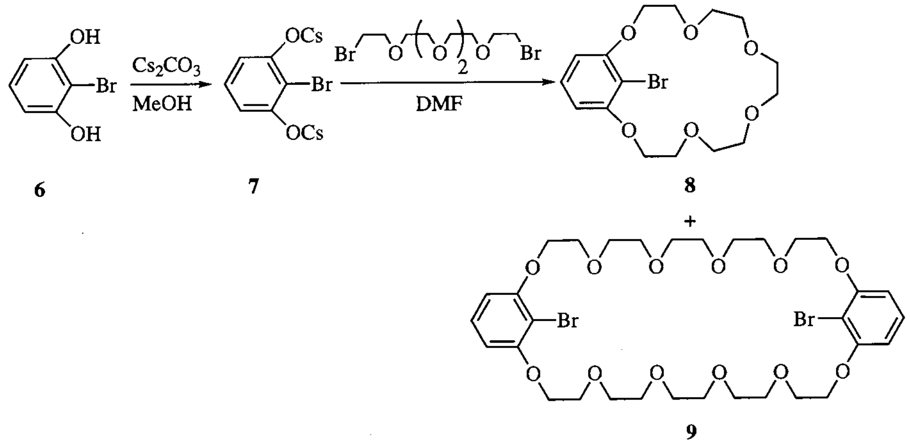
2.2. Synthesis and crystal structure of (2-bromo-1,3-phenylene)-19-crown-6 (8)

Although the synthesis of (2-bromo-1,3-xylylene)-crown ethers is known [2,5] (2-bromo-1,3-phenylene)-crown ethers have not been reported. The preparation of **8** was carried out by the reaction of equivalent amounts of the dicesium salt **7** of 2-bromo-resorcinol (**6**) (obtained from **6** and cesium carbonate) and pentaethylene glycol dibromide in DMF (Scheme 2); the advantage of cesium salts in crown ether synthesis is well established [6]. The separation of **8** from its dimeric byproduct **9** was achieved by column chromatography.

The ^{1}NMR spectra of a solution of **8** in toluene-d_8 at different temperatures (163.5–365 K) revealed the existence of five patterns for the five groups of the non-aromatic protons, indicating that expectedly, the crown ether ring flips over the bromine atom. At temperatures below 163 K, the ^{1}H-NMR spectra are more complicated, probably because this flipping motion stops gradually.

Crystals suitable for X-ray crystal structure determination were obtained by recrystallization of **8** from diethyl ether. The unit cell of **8** contains three chemically identical molecules which differ slightly in their conformations. An ORTEP illustration of molecule no. 1 is presented in Fig. 1. Fig. 2 gives a comparison of the three molecules; the conformation of the major disorder component of molecule no. 3 is very similar to that of molecule no. 1, while molecule no. 2 exhibits a significantly deviating puckering pattern. A selection of bond distances, angles and torsion angles is presented in Table 1.

The C(122)–Br(10) distance in molecule no. 1 (the corresponding values for molecules no. 2 and no. 3 are in the square brackets) of 1.890(8) [1.889(2), 1.885(8)] Å is normal. The bromine atom is coplanar with the aromatic ring with Br to least squares plane distance 0.011(1) [0.057(1), 0.182(1)] Å. The angle between the aromatic ring and the least squares plane of the crown ether ring is 73.7(3) [88.4(3), 78.8(3)]°, so that the bromine sticks out of the crown ether ring in a nearly perpendicular fashion (72.0(3) [86.4(3), 75.5(3)]°). The torsion angles of the OCH_2CH_2O units vary from



Scheme 2.

61.4(9) to 76.3(8)° with the exception of the torsion angle O(108)–C(109)–C(110)–O(111) (−175.8(6)°).

2.3. Synthesis of (2-lithio-1,3-phenylene)-19-crown-6 (4) and its reactions with electrophiles

Bromine–lithium exchange of **8** with *n*-butyllithium proceeded in high yield. The reaction conditions reported previously for the bromine–lithium exchange of the (2-bromo-1,3-xylylene)-crown ethers [2] were modified slightly. Best results were obtained when *n*-butyllithium (1.1 molar equivalents) was added to a solution of **8** in THF (about 0.1 M) at −65°C and the reaction mixture was kept for 2 h at this temperature (Scheme 3). The crown ether ring is stable under these conditions. The organolithium reagent **4** was quite soluble in THF at this concentration (0.1 M); this is in contrast to the low solubility of **3** which gave a cloudy suspension at the same concentration [1].

The yield of **4** was determined by quench reactions with deuterium oxide or dimethyl disulfide (Scheme 3); the products **2a** and **10**, respectively, were obtained in good yields (72 and 82%, respectively), while starting material was not detected by GC/MS and ^{1}H-NMR spectroscopy. Compound **4** was used for further functionalizations. In these reactions with electrophiles, **2** (hydrolyzed material) was formed as a byproduct, presumably because at the small scale of the reactions (usually 0.20 mmol), even minimal traces of water give a significant amount of hydrolysis.

Reaction of **4** with solid iodine or carbon dioxide yielded (2-iodo-1,3-phenylene)-19-crown-6 (**11**) and (2-carboxy-1,3-phenylene)-19-crown-6 (**12**), respectively, (Scheme 3) in analogy with the synthesis of the analogous derivatives of **1** [1]. The mercury compound **13** was synthesized by the reaction of **4** and mercuric bromide in a molar ratio of 1:1, while dropwise addition of 0.5 molar equivalents of mercuric bromide to **4** yielded the bis (crown ether) mercury compound **14** (Scheme 3). Both **13** and **14** were identified by ^{1}H-, ^{13}C-, ^{199}Hg-NMR spectroscopy, MS and elemental analysis.

*2.4. Synthesis of (2-bromomagnesio-1,3-phenylene)-19-crown-6 (**15**)*

The preparation of crown ether Grignard reagents by the reaction of the organolithium precursors with magnesium bromide has been reported [1,4]. This method was also successful for the synthesis of **15** (Scheme 3). Because this reaction was carried out in standard glassware with ground joints, and due to the small scale of the reaction (0.50 mmol), a significant amount of the Grignard reagent **15** was hydrolyzed by the traces of moisture. A deuterium oxide quench of the reaction mixture at room temperature yielded **2**/**2a** (66% deuterium incorporation, according to GC/MS), while no traces of ether cleavage products were detected; as the crown ether ring of the organolithium compound **4** is not stable at room temperature, this indicates that the conversion of **4** to **15** had been complete.

Compound **15** was also synthesized by the reaction of **8** with magnesium metal at room temperature. In this case, the reaction was carried out in a high vacuum glass apparatus in order to reduce hydrolysis. In a previous paper, we discussed the specific ether cleavage of the (2-bromomagnesio-1,3-xylylene)-crown ethers which occurs during their formation from the corresponding bromides [3]; the cleavage was ascribed to the attack of a carbanionic intermediate on the Grignard reagent already formed [3]. Compound **15** was stable for a long period; 3 months after the preparation, hydrolysis of the reaction mixture and titration of the aqueous phase revealed that the starting bromide **8** had been transformed completely into a Grignard reagent, while deuterolysis, followed by GC/MS analysis, confirmed the absence of **8** and of ether cleavage products, and the product (**2**/**2a**) was highly deuterated (ratio **2**:**2a** = 9:91). The crown ether ring of **15** was also stable

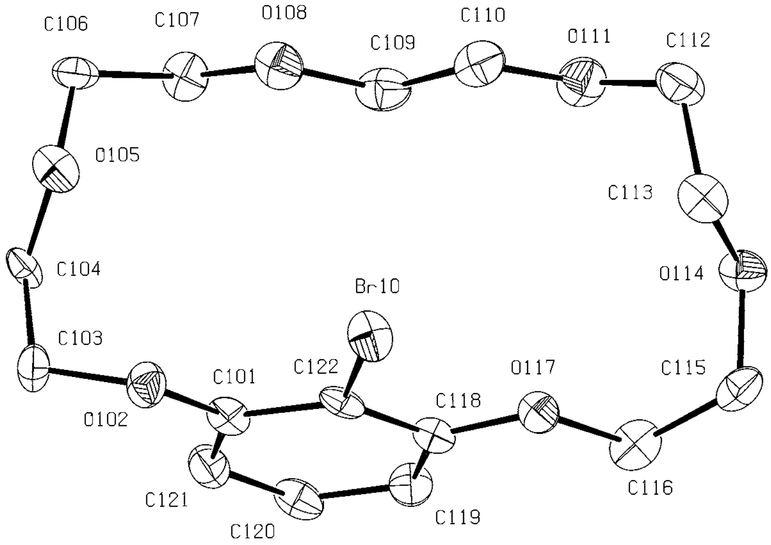


Fig. 1. ORTEP drawing (50% probability level) of one of the three similar, crystallographically independent molecules of **8**. Hydrogen atoms are omitted for clarity.

even when a tenfold molar excess of bromobenzene and magnesium was reacted in the presence of **15** under the same conditions; a deuterium oxide quench of the reaction mixture yielded **2**/**2a** (ratio **2**:**2a** = 11:89), while only traces of ether cleavage products were detected. Under identical conditions, (2-bromomagnesio-1,3-xylylene)-15-crown-4 was completely consumed by ether cleavage through attack by the phenyl anion which is an intermediate in the formation of phenylmagnesium bromide [3]. The high stability of the crown ether ring of **15** is in contrast to the lower stability of its lower homologues and of 1,3-xylylene-crown ethers; this might be ascribed to two factors: the ether functionalities in **15** may be less susceptible towards attack by the intermediate carbanion due to less favorable coordination between oxygens and magnesium, but in addition, the low solubility of **15** in THF will protect it against attack by the carbanion in solution.

2.5. Stability of **4** in the presence of *n*-butylbromide

While the solution of **4** as prepared from **8** and *n*-butyllithium was reasonably stable at low temperature, warming it up to room temperature led to the formation of appreciable amounts of (2-*n*-butyl-1,3-phenylene)-19-crown-6 (**16**) formed by reaction of **4** with *n*-butylbromide (in addition to the formation of **2** and unknown products (crown ether cleavage?), apparently arising by selfdecomposition of **4**). A GC/MS analysis of the residue of a deuterium oxide quench of the reaction mixture indicated a product distribution of 49% of **16** and 51% of a **2**/**2a** mixture (ratio 85:15). The formation of appreciable amounts of **2**-*n*-butylated product has also been observed when the reaction mixture of an analogous (2-bromo-1,3-xylylene)-crown ether with *n*-butyllithium was warmed to room temperature [4].

2.6. Conclusions

In contrast to 1,3-phenylene-16-crown-5 (**1**), the larger crown ether **2** could not be lithiated quantitatively at the intraannular position-2. On the other hand, (2-lithio-1,3-phenylene)-19-crown-6 (**4**) was quantitatively formed by bromine–lithium exchange from **8**, thus providing a convenient method for further intraannular functionalization of the crown ether system via **4**.

Interestingly, the synthesis of the Grignard reagent **15** from **8** and magnesium occurred without cleavage of the crown ether ring, in contrast to the analogous reaction of (2-bromo-1,3-xylylene)-crown ethers.

3. Experimental section

3.1. General

The crown ether **2** was obtained by a known procedure [6]. Pentaethylene glycol dibromide was prepared by the reaction of pentaethylene glycol with phosphorus tribromide [7]; the ^{1}H-NMR spectrum of pentaethylene glycol dibromide was similar to the one reported previously [8]. Pentaethylene glycol [5] and 2-bromo-resorcinol [9] were obtained by literature procedures. Lithiation reactions were performed in standard glassware with ground joints under argon. THF was predried and distilled from $LiAlH_4$. The reaction of **8** with magnesium was carried out in fully sealed glassware by using high vacuum techniques; for its synthesis, extremely dry THF was prepared by distillation from

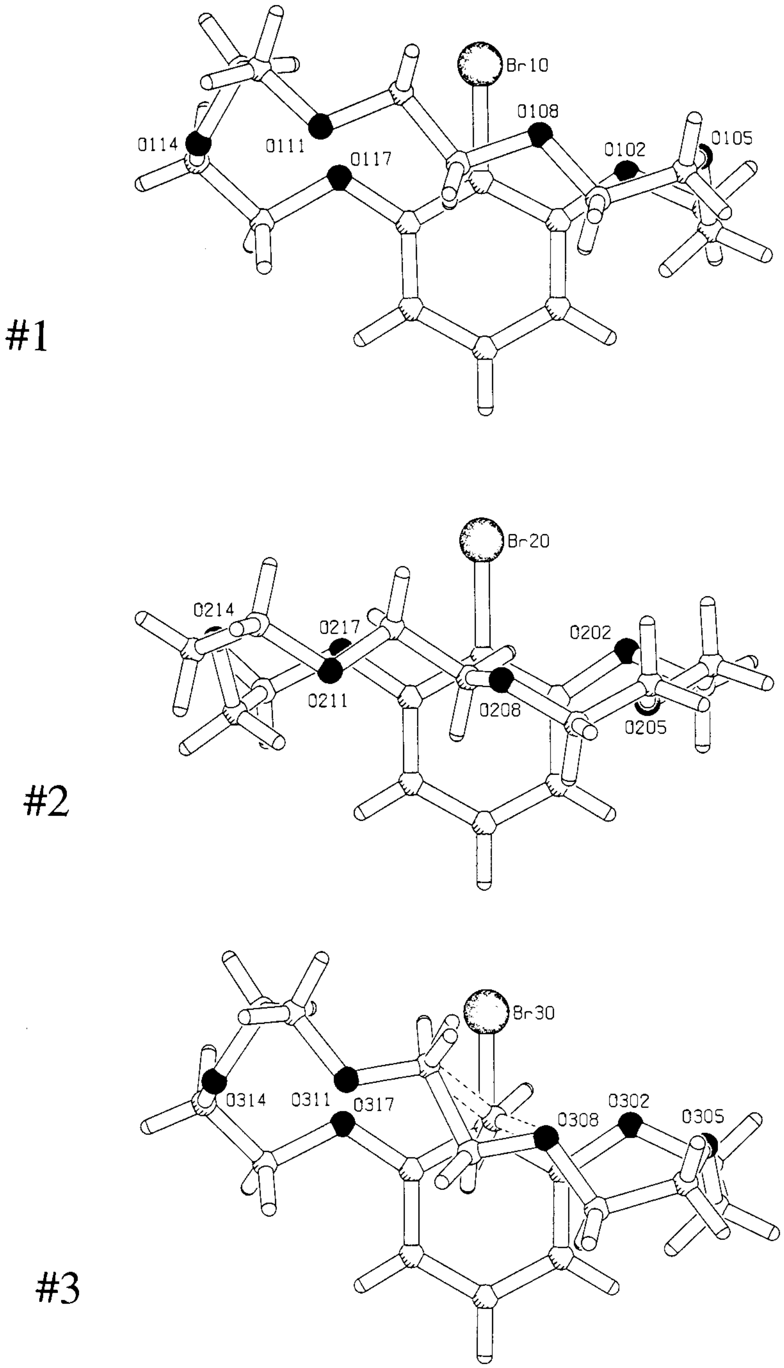


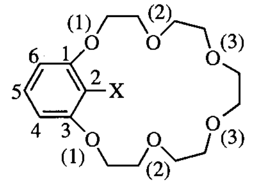
Fig. 2. Comparison of the conformation of the three crystallographically independent molecules (nos. 1, 2, 3) of **8**.

liquid Na/K alloy after predrying on NaOH. A solution of dry magnesium bromide was prepared by the reaction of dibromoethane and doubly sublimed magnesium in THF. Concentrations of 'total base' and Mg^{2+} of the organomagnesium solution were determined by titration of a hydrolyzed sample with acid–base and EDTA complexon, respectively [10]. The starting materials ethylene glycol (Baker), 1,2-bis (2-chloroethoxy)ethane (Janssen), phosphorus tribromide (Merck), bromine (Baker), resorcinol (Baker), cesium carbonate (Janssen), *n*-butyllithium (Janssen, Acros), deuterium oxide (Janssen), dimethyl disulfide (Aldrich), iodine (Janssen), mercuric bromide (Baker), dibromoethane (Janssen), bromobenzene (Merck) were available commercially. Column chromatography was performed over aluminium oxide 90, activity II-III (Merck). TLC chromatography was carried out on aluminium sheets, silica gel 60 F_{254} (Merck). Purification of **16** was carried out by preparative gas chromatography (Intersmat GC 120, katharometer

Table 1
Selected bond distances (Å), bond angles (°) and torsion angles (°) of 8

Bond distances (Å)	
Br(10)–C(122)	1.890(8)
O(102)–C(101)	1.355(11)
O(102)–C(103)	1.425(10)
O(105)–C(104)	1.418(11)
O(105)–C(106)	1.409(10)
O(108)–C(107)	1.422(9)
O(108)–C(109)	1.395(10)
O(111)–C(110)	1.417(12)
O(111)–C(112)	1.432(11)
O(114)–C(113)	1.428(11)
O(114)–C(115)	1.426(11)
O(117)–C(116)	1.450(11)
O(117)–C(118)	1.342(10)
O(102)–C(101)–C(122)	117.1(8)
O(117)–C(118)–C(119)	125.4(8)
O(117)–C(118)–C(122)	116.6(8)
Torsion angles (°)	
C(121)–C(101)–C(122)–Br(10)	179.7(7)
O(117)–C(118)–C(119)–C(120)	176.7(7)
C(119)–C(118)–C(122)–Br(10)	179.4(7)
O(102)–C(103)–C(104)–O(105)	61.4(9)
O(102)–C(101)–C(122)–Br(10)	2.5(10)
O(105)–C(106)–C(107)–O(108)	68.3(9)
O(117)–C(118)–C(122)–Br(10)	3.1(10)
O(108)–C(109)–C(110)–O(111)	175.8(6)
O(102)–C(101)–C(122)–Br(118)	177.7(7)
O(111)–C(112)–C(113)–O(114)	71.4(9)
O(102)–C(101)–C(121)–C(120)	176.9(8)
O(114)–C(115)–C(116)–O(117)	76.3(8)
O(117)–C(118)–C(122)–C(101)	176.7(7)

detection, 10% OV 101 column, 2.03 m, chromosorb WHP) at appropriate oven temperature. The yields of the products are based on the amount of the starting material. NMR spectra (for numbering, see Formula of (2-X-1,3-phenylene)-19-crown-6) were measured on a Bruker AC 200 (^{1}H-NMR, 200.13 MHz; ^{13}C-, $^{13}C\{^1H\}$-, 2D$\{^{13}C, ^1H\}$-NMR, 50.32 MHz) or a Bruker MSL 400 (^{1}H-NMR, NOESY, 400.13 MHz; ^{199}Hg-NMR, 71.60 MHz). The ^{13}C chemical shifts were obtained from the $^{13}C\{^1H\}$-NMR and the coupling constants $J(^{13}C-^1H)$ from the ^{13}C-NMR spectra. The correlation between carbons and hydrogens was found by 2D$\{^{13}C, ^1H\}$-NMR. GC/MS analyses were performed on a HP 5890 II GC/5971 A MSD combination, operating at 70 eV and equipped with a Chrompack CP sil SCB 50-m/0.21-mm column. Mass spectra and HRMS measurements were performed on a Finnigan MAT 90 mass spectrometer (direct inlet); in the case of **14**, CI with NH_3 was used to characterize the compound by its mass spectrum. Melting points were measured on a Buchi melting point apparatus and are not corrected. Elemental analyses were carried out at the Micro Analytical Department, Rijksuniversiteit Groningen, The Netherlands.

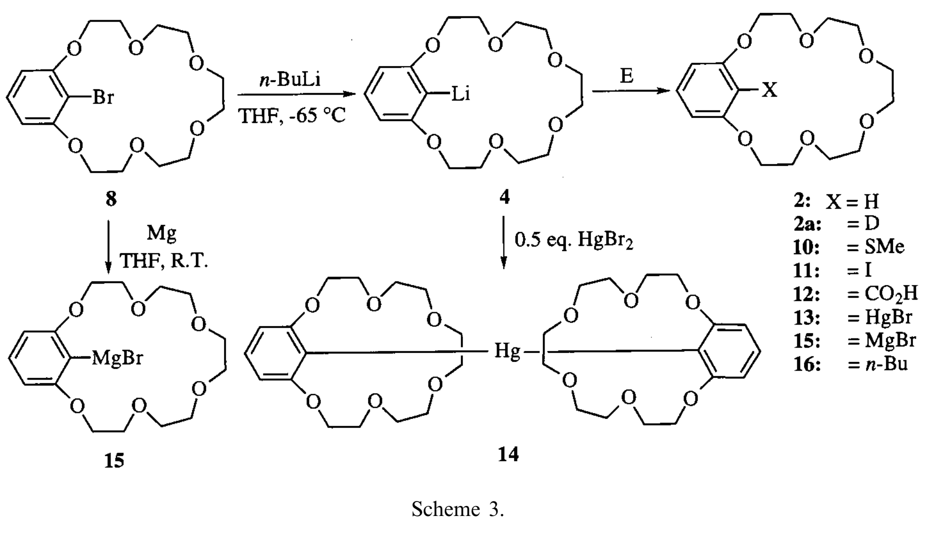


[Formula of (2-X-1,3-phenylene)-19-crown-6]

3.2. 1,3-Phenylene-19-crown-6 (*2*)

Crown ether **2** was synthesized by a known procedure [6]. Its purification was performed by column chromatography over aluminium oxide. It was obtained as a pure oil (Lit. [6]: oil). We report the spectra data and the mass spectrum of **2** which have not been reported previously [6].

2: ^{1}H-NMR (200.13 MHz, $CDCl_3$, ref. $CHCl_3 = 7.27$ ppm): δ 3.61–3.72 (m, 12H, $O(2)CH_2CH_2O(3)CH_2$), 3.78–3.82 (m, 4H, $O(1)CH_2CH_2O(2)$), 4.19–4.23 (m,



Scheme 3.

4H, O(1)CH_2CH$_2$O(2)), 6.48 (dd, $^3J = 8.2$ Hz, $^4J = 2.3$ Hz, 2H, aryl H(4,6)), 6.86 (t, $^4J = 2.3$ Hz, ^{1}H, aryl H(2)), 7.12 (t, $^3J = 8.2$ Hz, 1H, aryl H(5)). ^{13}C-NMR (50.32 MHz, CDCl$_3$, ref. CDCl$_3$ = 77 ppm): (68.14 (t, $^1J = 143$ Hz, 2C, O(1)CH$_2$CH$_2$O(2)), 69.85 (t, $^1J = 140$ Hz, 2C, O(1)CH$_2$$CH_2$O(2)), 70.58, 70.70 and 71.17 (3 × t, $^1J = 141$ Hz, 6C, O(2)CH_2CH_2O(3)CH_2), 103.49 (dtd, $^1J = 160$ Hz, $^3J = 5$ Hz, $^4J = 1.9$ Hz, 1C, aryl C(2)), 108.23 (dm, $^1J = 160$ Hz, 2C, aryl C(4,6)), 129.46 (d, $^1J = 158$ Hz, 1C, aryl C(5)), 160.12 (s, 2C, aryl C(1,3)). GC/MS: *m*/*z* (relative intensity) 312 (M$^+$, $C_{16}H_{24}O_6$, 86), 180 (15), 154 (14), 137 (56), 136 (47), 133 (12), 117 (10), 110 (59), 92 (100), 89 (26), 76 (40), 73 (49), 64 (42), 45 (69).

3.3. Reaction of **2** with n-butyllithium

To a solution of **2** (0.096 g, 0.31 mmol in 3 ml of THF) under argon, 0.20 ml (0.32 mmol) of *n*-butyllithium (1.6 M in *n*-hexane) was added, at −30°C. After 7 h of stirring at this temperature, an excess of deuterium oxide (0.50 ml, 27.63 mmol) was added after which the cooling bath was removed and the reaction mixture was stirred for 0.5 h, and then 5 ml of 1 M HCl was added. The volatile materials were removed by evaporation, the residue was extracted with dichloromethane (3 × 10 ml), the combined organic layers were washed with 5 ml of water, dried over MgSO$_4$, filtered and evaporated to dryness, yielding 0.068 g of a pale yellow oil, which was identified by GC/MS and ^{1}H-NMR spectroscopy as **2**/**2a** (44% deuterium incorporation, according to the ^{1}H-NMR spectrum).

3.4. (2-Bromo-1,3-phenylene)-19-crown-6 (**8**) and [2,2′-dibromo-[bis(1,3-phenylene)]]-38-crown-12 (**9**)

To a solution of 2-bromo-resorcinol (**6**) [9] (1.92 g, 10.16 mmol in 500 ml of methanol) under nitrogen, cesium carbonate (3.31 g, 10.16 mmol) was added. Once the cesium carbonate was dissolved, the methanol was removed under reduced pressure. Then 500 ml of dry DMF was added, which was removed under high vacuum along with the traces of remaining water and methanol. The dry precipitate was suspended in 500 ml DMF and the dibromide of pentaethylene glycol [7,8] (3.70 g, 10.16 mmol) was added. The reaction mixture was stirred at 65°C for 5 days. Then it was cooled down to room temperature and the DMF was evaporated under high vacuum. The residue was dissolved in dichloromethane (200 ml), the organic layer was washed once with 50 ml of a 10% aqueous NaCl and once with 50 ml of 1% aqueous KOH. The organic layers were dried over Na$_2$SO$_4$, filtered, and the solvent was evaporated, yielding 4.08 g of an oil. Purification was carried out by column chromatography over aluminium oxide. During the elution, the eluent was gradually changed in 10% increments from pure petroleum ether (40–60) to pure THF. The crown ether **8** (0.91 g, yield 23%) was isolated as an oil and crystallized upon standing. Repeated crystallizations were achieved from diethyl ether/pentane, yielding a white solid. It crystallized in two different modifications with m.p. 49–51°C and 55–57°C, respectively; the m.p. of a mixture of equal amounts of these modifications was 54–57°C. Colorless crystals suitable for X-ray crystal structure determination were obtained by slow recrystallization from diethyl ether by cooling from room temperature to −20°C.

The dimeric byproduct [2,2′-dibromo-[bis(1,3-phenylene)]]-38-crown-12 (**9**) was also isolated as a pure oil (0.39 g, yield 10%) and crystallized from diethyl ether, m.p. 79–82°C. By increasing the polarity of the eluent using mixtures of ethano/methanol, 0.66 g of a mixture of compounds with higher molecular weight was isolated, which were not identified further.

8: ^{1}H-NMR (200.13 MHz, CDCl$_3$, ref. CHCl$_3$ = 7.27 ppm): δ 3.43 (s, 4H, O(3)CH_2CH_2O(3)), 3.50–3.56 (m, 4H, O(2)CH$_2$CH_2O(3)), 3.63–3.69 (m, 4H, O(2)CH_2-CH$_2$O(3)), 3.79–3.83 (m, 4H, O(1)CH$_2$CH_2O(2)), 4.32–4.36 (m, 4H, O(1)CH_2CH$_2$O(2)), 6.60 (d, $^3J = 8.3$ Hz, 2H, aryl H(4,6)), 7.15 (t, $^3J = 8.3$ Hz, 1H, aryl H(5)). The ^{1}NMR spectrum was analyzed with the help of NOESY spectrum (^{1}H-NMR, 400.13 MHz). ^{13}C-NMR (50.32 MHz, CDCl$_3$, ref. CDCl$_3$ = 77 ppm): (69.35 (t, $^1J = 144$ Hz, 2C, O(1)CH$_2$CH$_2$O(2)), 69.63 (t, $^1J = 141$ Hz, 2C, O(1)CH$_2$$CH_2$O(2)), 70.14 (t, $^1J = 141$ Hz, 2C, O(2)CH_2CH_2O(3)), 70.41 (t, $^1J = 142$ Hz, 2C, O(3)CH_2CH_2O(3)), 71.48 (t, $^1J = 141$ Hz, 2C, O(2)CH$_2$CH$_2$O(3)), 104.03 (td, $^3J = 8.3$ Hz, $^4J = 1.7$ Hz, 1C, aryl C(2)), 107.24 (ddd, $^1J = 161$ Hz, $^3J = 8.4$ Hz, $^2J = 1.7$ Hz, 2C, aryl C(4,6)), 127.55 (d, $^1J = 160$ Hz, aryl C(5)), 156.66 (d, $^3J = 11.2$ Hz, 2C, aryl C(1,3)). GC/MS: *m*/*z* (relative intensity) 392/390 (M$^+$; $C_{16}H_{23}BrO_6$, 59), 311 ([M−Br]$^+$, 21), 216/214 (19), 205 (20), 179 (19), 177 (9), 172/170 (87), 161 (35), 151 (32), 133 (27), 107 (29), 89 (48), 73 (35), 45 (100). HRMS: Anal. Calc. for $C_{16}H^{79}_{23}BrO_6$ 390.0678, found 390.0678 ± 0.0008. Anal. Calc. (%) for $C_{16}H_{23}BrO_6$: C, 49.12; H, 5.92. Found (%): C, 48.93; H, 5.89.

9: ^{1}H-NMR (200.13 MHz, CDCl$_3$, ref. CHCl$_3$ = 7.27 ppm): δ 3.67–3.70 (m, 16H, CH_2O(3)CH_2CH_2O(3)-CH_2), 3.77–3.82 (m, 8H, O(2)CH_2CH$_2$O(3)), 3.88–3.93 (m, 8H, O(1)CH$_2$CH_2O(2)), 4.14–4.19 (m, 8H, O(1)CH_2CH$_2$O(2)), 6.56 (d, $^3J = 8.3$ Hz, 4H, aryl H(4,6)), 7.17 (t, $^3J = 8.3$ Hz, 2H, aryl H(5)). ^{13}C-NMR (50.32 MHz, CDCl$_3$, ref. CDCl$_3$ = 77 ppm): (69.25 (t, $^1J = 145$ Hz, 4C, O(1)CH$_2$CH$_2$O(2)), 69.41 (t, $^1J = 142$ Hz, 4C, O(1)CH$_2$$CH_2$O(2)), 70.61 and 70.62 (2 (t, $^1J = 141$ Hz, 8C, CH$_2$O(3)CH$_2$), 71.14 (t, $^1J = 141$ Hz, 4C, O(2)CH$_2$CH$_2$O(3)), 102.19 (td, 3J = 8.5 Hz, $^4J = 1.5$

Hz, 2C, aryl C(2)), 106.14 (dd, $^1J = 161$ Hz, $^3J = 8.4$ Hz, 4C, aryl C(4,6)), 128.02 (d, $^1J = 160$ Hz, 2C, aryl C(5)), 156.52 (d, $^3J = 11.0$ Hz, 4C, aryl C(1,3)). MS (direct inlet, Finnigan MAT 90): m/z (relative intensity) 782 (M^+; $C_{32}H_{46}^{79}Br^{81}BrO_{12}$, 72), 701 ($[M-Br]^+$, ^{79}Br, 15), 700 ($[M-HBr]^+$, ^{79}Br, 7), 436/434 (10), 392/390 (19), 311 (14), 216/214 (11), 205 (8), 179 (17), 177 (9), 172/170 (56), 161 (23), 151 (26), 133 (25), 107 (21), 89 (40), 73 (33), 45 (100). HRMS: Anal. Calc. for $C_{32}H_{46}79Br_2O_{12}$ 780.1356, found 780.1352 ± 0.0006. Anal. Calc. (%) for $C_{32}H_{46}Br_2O_{12}$: C, 49.12; H, 5.92. Found (%): C, 49.07; H, 6.04.

*3.5. (2-Lithio-1,3-phenylene)-19-crown-6 (**4**)*

To a solution of **8** (0.079 g, 0.20 mmol in 2 ml of THF) under argon, 1.1 molar equivalent of *n*-butyllithium (1.6 M in *n*-hexane) was added at − 65°C. The exchange was completed after 2 h, and **4** was reacted with the corresponding electrophile (vide infra).

*3.6. (2-Deuterio-1,3-phenylene)-19-crown-6 (**2a**)*

An excess of deuterium oxide (0.20 ml, 11.05 mmol) was added at − 65°C to the solution of **4** (0.20 mmol in 2 ml of THF). The reaction mixture was warmed slowly to room temperature, after which 5 ml of 1 M HCl was added. The volatile materials were removed by evaporation and the organic material was extracted with dichloromethane (3 × 10 ml). The combined organic layers were washed with 5 ml of water, dried over $MgSO_4$, filtered and evaporated to dryness, to yield an oil of **2**/**2a** (0.051 g, 72, 88% deuterium incorporation, according to GC/MS and ^{1}H-NMR spectroscopy).

2a: The ^{1}H-NMR spectrum (200.13 MHz, $CDCl_3$, ref. $C\mathit{H}C1_3 = 7.27$ ppm) is identical with that of **2** except for the signal of the aryl H(4,6), being a doublet δ 6.49, d, $^3J = 8.2$ Hz, 2H) and the absence of the aryl H(2) signal. The ^{13}C-NMR spectrum (50.32 MHz, $CDCl_3$, ref. $\mathit{C}DCl_3 = 77$ ppm) is identical with that of **2** except for the signal of the aryl C(2), being a triplet (δ 103.12, t, $^1J(C-^2H) = 24$ Hz, 1C) of low intensity, and the signal of the aryl C(4,6) (δ 108.17, ddd, $^1J = 161$ Hz, $^3J = 7.7$ Hz, $^2J = 1.3$ Hz, 2C). GC/MS: m/z (relative intensity) 313 (M^+; $C_{16}H_{23}{}^2HO_6$, 100), 181 (10), 155 (9), 138 (33), 137 (36), 133 (7), 117 (7), 111 (42), 93 (70), 89 (22), 77 (31), 73 (42), 65 (34), 45 (87). HRMS: Anal. Calc. for $C_{16}H_{23}{}^2HO_6$ 313.1636. Found 313.1640 ± 0.0007.

*3.7. (2-Methylthio-1,3-phenylene)-19-crown-6 (**10**)*

An excess of dimethyl disulfide (0.10 ml, 1.11 mmol) was added at − 65°C to the solution of **4** (0.20 mmol in 2 ml of THF), after which the cooling bath was removed and the reaction mixture was stirred for 1 h. The work up procedure was as described for **2a**, yielding the sulfide **10** (0.059 g, 82%, > 95% pure according to GC/MS and ^{1}H-NMR spectroscopy) as an oil. It was crystallized from diethyl ether at (20°C, yielding a white solid, m.p. 43–44.5°C.

10: ^{1}H-NMR (200.13 MHz, $CDCl_3$, ref. $C\mathit{H}Cl_3 = 7.27$ ppm): δ 2.42 (s, 3H, SMe), 3.41 (s, 4H, $O(3)C\mathit{H}_2C\mathit{H}_2O(3)$), 3.49–3.53 (m, 4H, $O(2)C\mathit{H}_2CH_2O$-(3)), 3.64–3.68 (m, 4H, $O(2)CH_2C\mathit{H}_2O(3)$), 3.80–3.84 (m, 4H, $O(1)CH_2C\mathit{H}_2O(2)$), 4.34–4.38 (m, 4H, $O(1)C\mathit{H}_2CH_2O(2)$), 6.60 (d, $^3J = 8.3$ Hz, 2H, aryl H(4,6)), 7.15 (t, $^3J = 8.3$ Hz, 1H, aryl H(5)). ^{13}C-NMR (50.32 MHz, $CDCl_3$, ref. $\mathit{C}DC1_3 = 77$ ppm): δ 17.74 (q,$^1J = 140$ Hz, 1C, SMe), 68.81 (t, $^1J = 144$ Hz, 2C, $O(1)\mathit{C}H_2CH_2O(2)$), 69.71 (t, $^1J = 141$ Hz, 2C, $O(1)\mathit{C}H_2CH_2O(2)$), 70.21 (t, $^1J = 141$ Hz, 2C, $O(1)CH_2\mathit{C}H_2O(2)$), 70.41 (t, $^1J = 142$ Hz, ^{2}C, $O(3)\mathit{C}H_2\mathit{C}H_2O(3)$), 71.30 (t, $^1J = 141$ Hz, 2C, $O(2)\mathit{C}H_2CH_2O(3)$), 106.67 (dd, $^1J = 160$ Hz, $^3J = 7.9$ Hz, 2C, aryl C(4,6)), 115.23 (s, 1C, aryl C(2)), 128.24 (d, $^1J = 159$ Hz, 1C, aryl C(5)), 159.94 (s, 2C, aryl C(1,3)). GC/MS: m/z (relative intensity) 358 (M^+; $C_{17}H_{26}O_6S$, 87), 311 ($[M-SMe]^+$, 1), 226 (11), 200 (11), 182 (20), 167 (20), 156 (100), 139 (15), 123 (22), 111 (11), 95 (12), 73 (9), 45 (65). HRMS: Anal. Calc. for $C_{17}H_{26}O_6^{32}S$ 358.1450, found 358.1455 ± 0.0005. Anal. Calc. (%) for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31. Found (%): C, 56.60; H, 7.40.

*3.8. (2-Iodo-1,3-phenylene)-19-crown-6 (**11**)*

An excess of solid iodine (0.111 g, 0.44 mmol) was added at − 65°C to the solution of **4** (0.20 mmol in 2 ml of THF) and the reaction mixture was warmed slowly to room temperature overnight, after which 5 ml of an aqueous solution of sodium thiosulphate (2 g, 12.65 mmol) was added. The standard work up yielded 0.080 g of the crude product as a slightly yellow oil, which solidified upon standing. It was identified by GC/MS analysis as a mixture of **2** (18%) and **11** (82%). The crude product was recrystallized from diethyl ether, yielding a white solid (0.066 g, 75%), m.p. 69–70°C.

11: The ^{1}H-NMR (200.13 MHz, $CDCl_3$, ref. $C\mathit{H}Cl_3 = 7.27$ ppm) is in accordance with that of **8**. The ^{13}C-NMR (50.32 MHz, $CDCl_3$, ref. $\mathit{C}DCl_3 = 77$ ppm) is also in accordance with that of **8** except for the chemical shifts for the signals of the aryl C, being (81.41 (C(2)), 106.54 (C(4,6)), 129.06 (C(5)), 159.03 (C(1,3)). GC/MS: m/z (relative intensity) 438 (M^+; $C_{16}H_{23}IO_6$, 100), 311 ($[M-I]^+$, 2), 262 (9), 236 (12), 218 (56), 161 (12), 151 (10), 133 (10), 107 (14), 89 (17), 73 (14), 45 (61). HRMS: Anal. Calc. for $C_{16}H_{23}IO_6$ 438.0538, found 438.0536 ± 0.0005. Anal. Calc. (%) for $C_{16}H_{23}IO_6$: C, 43.85; H, 5.29. Found (%): C, 43.23; H, 5.33.

3.9. (2-Carboxy-1,3-phenylene)-19-crown-6 (*12*)

Carbon dioxide was bubbled through the solution of **4** (0.20 mmol in 2 ml of THF) at −65°C for 30 min. Then the reaction mixture was poured rapidly into a beaker containing a slurry of crushed dry ice and anhydrous diethyl ether. When the carboxylation mixture had reached room temperature, water was added, and the volatile materials were removed by evaporation. The aqueous phase was washed once with 10 ml of toluene and once with 10 ml of hexane, after which 5 ml of 20% H_2SO_4 was added to liberate the acid, which was extracted with dichloromethane (4 × 10 ml). The combined organic layers were washed with 5 ml of water and dried over $MgSO_4$. After filtration, the solvent was evaporated, yielding **12** (0.055 g, 77%) as an oil, which solidified upon standing; it was identified by ^{1}H-NMR spectroscopy as pure **12**. Repeated crystallizations from dichloromethane/pentane yielded a white solid, m.p. 104–106°C.

12: ^{1}H-NMR (200.13 MHz, $CDCl_3$, ref. $\mathrm{C}\mathit{H}\mathrm{Cl}_3 = 7.27$ ppm): δ 3.56–3.61 (m, 8H, $\mathrm{C}\mathit{H}_2\mathrm{O(3)C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{O(3)CH_2}$), 3.68–3.73 (m, 4H, $\mathrm{O(2)C}\mathit{H}_2\mathrm{CH_2O(3)}$), 3.76–3.81 (m, 4H, $\mathrm{O(1)CH_2C}\mathit{H}_2\mathrm{O(2)}$), 4.25–4.29 (m, 4H, $\mathrm{O(1)C}\mathit{H}_2\mathrm{CH_2O(2)}$), 6.59 (d, $^3J = 8.4$ Hz, 2H, aryl H(4,6)), 7.26 (t, $^3J = 8.4$ Hz, 1H, aryl H(5)), 10.18 (brs, 1H, COOH). ^{13}C-NMR (50.32 MHz, $CDCl_3$, ref. $\mathit{C}\mathrm{DCl}_3 = 77$ ppm): (68.89) (t, $^1J = 141$ Hz, 2C, $\mathrm{O(1)CH_2}\mathit{C}\mathrm{H_2O(2)}$), 69.26 (t, $^1J = 144$ Hz, 2C, $\mathrm{O(1)}\mathit{C}\mathrm{H_2CH_2O(2)}$), 70.16 and 70.35 (2 (t, $^1J = 142$ Hz and $^1J = 141$ Hz, 4C, $\mathit{C}\mathrm{H_2O(3)}\mathit{C}\mathrm{H_2}\mathit{C}\mathrm{H_2O(3)}\mathit{C}\mathrm{H_2}$), 70.85 (t, $^1J = 142$ Hz, 2C, $\mathrm{O(2)}\mathit{C}\mathrm{H_2CH_2O(3)}$), 107.15 (dd, $^1J = 162$ Hz, $^3J = 7.0$ Hz, 2C, aryl C(4,6)), 116.68 (s, 1C, aryl C(2)), 130.92 (d, $^1J = 160$ Hz, 1C, aryl C(5)), 156.38 (d, $^3J = 10.9$ Hz, 2C, aryl C(1,3)), 165.76 (s, 1C, COOH). MS (direct inlet, Finnigan MAT 90): *m*/*z* (relative intensity) 356 (M^+; $C_{17}H_{24}O_8$, 31), 339 ($[M-OH]^+$, 100), 311 ($[M-COOH]^+$ (2), 269 (11), 225 (10), 207 (17), 180 (61), 163 (24), 136 (39), 108 (30), 89 (14), 73 (19), 45 (63). HRMS: Anal. Calc. for $C_{17}H_{24}O_8$ 356.1471, found 356.1472 ± 0.0007. Anal. Calc. (%) for $C_{17}H_{24}O_8$: C, 57.30; H, 6.79. Found (%): C, 57.22; H, 6.92.

3.10. (2-Bromomercurio-1,3-phenylene)-19-crown-6 (*13*) and bis[(l,3-phenylene-19-crown-6)-2-yl]mercury (*14*)

A solution of mercuric bromide (0.042 g, 0.12 mmol in 2 ml of THF) was added rapidly to the solution of **4** (0.11 mmol in 1 ml of THF) at −65°C. Then it was warmed slowly to room temperature overnight, after which the clear solution turned slightly cloudy. Then 5 ml of water was added, and after the standard work up 0.043 g of a crude solid was obtained. According to the ^{1}H-NMR spectrum, two compounds were present: **2** (32%) and **13** (68%). Purification of **13** was achieved by recrystallization from acetone at −20°C, yielding a white solid (0.027 g, 41%), m.p. 123–125°C.

Upon dropwise addition of a mercuric bromide solution (0.035 g, 0.10 mmol in 5 ml of THF) during 30 min to the solution of **4** (0.20 mmol in 2 ml of THF) and the standard work up, 0.075 g of a crude solid was obtained. According to ^{1}H-NMR spectrum, it contained: **2** (42%) and **14** (58%). Purification of **14** was achieved as described for **13**, yielding a white solid (0.022 g, 27%), m.p. 121–123°C.

13: ^{1}H-NMR (200.13 MHz, $CDCl_3$, ref. $\mathrm{C}\mathit{H}\mathrm{Cl}_3 = 7.27$ ppm): δ 3.51–3.62, 3.66–3.82 and 3.89–4.00 (3 × m, 16H, $\mathrm{C}\mathit{H}_2\mathrm{O(2)C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{O(3)C}\mathit{H}_2$), 4.06–4.16 (m, 4H, $\mathrm{O(1)C}\mathit{H}_2\mathrm{CH_2O(2)}$), 6.64 (d, $^3J(^1\mathrm{H}{-}\mathrm{lH}) = 8.1$ Hz, Hg satellites $^4J(^{199}\mathrm{Hg}{-}^1\mathrm{H}) = 80$ Hz, 2H, aryl H(4,6)), 7.20 (t, $^3J = 8.1$ Hz, 1H, aryl H(5)). ^{13}C-NMR (50.32 MHz, $CDCl_3$, ref. $\mathit{C}\mathrm{DCl}_3 = 77$ ppm): δ 68.83 (t, $^1J = 140$ Hz, 2C, OCH_2), 69.78 (t, $^1J = 142$ Hz, 2C, OCH_2), 70.05 (t, $^1J = 141$ Hz, 2C, OCH_2), 70.43 (t, $^1J = 142$ Hz, 2C, OCH_2), 71.50 (t, $^1J = 140$ Hz, 2C, OCH_2), 107.50 (ddd, $^1J = 160$ Hz, $^3J = 7.7$ Hz, $^2J = 1.5$ Hz, Hg satellites ^3J ($^{13}\mathrm{C}{-}^{199}\mathrm{Hg}$) = 107 Hz, 2C, aryl C (4,6)), 130.63 (d, $^1J = 159$ Hz, 1C, aryl C(5)), 132.72 (s, low intensity, 1C, aryl C(2)), 161.59 (d, ^3J ($^{13}\mathrm{C}{-}^{13}\mathrm{C}$) = 12.6 Hz, Hg satellites ^2J ($^{13}\mathrm{C}{-}^{199}\mathrm{Hg}$) = 43 Hz, 2C, aryl C(1,3)). ^{199}Hg-NMR (71.60 MHz, $CDCl_3$, ref. $\mathrm{Me_2}\mathit{Hg} = 0$ ppm): δ −1242.70 (s, 1Hg). MS (direct inlet, Finnigan MAT 90): *m*/*z* (relative intensity) 592 (M^+; $C_{16}H_{23}^{79}Br^{202}HgO_6$, 1), 513 ($[M-^{79}Br]^+$, ^{202}Hg, (20), 311 (11), 45 (100). The signal of M^+; was too weak for exact mass determination. Parent ion mass calc. for $C_{16}H_{23}^{198}HgO_6$ ($[M-Br]^+$) 509.1163, found 509.1159 ± 0.0006. Anal. Calc. (%) for $C_{16}H_{23}BrHgO_6$: C, 32.47; H, 3.92. Found (%): C, 32.48; H, 4.38.

14: ^{1}H-NMR (200.13 MHz, $CDCl_3$, ref. $\mathrm{C}\mathit{H}\mathrm{Cl}_3 = 7.27$ ppm): δ 3.37–3.65 and 3.70–3.90 (2 × m, 32H, 6 × C_2H_4 and 4 × $\mathrm{O(1)CH_2CH_2O(2)}$), 4.17–4.38 (m, 8H, $\mathrm{O(1)C}\mathit{H}_2\mathrm{CH_2O(2)}$), 6.68 (d, $^3J(^1\mathrm{H}{-}^1\mathrm{H}) = 8.0$ Hz, Hg satellites $^4J(^{199}\mathrm{Hg}{-}^1\mathrm{H}) = 39$ Hz, 4H, aryl H(4,6)), 7.13 (t, $^3J = 8.0$ Hz, 2H, aryl H(5)). ^{13}C-NMR (50.32 MHz, $CDCl_3$, ref. $\mathit{C}\mathrm{DCl}_3 = 77$ ppm): δ 68.54 (t, $^1J = 142$ Hz, 4C, OCH_2), 69.50 (t, $^1J = 140$ Hz, 4C, OCH_2), 70.14 (t, $^1J = 142$ Hz, 4C, OCH_2), 70.51 (t, $^1J = 142$ Hz, 4C, OCH_2), 71.13 (t, $^1J = 141$ Hz, 4C, OCH_2), 107.17 (ddd, $^1J = 157$ Hz, $^3J = 7.0$ Hz, $^2J = 3.0$ Hz, 4C, aryl C(4,6)), 129.14 (d, $^1J = 158$ Hz, 2C, aryl C(5)), 146.45 (s, 2C, aryl C(2)), 163.80 (d, $^3J = 11.1$ Hz, 4C, aryl C(1,3)). The Hg satellites were not observed due to the low concentration. ^{199}Hg-NMR (71.60 MHz, $CDCl_3$, ref. $\mathrm{Me_2}\mathit{Hg} = 0$ ppm): δ −708.84 (s, 1 Hg). MS (CI, NH_3, Finnigan MAT 90): *m*/*z* (relative intensity) 842 ($M \cdot NH_4^+$, $C_{32}H_{50}^{202}HgNO_{12}$, 100), 530 ($[\mathrm{aryl}^{202}\mathrm{Hg} \cdot \mathrm{NH_3}]^+$, 75), 513 ($\mathrm{aryl}^{202}\mathrm{Hg}^+$, 19). Anal. Calc. (%) for $C_{32}H_{46}HgO_{12}$: C, 46.68; H, 5.63. Found (%): C, 46.16; H, 5.59.

3.11. Reaction of **4** with magnesium bromide

In standard glassware with ground joints under argon, a solution of 0.21 M magnesium bromide in THF (2.50 ml, 0.53 mmol) was added at −65°C to the solution of **4** (0.50 mmol in 2 ml of THF), after which the reaction mixture was warmed slowly to room temperature overnight. Owing to its low solubility in THF, the Grignard reagent was present in suspension. A sample of the reaction mixture was quenched with an excess of deuterium oxide. Standard acidic work up yielded a pale yellow oil, which was identified by ^{1}H-NMR spectroscopy and GC/MS as **2**/**2a** (66% deuterium incorporation).

3.12. Reaction of **8** with magnesium in THF

In a high-vacuum glass apparatus, **8** (0.079 g, 0.20 mmol) was stirred with an excess of doubly sublimed magnesium (0.102 g, 4.20 mmol) in dry THF (10 ml) at room temperature. Gradually, a white precipitate formed. After 13 days of stirring, the black magnesium dust and the precipitate was allowed to settle, and the vessel was stored at room temperature for a long period. After 3 months, a sample (3.70 ml) of the clear supernatant was decanted into a second vessel connected to the reaction vessel, after which it was disconnected by sealing off at a capillary. Titration of this sample showed that 0.019 mmol of 'total base' and 0.018 mmol of Mg^{2+} were present [10]. The solubility of **15** in THF was too low for ^{1}H-NMR spectroscopy.

The remaining reaction mixture was quenched with an excess of deuterium oxide (0.50 ml, 27.63 mmol). Standard acidic work up yielded 0.043 g of a pale yellow oil, which was identified by ^{1}H-NMR spectroscopy and GC/MS as **2**/**2a** (91% deuterium incorporation). The presence of about 0.02 mmol of **15** in the sample which was titrated and 0.13 mmol in the remaining mixture which was quenched with deuterium oxide, indicates a total yield of about 75% of **15**.

3.13. Reaction of bromobenzene with magnesium in the presence of **15**

In sealed glass apparatus, a solution of bromobenzene (0.20 ml, 1.91 mmol) in THF (10 ml) was added at room temperature to a vessel containing excess of magnesium, and **15** (0.20 mmol) in THF (10 ml), prepared from **8** with an excess of doubly sublimed magnesium (0.170 g, 6.99 mmol) as described above. In order to prevent a too vigorous reaction, the bromobenzene was added in small portions during 2 h, after which the stirring was continued for additional 45 min. The reaction vessel was opened and the reaction mixture quenched carefully with deuterium oxide (0.70 ml, 38.68 mmol). After evaporating to dryness, dichloromethane (10 ml) and 5 ml of aqueous saturated solution of ammonium chloride were added. After a thorough extraction with dichloromethane, the organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. According to its ^{1}H-NMR spectrum, the oily residue was essentially pure **2**/**2a** (89% deuterium incorporation). GC/MS analysis of this residue revealed only 3% of unidentified products, possibly ether cleavage products which, however, were not identified.

3.14. (2-n-Butyl-1,3-phenylene)-19-crown-6 (**16**)

A solution of **4** (0.20 mmol) in THF (2 ml), prepared at −65°C from **8** and *n*-butyllithium, was allowed to warm to room temperature overnight and then quenched with deuterium oxide (0.50 ml, 27.63 mmol). The standard work up procedure yielded 0.040 g of a pale yellow oil, which was analyzed by GC/MS and ^{1}H-NMR spectroscopy. In addition to unknown products, three compounds were identified by GC/MS analysis: a mixture of **2**/**2a** (51%, ratio 85:15), and **16** (49%). Purification of **16** was performed by preparative GC,

Table 2
Numerical data of the structure determination for 8

Crystal data	
Empirical formula	$C_{16}H_{23}Br_{1}O_{6}$
Formula weight	391.26
Crystal system	Orthorhombic
Space group	*P*212121 (No. 19)
a (Å)	8.451 (2)
b (Å)	23.171 (6)
c (Å)	25.837 (6)
V (Å^{3})	5059 (2)
Z	12
$D_{calc.}$ (g cm^{-3})	1.541
F(000) (electrons)	2424
μ (Mo–K_{α}) (cm)	24.7
Crystal size (mm)	0.25 × 0.45 × 0.50
Data collection	
Temperature (K)	150
Radiation (Å) Mo–K_{α} (with monochromator)	0.71073
θ min-max (°)	1.2, 22.5
Scan type, scan (°)	ω, 0.90 + 0.35 Tan(θ)
Data set	0:9/0:24/0.27
Total, unique data	3761, 3730
Observed data [I > 2.0σ(I)]	2993
DELABS transmission range	0.533, 1.000
Refinement	
N_{ref}, N_{par}	3730, 622
R, *wR*, *S*	0.0396, 0.0831, 1.05
Maximum and average shift/error	0.000, 0.000
Largest difference peak and hole (e Å^{-3})	−0.32, 0.49
Flack absolute structure parameter	0.02 (1)

$w = 1/[\sigma^2(F_o^2) + (0.0345P)^2 + 1.8276P]$ where $P = (F_o^2 + 2F_c^2)/3$.

Table 3
Final coordinates and equivalent isotropic thermal parameters of the non-hydrogen atoms for **8**

Atom	x	y	z	U_{eq} (Å^2)
Br(30)	0.47086(13)	.38009(4)	−0.00551(3)	−0.0369(3)
O(302)	0.5656(8)	0.4887(2)	0.0445(2)	0.0277(19)
O(305)	0.3585(9)	0.5309(3)	0.1262(3)	0.048(3)
O(308)	0.2823(8)	0.4164(3)	0.1658(3)	0.069(3)
O(311)	0.2810(9)	0.2740(3)	0.1386(2)	0.049(3)
O(314)	0.4744(8)	0.1889(3)	0.0883(2)	0.035(2)
O(317)	0.6533(7)	0.2898(2)	0.0495(2)	0.026(2)
C(301)	0.6567(11)	0.4458(4)	0.0637(3)	0.022(3)
C(303)	0.5717(13)	0.5450(4)	0.0670(3)	0.035(3)
C(304)	0.5207(13)	0.5479(4)	0.1228(3)	0.042(4)
C(306)	0.3141(13)	0.5164(5)	0.1778(3)	0.048(4)
C(307)	0.3683(13)	0.4582(4)	0.1936(4)	0.052(4)
C(309)[a]	0.3501(17)	0.3671(6)	0.1646(7)	0.040(5)
C(310)	0.2650(14)	0.3305(4)	0.1215(5)	0.072(6)
C(312)	0.2261(12)	0.2314(4)	0.1039(4)	0.040(4)
C(313)	0.3449(11)	0.2151(4)	0.0635(3)	0.033(3)
C(315)	0.6191(11)	0.1887(4)	0.0590(3)	0.026(3)
C(316)	0.7196(11)	0.2387(3)	0.0721(3)	0.025(3)
C(318)	0.7029(11)	0.3425(4)	0.0659(3)	0.021(3)
C(319)	0.8251(11)	0.3508(4)	0.1004(3)	0.026(3)
C(320)	0.8637(11)	0.4059(4)	0.1158(3)	0.029(3)
C(321)	0.7810(10)	0.4539(4)	0.0980(3)	0.025(3)
C(322)	0.6244(10)	0.3909(4)	0.0465(3)	0.020(3)
C(409)[a]	0.351(4)	0.3830(15)	0.1309(16)	0.025(12)
Br(10)	−0.05348(11)	0.11002(4)	0.65837(3)	0.0293(3)
O(102)	0.0963(7)	0.0037(2)	0.6208(2)	0.0267(19)
O(105)	−0.0955(7)	−0.0329(3)	0.5368(2)	0.027(2)
O(108)	−0.1752(7)	0.0850(2)	0.5022(2)	0.030(2)
O(111)	−0.1440(8)	0.2382(3)	0.5111(2)	0.034(2)
O(114)	0.0330(8)	0.3125(2)	0.5830(2)	0.027(2)
O(117)	0.1625(7)	0.2034(2)	0.6266(2)	0.0230(19)
C(101)	0.1890(11)	0.0488(4)	0.6068(3)	0.020(3)
C(103)	0.1156(12)	−0.0501(4)	0.5948(3)	0.030(3)
C(104)	0.0674(11)	−0.0474(3)	0.5391(3)	0.021(3)
C(106)	−0.1463(11)	−0.0161(4)	0.4871(3)	0.027(3)
C(107)	−0.0959(11)	0.0430(3)	0.4716(3)	0.027(3)
C(109)	−0.1108(11)	0.1399(4)	0.4953(3)	0.033(3)
C(110)	−0.2097(11)	0.1835(4)	0.5230(3)	0.032(3)
C(112)	−0.2057(12)	0.2828(4)	0.5437(3)	0.035(3)
C(113)	−0.1191(11)	0.2883(4)	0.5934(3)	0.027(3)
C(115)	0.1428(12)	0.3060(4)	0.6245(3)	0.030(3)
C(116)	0.2510(11)	0.2556(4)	0.6156(3)	0.031(3)
C(118)	0.2271(11)	0.1531(4)	0.6119(3)	0.022(3)
C(119)	0.3683(11)	0.1470(4)	0.5859(3)	0.025(3)
C(120)	0.4190(10)	0.0930(4)	0.5705(3)	0.026(3)
C(121)	0.3333(11)	0.0448(4)	0.5802(3)	0.027(3)
C(122)	0.1401(10)	0.1037(4)	0.6222(3)	0.020(3)
Br(20)	0.04532(12)	0.10723(4)	0.35084(3)	0.0301(3)
O(202)	0.2089(8)	0.0233(2)	0.2836(2)	0.028(2)
O(205)	0.0257(8)	0.0118(3)	0.1925(2)	0.036(2)
O(208)	−0.2295(7)	0.1047(3)	0.1677(2)	0.036(2)
O(211)	−0.2379(7)	0.2239(3)	0.2014(2)	0.033(2)
O(214)	−0.1094(8)	0.3029(3)	0.2785(2)	0.032(2)
O(217)	0.1316(7)	0.2209(2)	0.3101(2)	0.031(2)
C(201)	0.2435(10)	0.0774(4)	0.2669(3)	0.023(3)
C(203)	0.2218(13)	−0.0245(4)	0.2484(3)	0.039(4)
C(204)	0.0649(12)	−0.0361(4)	0.2229(3)	0.033(3)
C(206)	0.1263(11)	0.0047(4)	0.1680(3)	0.035(3)
C(207)	−0.1637(12)	0.0593(4)	0.1383(3)	0.038(3)
C(209)	−0.1211(11)	0.1298(4)	0.2030(3)	0.033(3)
C(210)	−0.2047(11)	0.1759(4)	0.2334(3)	0.027(3)
C(212)	−0.3258(12)	0.2678(4)	0.2275(3)	0.035(4)
C(213)	−0.2290(12)	0.3180(4)	0.2427(4)	0.040(4)
C(215)	0.0433(14)	0.3014(4)	0.2572(4)	0.040(3)
C(216)	0.1533(12)	0.2811(4)	0.2977(4)	0.040(4)
C(218)	0.2043(11)	0.1801(4)	0.2807(3)	0.027(3)
C(219)	0.3018(12)	0.1919(4)	0.2391(4)	0.036(4)
C(220)	0.3740(12)	0.1463(4)	0.2134(3)	0.036(3)
C(221)	0.3483(11)	0.0897(4)	0.2262(3)	0.032(3)
C(222)	0.1787(10)	0.1231(4)	0.2939(3)	0.022(3)

U_{eq}, one-third of the trace of the orthogonalized U.
[a] C(309)/C(409) are disordered in the ratio 0.73:0.27; atom sites have a population less than 1.0.

although complete separation from **2**/**2a** was not possible.

^{1}H-NMR (200.13 MHz, $CDCl_3$, ref. $C\mathit{H}Cl_3 = 7.27$ ppm): δ 0.93 (t, $^3J = 6.8$ Hz, 3H, n-C_3H_6–$C\mathit{H}_3$), 1.26–1.59 (m, 4H, $CH_2C\mathit{H}_2C\mathit{H}_2CH_3$), 2.81 (t, $^3J = 7.3$ Hz, 2H, $C\mathit{H}_2$–C_3H_7), 3.49–3.89 (m, 16H, $C\mathit{H}_2O(2)C\mathit{H}_2$-$C\mathit{H}_2O(3)C\mathit{H}_2$), 4.06–4.33 (m, 4H, $O(1)C\mathit{H}_2CH_2O(2)$), 6.54 (d, $^3J = 8.2$ Hz, 2H, aryl H(4,6)), 7.04 (t, $^3J = 8.2$ Hz, 1H, aryl H(5)). $^{13}C\{^1H\}$-NMR (50.32 MHz, $CDCl_3$, ref. $\mathit{C}DCl_3 = 77$ ppm): δ 14.18, 22.94, 23.22 and 31.84 (4C, n-Bu), 68.71, 69.68, 70.34, 70.60 and 71.29 (10C, C_2H_4), 106.78, 108.30, 125.83 and 157.63 (6C, aryl C). GC/MS: m/z (relative intensity) 368 (M^+; $C_{20}H_{32}O_6$, 63), 192 (19), 177 (8), 164 (26), 149 (37), 133 (21), 124 (23), 117 (9), 107 (13), 91 (18), 89 (27), 73 (28), 45 (100). HRMS: Anal. Calc. for $C_{20}H_{32}O_6$ 368.2199, found 368.2194 ± 0.0010.

3.15. X-ray structure determination of **8**

Numerical data on the structure determination have been collected in Table 2. X-ray data were collected for a colorless transparent crystal cut to shape and transferred into the cold dinitrogen stream on an ENRAF-NONIUS CAD4 diffractometer (rotating anode, Mo–K_α radiation). Intensity data were corrected for absorption (PLATON/DELABS [11]). The structure was solved with standard direct methods (SHELXS-86 [12]) and difference Fourier techniques and refined on F^2 with SHELXL-93 [13]. Molecule no. 3 was refined with a disorder model (0.73(3):0.27) for the pair C309/C409. Hydrogen atoms were taken into account at calculated positions and refined riding on the atoms they are attached to with isotropic displacement parameters related to U_{eq} of the carrier atom (Table 3). Geometrical calculations and the illustrations were performed with PLATON [11]. Final coordinates are given in [3]. Full details may be obtained from the author, A.L. Spek.

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