Chapter 2
Crown Ethers

2.1. Introduction

Since Pedersen's discovery of crown ethers and their abilities to bind strongly with metal ions in 1967,[1,2] the study of crown ethers has grown at an incredible rate. The syntheses of many different types of crown ethers, *e.g.*, crown ether diesters, azacrown ethers, thiacrown ethers, and chiral crown ethers, have been documented in the literature and their binding properties such as binding selectivity and strength toward a wide range of metal ions, nonmetal ions, and neutral molecules have been investigated.[3,4] Because of their remarkable binding properties, the study of crown ethers has largely contributed to the development of host-guest chemistry and the emergence of supramolecular chemistry (section 1.3.1). In 1987 the Nobel Prize was awarded to recognize three chemists, Pederson,[5] Cram,[6] and Lehn,[7] who made important advances in host-guest and supramolecular chemistry.

As stated in section 1.5 our research was inspired primarily by the work of Stoddart and his coworkers on pseudorotaxanes using crown ethers and nonmetal ions.[8-32] In order to construct large ordered aggregates such as dendrimers and linear arrays utilizing this concept, it was essential to prepare functionalized crown ethers. In this chapter the syntheses of a nonfunctional crown ether, monofunctional crown ethers, and difunctional crown ethers are described.

2.2. Syntheses of the Crown Ethers

Crown ethers are named as x-crown-y where x denotes the total number of atoms in the cyclic backbone and y denotes the number of oxygen atoms. All the crown ethers were synthesized by "2+2" approaches but in two steps because our previous studies indicated that one-step methods generally gave poor yields.[33] The low yields are partially due to the formation of the 1+1 products. As an example, the one-pot synthesis of bis(5-carbomethoxy-1,3-phenylene-32-crown-10 (the 2+2 product) from methyl 3,5-dyhydroxybenzoate and tetra(ethylene glycol) dichloride resulted in 9% yield in a one

step process,[33] while the two-step approach to the same crown ether gave a 46% yield for the second step.[34]

The first steps involved the Williamsen ether syntheses between excess dichloride derivatives of the appropriate ethylene glycols and the appropriate bishydroxy benzenes in the presence of a base to obtain the corresponding precursors. In the cyclization steps the precursors were reacted with the appropriate bishydroxy benzenes in the presence of a weak base by utilizing the Williamsen ether synthesis and the pseudo high dilution technique. This section is divided into three subsections to describe the synthesis of the three types of crown ethers.

2.2.1. Nonfunctional crown ether

The strategy employed to synthesize the known bis-*p*-phenylene-34-crown-10 (**4**)[35] is shown in Figure 2.1. Tetra(ethylene glycol) (**1**) was halogenated by using a standard protocol[36] with thionyl chloride and pyridine in refluxing toluene to obtain tetra(ethylene glycol) dichloride (**2**). The dianion derived from hydroquinone was reacted *in situ* with 20-fold excess of **2** to afford the bis[*ω*-chlorotetra(ethyleneoxy)] derivative (**3**) of hydroquinone.[35] In the subsequent step, equimolar solutions of **3** and hydroquinone were slowly added *via* syringe to a flask containing a suspension of potassium carbonate in DMF to yield the cyclization product **4**.[35] In the ^{1}H NMR spectrum of **4** a sharp singlet corresponding to the aromatic protons observed at 6.75 ppm is indicative of formation of the desired product.

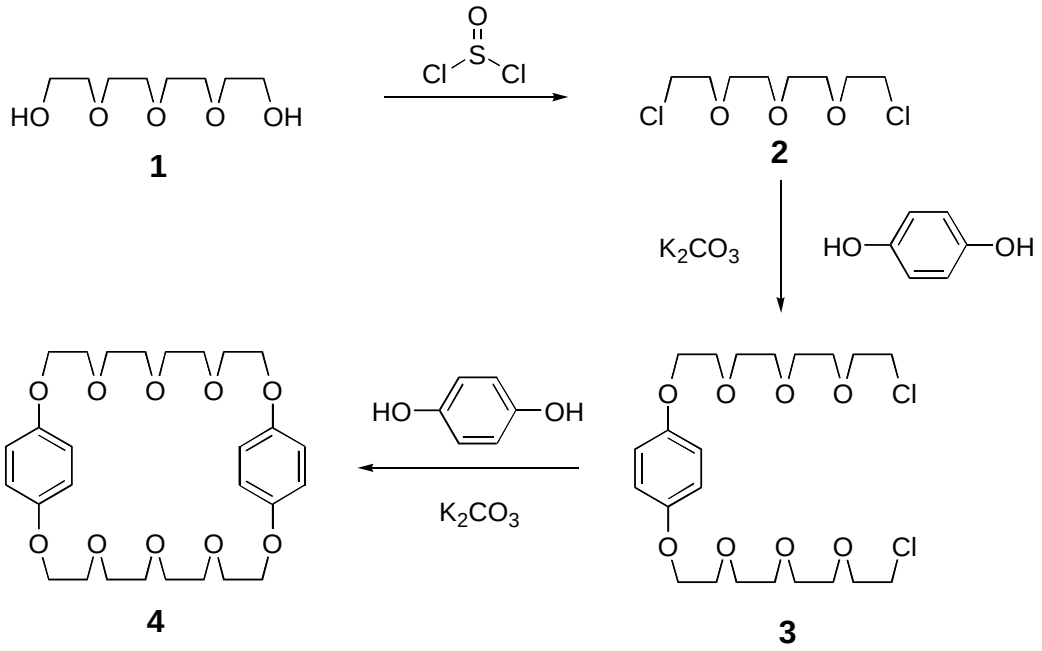

Figure 2.1. The synthetic routes to **4**.

2.2.2. Monofunctional crown ethers

The two-step approach employed to synthesize 5-methoxycarbonyldibenzo-25-crown-8 (**9**), a new compound, is depicted in Figure 2.2. In the first step a 13-fold excess of commercially available 1,2-bis(2-chloroethoxy)ethane (**5**) was reacted with the dianion derived from catechol to obtain *o*-bis(8-chloro-3,6-dioxaoctyloxy)benzene (**6**) in 83% yield. In the second step, this dichloride precursor **6** was cyclized with methyl 3,5-dihydroxybenzoate (**7**), prepared by esterification of 3,5-dihydroxybenzoic acid and methanol, to form the new ester functionalized crown ether **8** in 14% yield. The ester group in **8** was later converted to a primary alcohol group in new compound **9** by reduction with lithium aluminum hydride (LAH) (Figure 2.5).

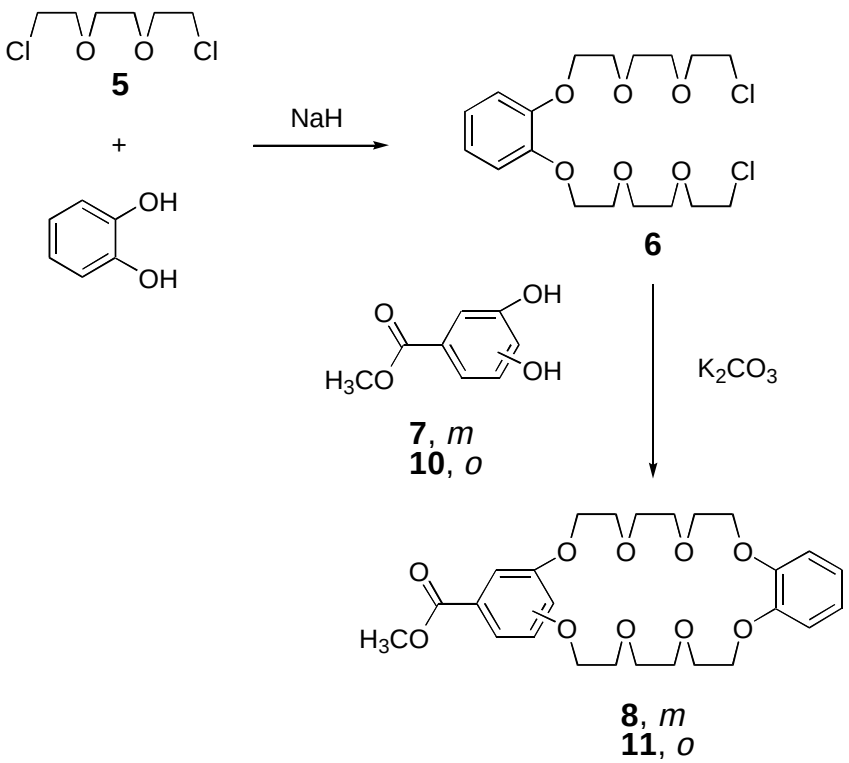

Figure 2.2. Two-step syntheses of **8** and **11**.

The ^{1}H NMR spectrum of **8** (Figure 2.3) reveals that the signal corresponding to the protons adjacent to the ester group, H_a, is shifted downfield from the proton located in the cavity of the crown ether, H_b. This deshielding effect on the H_a protons is a direct consequence of the adjacent electron withdrawing ester group. The signals for the protons in the ethyleneoxy units and –COOCH_3 are in good agreement with the structure of **8**.

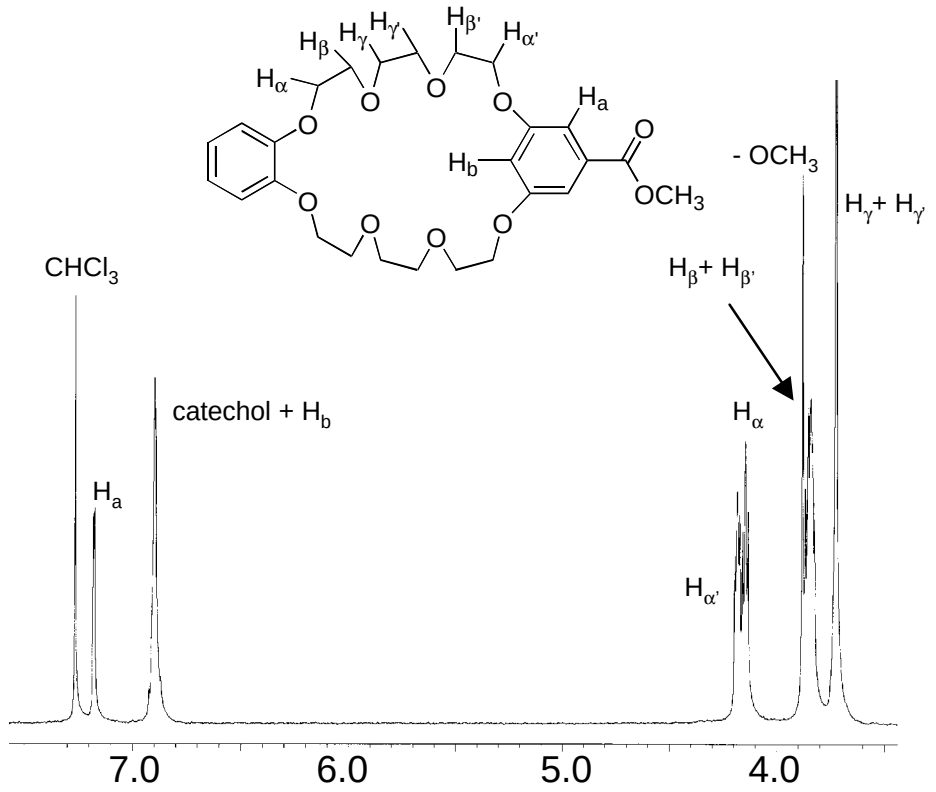

Figure 2.3. The ^{1}H NMR spectrum of **8** (400 MHz, chloroform-*d*, 22^{o}C).

Similarly, the dichloride precursor **6** was reacted with a stoichiometric amount of methyl 3,4-dihydroxybenzoate (**10**), prepared by the esterification of 3,4-dihydroxybenzoic acid and methanol, to yield 4-methoxycarbonyldibenzo-24-crown-8 (**11**), a new compound, in 40% yield.

The ^{1}H NMR spectrum of **11** (Figure 2.4) exhibits four sets of triplets for H_α, $H_{\alpha'}$, H_β, and $H_{\beta'}$ of the ethyleneoxy units and a singlet for H_γ and $H_{\gamma'}$. A sharp singlet at 3.83 ppm corresponds to the signal for the protons of –COOCH_3. The signals for the protons on the catechol emerge as a multiplet in the region of 6.86-6.96 ppm. The signals at 7.52, 7.61, and 7.04 ppm are due to the protons on the substituted catechol, H_c, H_d, and H_e, respectively. The deshielded nature of those protons, particularly H_c and H_d, can be understood in terms of the electron withdrawing ability of the ester group attached on the catechol unit.

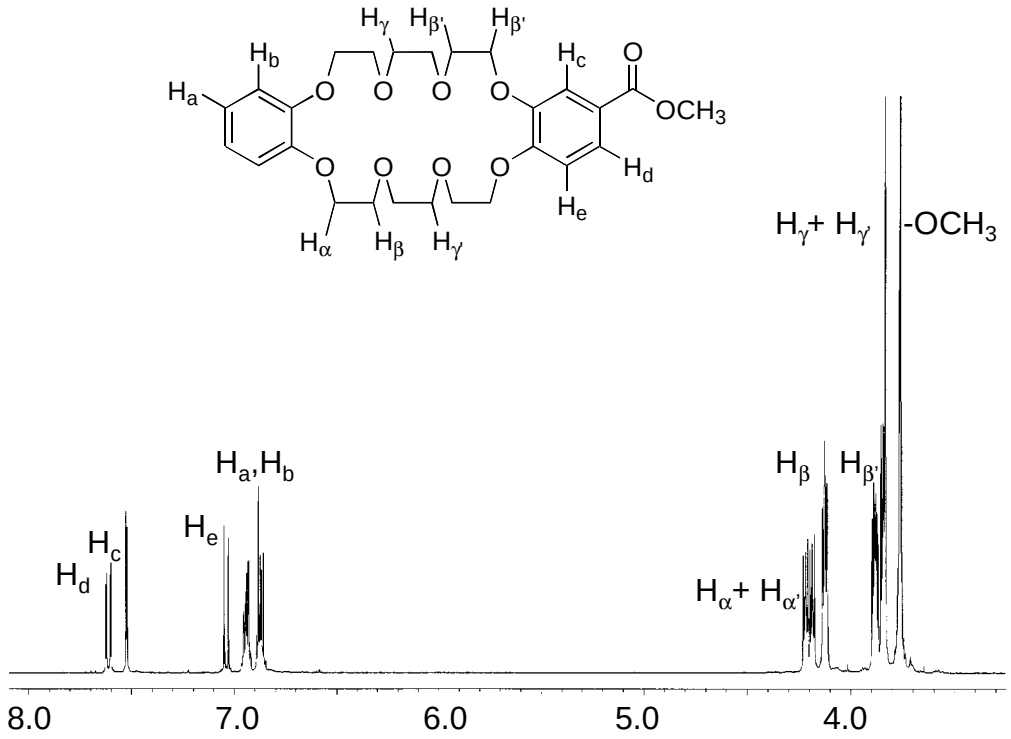

Figure 2.4. The ^{1}H NMR spectrum of **11** (400 MHz, acetone-d_6, 22^{o}C).

As illustrated in Figure 2.5 the ester group of **11** was first reduced to give a primary alcohol (**12**), a new compound, which was then oxidized with pyridinium chlorochromate (PCC) to an aldehyde (**13**), a known compound,[37] in 92 and 60% yields, respectively. The ^{1}H NMR spectrum of **12** exhibits a triplet for -O*H* and a doublet for the benzylic protons at 5.00 and 4.59 ppm, respectively. The signals for all the catechol protons appear as a multiplet, integrated for seven protons, in the region of 6.84-6.92 ppm, since the protons on the substituted catechol unit no longer experience a deshielding effect from the functional group. In contrast, the ^{1}H NMR spectrum of **13** shows that the signals for the aromatic protons on the substituted catechol unit emerge further downfield from those on the unsubstituted catechol unit due to the electron withdrawing nature of the aldehyde group. Additional evidence for the formation of **13** came from a characteristic singlet for -C*H*O at 9.82 ppm.

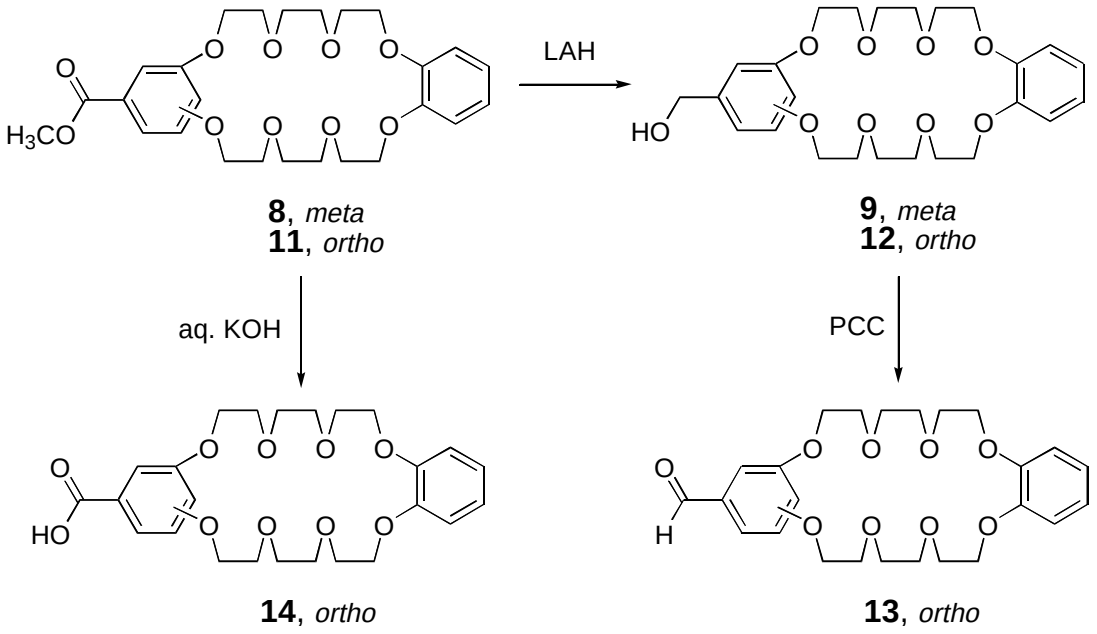

Figure 2.5. The syntheses of monosubstituted 24- and 25-crown-8 derivatives.

The ester **11** was also converted to the new carboxylic acid **14** (Figure 2.5). The melting point of **14** (182-183^{o}C) was significantly higher than that of **11** (83-85^{o}C) and the IR spectrum revealed an intense –OH stretch at 3400 cm^{-1}, indicating the formation of the acid functionality in **14**.

The synthetic methods employed to prepare 5-methoxycarbonyl-1,3-phenylene-*m*-phenylene-32-crown-10 (**16**) are shown in Figure 2.6. The bis[ω-chlorotetra(ethyleneoxy)] derivative **15**[34] of resorcinol was prepared by reacting tetra(ethylene glycol) dichloride (**2**) and the anion derived from resorcinol. Compound **15** was then reacted with methyl 3,5-dihydroxybenzoate (**7**) in the presence of weak base using a high dilution condition to give the ester substituted crown ether **16**[34] in 26% yield. The LAH reduction of **16** gave **17**,[34] which was subsequently brominated to afford **18**.[34] Bromination of **16** was initially carried out in an acidic aqueous medium with sodium bromide. Since the starting materials were left unreacted, an alternative synthetic path was sought. Bromination was eventually achieved using tribromophosphine in ethereal solution. The first indication of the product formation was an upfield chemical shift of the resonance for the benzyl protons in the ^{1}H NMR spectrum. Shielding of the benzyl protons results from the substitution of -OH with less

electronegative -Br. Further evidence of the successful bromination came from a sharp singlet resonance for the benzylic protons.

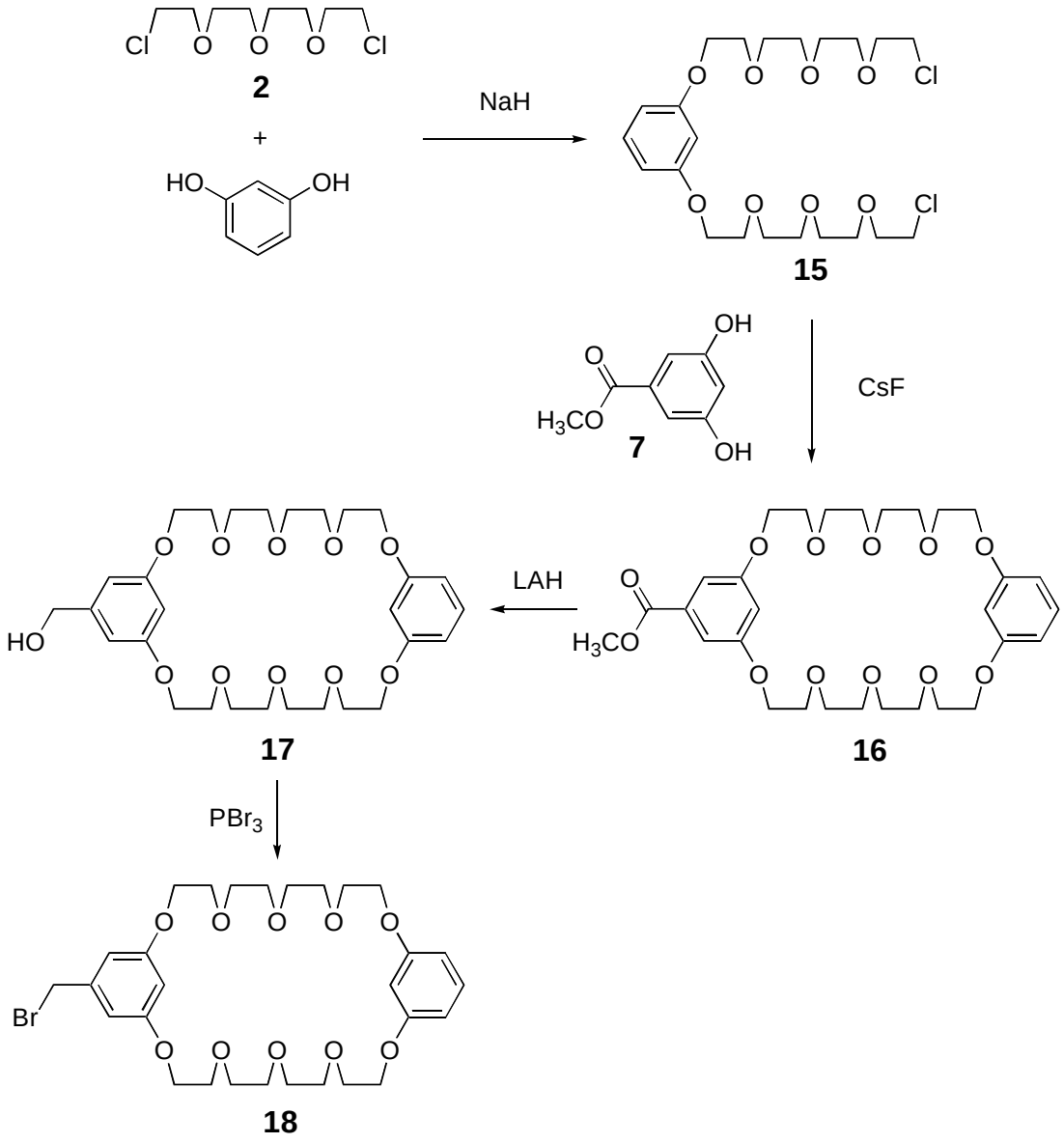

Figure 2.6. The syntheses of monosubstituted 32-crown-10 derivatives.

2.2.3. Difunctional crown ethers

The dianion derived from **7** was reacted *in situ* with excess **2** to give **19** (Figure 2.7).[38] In the subsequent step, **19** and **7** was reacted in a pseudo high dilute condition to obtain the disubstituted 32-crown-10 (**20**).[38] A sharp singlet for the methoxy protons

observed at 3.87 ppm in the ^{1}H NMR spectrum of **20** integrated for six protons, indicating that **20** is substituted with two methyl ester groups. The successful reduction of **20** with LAH gave **21**.[38] The ^{1}H NMR spectrum of **21** showed a new signal at 4.56 ppm for the benzylic protons.

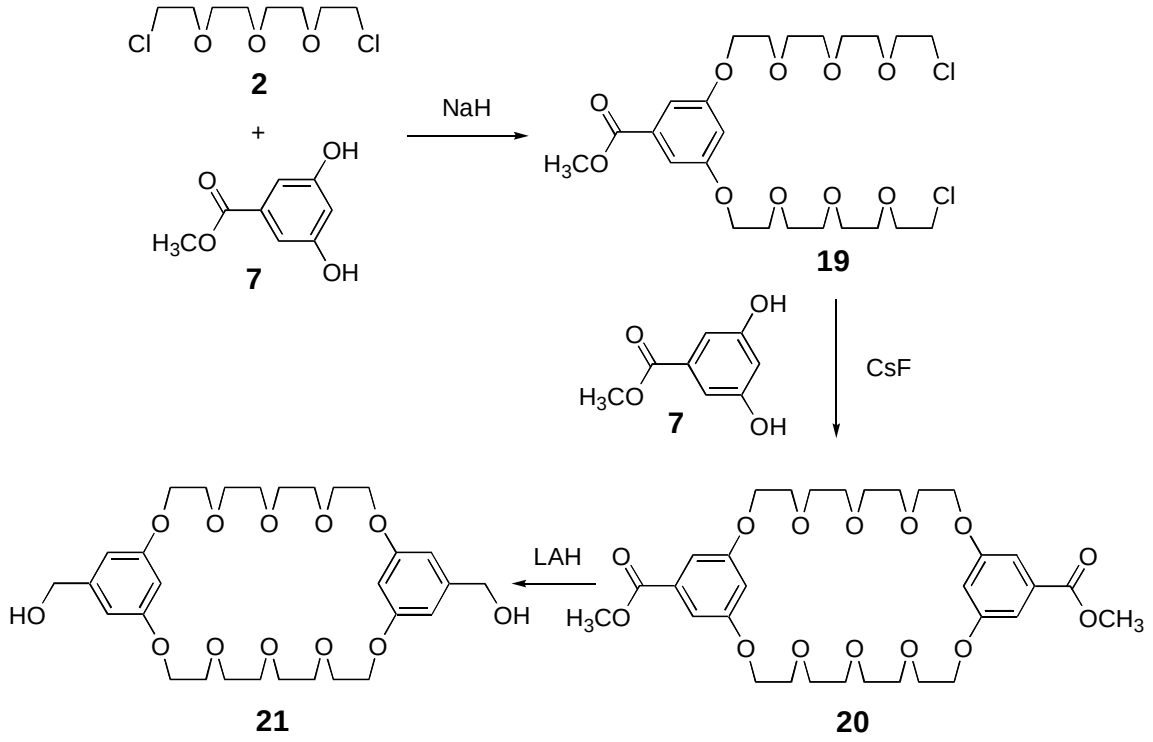

Figure 2.7. The syntheses of difunctionalized 32-crown-10 derivatives.

2.3. Conclusions

As stated in section 1.5 several non-, mono-, and di-substituted crown ethers were synthesized with the intention of preparing building blocks that are capable of self-assembling into supramolecular structures of different sizes and shapes. The two-step approaches significantly improved the yields of the crown ether syntheses by minimizing the formation of linear and cyclic oligomeric by-products. In general, the cyclization reactions were scaled up compared to the previous attempts in our laboratories[34,35,38] so as to obtain the crown ethers in gram quantities.

2.4. Experimental

Tetrahydrofuran (THF) was distilled from Na and benzophenone. Pyridine and was stirred with CaH_2 overnight and distilled prior to use. All other solvents were used as received. Tetra(ethylene glycol) dichloride (**2**) and 1,2-bis(2-chloroethoxy)ethane (**5**) were distilled *in vacuo* just before use. Melting points were taken on a Mel-Temp II melting point apparatus and are uncorrected. The 400 MHz ^{1}H NMR spectra were recorded on a Varian Unity with tetramethylsilane (TMS) as an internal standard. The following abbreviations are used to denote splitting patterns: s (singlet), d (doublet), t (triplet), and m (multiplet). The IR spectra were taken on a Nicolet Impact 400 infrared spectrometer using pulverized KBr as the medium. Differential scanning calorimetry (DSC) was performed on a Perkin-Elmer Series-4 calorimeter under a nitrogen purge using indium as the calibration standard. Elemental analyses were obtained from Atlantic Microlab, Norcross, GA. Mass spectra were provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).

Tetra(ethylene glycol) dichloride (2). To a 5 L round bottom flask equipped with a magnetic stirrer, condenser, and N_2 inlet were added tetra(ethylene glycol) (**1**) (500 g, 2.57 mol), pyridine (468 mL, 5.79 mol), and toluene (2 L). To this was added thionyl chloride (420 mL, 5.76 mol) dropwise over the period of 6 hours and the reaction mixture was refluxed for 2 days. The salts were filtered and the filtrate was concentrated to give a brown liquid. The crude product was subject to vacuum distillation to yield a colorless liquid (430 g, 72% yield), bp 107^{o}C @0.50 mmHg (lit.[36] bp 98-100^{o}C @0.20 mmHg). ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=3.60 (4H, t, J = 5.6 Hz), 3.64 (8H, s), and 3.73 (4H, t, J = 5.6 Hz).

***p*-Bis(11-chloro-3,6,9-trioxa-1-undecyloxy)benzene (3).** To a 250 mL round bottom flask equipped with a magnetic stirrer were added hydroquinone (3.00g, 27.2 mmol) and DMF (55 mL). To this was added in small portions K_2CO_3 (4.14 g, 30.0 mmol) and the mixture was stirred for 3 h at 110°C and cooled to 25°C. A solution of **2** (126 g, 545 mmol) in DMF (40 mL) was then added to it at once and the mixture was stirred for 5 days at 50°C. Upon completion of the reaction the salts were filtered with an aid of

Celite and the filtrate was concentrated on a rotary evaporator to give a brown liquid, which was vacuum distilled to remove excess dichloride **2**. The crude product was subjected to liquid-liquid extraction using petroleum ether to afford a yellow liquid[35] (9.36 g, 67% yield). ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=3.63 (4H, t, *J* = 5.6 Hz), 3.69 (12H, m), 3.75 (8H, t, *J* = 5.6 Hz), 3.83 (4H, t, *J* = 5.6 Hz), 4.09 (4H, t, *J* = 5.6 Hz) and 6.83 (4H, s).

Bis-*p*-phenylene-34-crown-10 (4). To a 5 L three necked round bottom flask equipped with a mechanical stirrer, N_2 inlet and a thermometer were added DMF (3.5 L), *n*Bu_4NI (100 mg) and K_2CO_3 (80.6 g, 584 mmol) and the mixture was brought to 110^{o}C. To this was added a solution of **3** (25.4 g, 61.8 mmol) and hydroquinone (10.4 g, 61.8 mmol) in DMF (120 mL) *via* syringe pump at the rate of 0.75 mL/h. After the completion of the addition, the reaction mixture was vigorously stirred for 3 days, cooled to 25^{o}C, and filtered with the aid of Celite. The solvent was rotary evaporated to give a brown viscous liquid. This was preabsorbed onto silica gel and the product was continuously extracted with Et_2O using a Soxhlet extraction apparatus. After the solvent was removed the resulting yellow solid was recrystallized from EtOH to give a white powder (1.72 g, 10% yield), mp 107-108^{o}C (lit.[35] mp 94.3-95.6^{o}C). ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=3.71 (16H, s), 3.84 (8H, t, *J* = 4.8 Hz), 3.99 (8H, t, *J* = 4.8 Hz), and 6.75 (8H, s).

***o*-Bis(8-chloro-3,6-dioxa-1-octyloxy)benzene (6).** To a 250 mL round bottom flask equipped with a magnetic stirrer were added catechol (11.0 g, 0.100 mmol) and DMF (60 mL). To this were added small portions of NaH (10.0 g, 0.251 mmol) and the mixture was stirred for 3 h at 110°C and cooled to 25°C. A solution of **5** (245 g, 1.31 mmol) in DMF (40 mL) was then added to it at once and the mixture was stirred for 5 days at 50°C. Upon completion of the reaction the salts were filtered with the aid of Celite and the filtrate was concentrated on a rotary evaporator to give a brown liquid, which was vacuum distilled to remove excess of dichloride **5**. The crude product was subjected to a short column of silica gel using diethyl ether to afford a yellow liquid[39] (34.3 g, 83% yield). ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=3.63 (4H, t, *J* = 5.6 Hz), 3.69 (8H,

m), 3.75 (4H, t, J = 5.6 Hz), 3.87 (4H, t, J = 5.6 Hz), 4.17 (4H, t, J = 5.6 Hz) and 6.92 (4H, m).

Methyl 3,5-dihydroxybenzoate (7). To a 250 mL round bottom flask equipped with a magnetic stirrer and condenser were added 3,5-dihydroxybenzoic acid (10.1 g, 65.6 mmol), methanol (55 mL), and concentrated sulfuric acid (5 mL) and the reaction mixture was refluxed for 2 days. Upon completion of the reaction the solvent was removed *in vacuo* and the resulting black solid was diluted with acetone and decolorized. The filtrate was concentrated and recrystallized twice from water to afford a brown solid (8.32 g, 76% yield), mp 140-142°C (lit.[33] mp 167-169°C). ^{1}H NMR (400 MHz, DMSO-d_6, 22°C): δ=3.75 (3H, s), 6.79 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 8.0 Hz), 7.34 (1H, d, J = 2.0 Hz) and 9.55 (2H, s).

5-Methoxycarbonyldibenzo-25-crown-8 (8). To a 5 L three necked round bottom flask equipped with a mechanical stirrer, N_2 inlet and a thermometer were added DMF (3.5 L), nBu$_4$NI (100 mg) and K_2CO_3 (40.3 g, 292 mmol) and the mixture was brought to 110°C. To this was added a solution of **6** (11.9 g, 29.0 mmol) and **7** (4.87 g, 29.0 mmol) in DMF (120 mL) *via* syringe pump at the rate of 0.75 mL/h. After the completion of the addition, the reaction mixture was vigorously stirred for 3 days, cooled to 25°C, and filtered with the aid of Celite. The solvent was rotary evaporated to give a brown viscous liquid. This was preabsorbed onto silica gel and the product was continuously extracted with Et_2O using a Soxhlet extraction apparatus. After the solvent was removed the resulting yellow solid was recrystallized from EtOH to give a white powder (2.03 g, 14% yield), mp 73-74°C. ^{1}H NMR (400 MHz, acetone-d_6, 22°C): δ=3.68 (8H, s), 3.80 (8H, t, J = 4.8 Hz), 4.21 (8H, t, J = 4.8 Hz), 6.83-6.94 (4H, m), 6.97 (1H, t, J = 2.4 Hz), and 7.07 (2H, d, J = 2.4 Hz). LRFAB: m/z = 506.3 $[M]^+$. HRFAB: calcd for $[M]^+$ $C_{26}H_{34}O_{10}$ 506.2152, found 506.2155. Anal. Calcd for $C_{26}H_{34}O_{10}$: C, 61.65; H, 6.77, found: C, 61.77; H, 6.81.

5-Hydroxymethyldibenzo-25-crown-8 (9). To a 250 mL two necked round bottom flask equipped with a mechanical stirrer and a N_2 inlet were added **8** (1.00 g, 1.97 mmol)

and anhydrous THF (100 mL). To this was added LAH (2.16 mL 1.0 M THF solution, 1.1 equiv.) *via* syringe and the mixture was vigorously stirred for 12 h at room temperature. A small amount of EtOAc was added to quench the reaction and the solvents were removed to give a white solid, which was suspended in H_2O and neutralized with 2M HCl. The solution was extracted with $CHCl_3$ and the organic layers were combined, dried over $MgSO_4$ and concentrated to give a white solid, which was recrystallized from EtOH (0.78 g, 83% yield), mp 78–80°C. ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.72 (8H, s), 3.81 (8H, m), 4.14 (8H, m), 4.58 (2H, d, *J* = 6.4 Hz), 6.52 (2H, d, *J* = 1.6 Hz), 6.61 (1H, t, *J* = 1.6 Hz), and 6.88-6.93 (4H, m). LRFAB: *m/z* = 478.3 $[M]^+$. HRFAB: calcd for $[M]^+$ $C_{25}H_{34}O_9$: 478.2203, found 478.2183. Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.73; H, 7.17, found: C, 62.58; H, 7.17.

Methyl 3,4-dihydroxybenzoate (10). To a 250 mL round bottom flask equipped with a magnetic stirrer and condenser were added 3,4-dihydroxybenzoic acid (10.1 g, 65.6 mmol), methanol (55 mL), and concentrated sulfuric acid (5 mL) and the reaction mixture was refluxed for 2 days. Upon completion of the reaction the solvent was removed *in vacuo* and the resulting black solid was diluted with acetone and decolorized. The filtrate was concentrated and recrystallized twice from water to afford a brown solid (8.32 g, 76% yield), mp 140-142°C (lit.[40] mp 134.5-135°C). ^{1}H NMR (400 MHz, DMSO-d_6, 22°C): δ=3.75 (3H, s), 6.79 (1H, d, *J* = 8.0 Hz), 7.30 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 2.0 Hz), and 9.55 (2H, s).

4-Methoxycarbonyldibenzo-24-crown-8 (11). To a 5 L three necked round bottom flask equipped with a mechanical stirrer, N_2 inlet and a thermometer were added DMF (3.5 L), nBu$_4$NI (100 mg) and K_2CO_3 (80.6 g, 584 mmol) and the mixture was brought to 110°C. To this was added a solution of **6** (25.4 g, 61.8 mmol) and **10** (10.4 g, 61.8 mmol) in DMF (120 mL) via syringe pump at the rate of 0.75 mL/h. After the completion of the addition, the reaction mixture was vigorously stirred for 3 days, cooled to 25°C, and filtered with the aid of Celite. The solvent was rotary evaporated to give a brown viscous liquid. This was preabsorbed onto silica gel and the product was continuously extracted with Et_2O using a Soxhlet extraction apparatus. After the solvent

was removed the resulting yellow solid was recrystallized from EtOH to give a white powder (12.5 g, 40% yield), mp 83-85°C. ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ = 3.84 (8H, m), 3.87 (3H, s), 3.93 (8H, m), 4.15 (4H, t, *J* = 8.0 Hz), 4.19 (4H, t, *J* = 8.0 Hz), 6.84 (1H, d, *J* = 8.4 Hz), 6.88 (4H, m), 7.52 (1H, d, *J* = 2.0 Hz), and 7.64(1H, dd, *J* = 2.0 and 8.4 Hz). LRFAB: *m/z* = 506.2 $[M]^+$, 475.2 $[M\text{-}OCH_3]^+$. HRFAB: calcd for $[M]^+$ $C_{26}H_{34}O_{10}$ 506.2152, found 506.2132. Anal. Calcd for $C_{26}H_{34}O_{10}$: C, 61.65; H, 6.77, found: C, 61.75; H, 6.80.

4-Hydroxymethyldibenzo-24-crown-8 (12). To a 250 mL two necked round bottom flask equipped with a mechanical stirrer and a N_2 inlet were added **11** (1.78 g, 3.51 mmol.) and anhydrous THF. To this was added LAH (3.86 mL of 1.0 M THF solution, 1.1 equiv.) *via* syringe and the mixture was vigorously stirred for 12 h at room temperature. A small amount of EtOAc was added to quench the reaction and the solvents were removed to give a white solid, which was suspended in H_2O and neutralized with 2M HCl. The solution was extracted with $CHCl_3$ and the organic layers were combined, dried over $MgSO_4$ and concentrated to give a white solid, which was recrystallized from EtOH (1.54 g, 92% yield), mp 82–84°C. ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.83 (8H, s), 3.91 (8H, t, *J* = 4.4 Hz), 4.13-4.17 (8H, m), 4.58 (2H, s), and 6.82-6.90 (7H, m). LRFAB: *m/z* = 478.3 $[M]^+$. HRFAB: calcd for $[M]^+$ $C_{25}H_{34}O_9$: 478.2203, found 478.2200. Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.73; H, 7.17, found: C, 62.61; H, 7.15.

4-Formyldibenzo-24-crown-8 (13). To a 50 mL round bottom flask equipped with a magnetic stirrer and nitrogen bubbler were added pyridinium chlorochromate (0.32 g, 1.48 mmol, 1.1 equiv.) and dry dichloromethane (CaH_2) (15 mL). To this was added a solution containing **12** (0.6430 g, 1.344 mmol) in dichloromethane (5 mL) at room temperature and the mixture was vigorously stirred for 2 h. Upon completion of the reaction the solvent was removed *in vacuo* to give a brown solid which was subjected to a silica gel chromatography using ethyl acetate as an eluent. The product was recrystallized from ethanol twice to afford a white solid (0.39 g, 60% yield), mp=97-

99°C (lit.[14] mp105-107°C). ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.85 (8H, m), 3.93 (8H, m), 4.15 (4H, m), 4.22 (4H, m), 6.88-7.44 (7H, m), and 8.92 (1H, s).

4-Carboxydibenzo-24-crown-8 (14). To a 250 mL one-necked round bottom flask were added **11** (3.16 g, 6.24 mmol) and 100 mL of EtOH. To this was added aq. KOH (4M, 10 mL) dropwise and the reaction mixture was refluxed for 12 h. Upon completion of the reaction the solvent was rotary evaporated to give an off-white solid which was redissolved in H_2O (100 mL) and neutralized with H_2SO_4. The solution was extracted with CH_2Cl_2 (100 mL x 2) and the organic layers were combined, dried over $MgSO_4$ and concentrated to give a white solid which was recrystallized from EtOH to give a white solid (2.73 g, 89% yield), mp 182-183°C. ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ = 3.84 (8H, m), 3.93 (8H, m), 4.15 (4H, t, *J* = 4.0 Hz), 4.20 (4H, t, 4.0 Hz), 6.88 (5H, m), 7.56 (1H, d, *J* = 1.6 Hz), and 7.71 (1H, dd, *J* = 1.6 and 8.4 Hz). LRFAB: *m/z* = 531.1 $[M+K]^+$, 492.2 $[M]^+$. HRFAB: calcd for $[M]^+$ $C_{25}H_{32}O_{10}$ 492.1995, found 492.1985. Anal. Calcd for $C_{25}H_{32}O_{10}$: C, 60.97; H, 6.55, found: C, 61.19; H, 6.60.

***m*-Bis(11-chloro-3,6,9-trioxaundecyloxy)benzene (15).** To a 2 L round bottom flask equipped with a magnetic stirrer were added resorcinol (30.6 g, 0.278 mol) and DMF (60 mL). To this were added small portions of NaH (17.5 g, 0.727 mol) and the mixture was vigorously stirred for 3 hours at 110°C and cooled to 25°C. A solution of **2** (642 g, 2.78 mol) in DMF (190 mL) was then added to it at once and the mixture was stirred for 5 days at 50°C. Upon completion of the reaction the salts were filtered with the aid of Celite and the filtrate was concentrated on a rotary evaporator to give a brown liquid, which was vacuum distilled to remove the unreacted **5**. The crude product was subjected to liquid-liquid extraction using petroleum ether to afford a yellow liquid[34] (103 g, 75% yield). ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ =3.61-3.77 (24H, m), 3.85 (4H, t, *J* = 5.6 Hz), 4.11 (4H, t, *J* = 5.6 Hz), 6.50 (1H, t, *J* = 2.4 Hz), 6.51 (2H, dd, *J* = 2.4 and 8.0 Hz), and 7.15 (1H, t, *J* = 8.0 Hz).

5-Carbomethoxy-1,3-phenylene-*m*-phenylene-32-crown-10 (16). To a 5 L three necked round bottom flask equipped with a mechanical stirrer, N_2 inlet and a

thermometer were added DMF (3 L), nBu$_4$NI (100 mg) and CsF (50.1 g, 330 mmol) and the mixture was brought to 110^{o}C. To this was added a solution of **15** (16.5 g, 33.0 mmol) and **7** (5.55 g, 33.0 mmol) in DMF (55 mL) *via* syringe pump at the rate of 0.75 mL/h. After the completion of the addition, the reaction mixture was vigorously stirred for 3 days, cooled to 25^{o}C, and filtered with the aid of Celite. The solvent was rotary evaporated to give a brown viscous liquid. This was preabsorbed onto silica gel and the product was continuously extracted with Et_2O using a Soxhlet extraction apparatus. After the solvent was removed the resulting yellow solid was recrystallized from EtOH to give a white powder (5.07 g, 26% yield), mp 73-75^{o}C (lit.[34] mp 74.8-75.5^{o}C). ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=3.65-3.74 (16H, m), 3.81-3.86 (8H, m), 3.88 (3H, s), 4.07 (4H, t, *J* = 5.6 Hz), 4.10 (4H, t, *J* = 5.6 Hz), 6.47-6.50 (3H, m), 6.69 (1H, t, *J* = 2.4 Hz), 7.11 (1H, t, *J* = 2.4 Hz), and 7.18 (2H, d, *J* = 8.0 Hz).

5-Hydroxymethyl-1,3-phenylene-*m*-phenylene-32-crown-10 (17). To a 250 mL two necked round bottom flask equipped with a mechanical stirrer and a N_2 inlet were added **16** (2.06 g, 3.46 mmol.) and anhydrous THF (80 mL). To this was added LAH (1.0 M THF solution, 1.1 equiv.) via syringe and the mixture was vigorously stirred for 12 h at room temperature. A small amount of EtOAc was added to quench the reaction and the solvents were removed to give a white solid, which was suspended in H_2O and neutralized with 2M HCl. The solution was extracted with $CHCl_3$ and the organic layers were combined, dried over $MgSO_4$ and concentrated to give a white solid, which was subsequently recrystallized from EtOH to afford a white solid (1.87 g, 95% yield), mp 77-82^{o}C (lit.[34] mp 88.2-89.6^{o}C). ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=3.66-3.72 (16H, m), 3.83 (8H, t, *J* = 4.8 Hz), 4.04 (4H, t, *J* = 4.8 Hz), 4.08 (4H, t, *J* = 4.8 Hz), 4.56 (2H, d, *J* = 6.0 Hz), 6.39-6.53 (6H, m), and 7.13 (1H, t, *J* = 2.4 Hz).

5-Bromomethyl-1,3-phenylene-*m*-phenylene-32-crown-10 (18). To a 250 mL two necked round bottom flask equipped with a magnetic stirrer and N_2 inlet were added phosphorous tribromide (1 mL), **17** (69.2 mg, 1.22 mmol), and a mixture of toluene and Et_2O (130/30 mL) and the reaction mixture was vigorously stirred for 18 h at 25^{o}C. The reaction was quenched with a small amount of H_2O. The solvents were removed in

vacuo to give a brown viscous liquid. The crude product was suspended in H_2O and extracted with $CHCl_3$ (2x150 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated on rotary evaporator to give a clear liquid, which was subsequently recrystallized form EtOH to afford a white solid (72.1 mg, 94% yield), mp 64–65°C (lit.[34] mp 63.7-65.4°C). ^{1}H NMR (400 MHz, DMSO-d_6, 22°C): δ=3.54 (16H, m), 3.69 (8H, m), 3.02 (8H, m), 4.56 (2H, s), 6.45-6.57 (6H, m), and 7.11 (1H, t, J = 3.2 Hz).

Methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (19). To a 1 L round bottom flask equipped with a magnetic stirrer were added **7** (25.0 g, 0.149 mol) and DMF (150 mL). To this NaH (9.37 g, 0.390 mol) was added in small portions and the mixture was vigorously stirred for 3 h at 110°C and cooled to 25°C. This mixture was added dropwise over a period of 6 h to a solution containing **2** (344 g, 1.49 mol) and DMF (100 mL) and the reaction mixture was stirred for 5 days at 50°C. Upon completion of the reaction the salts were filtered with the aid of Celite® and the filtrate was concentrated on a rotary evaporator to give a brown liquid, which was vacuum distilled (128-130°C @2.5 mmHg) to remove the unreacted **2**. The crude product was subjected to liquid-liquid extraction using petroleum ether to afford a yellow liquid[38] (52.9 g, 64% yield). ^{1}H NMR (400 MHz, chloroform-d, 22°C): δ=3.60-3.65 (4H, m), 3.66-3.78 (20H, m), 3.86 (4H, t, J = 5.2 Hz), 3.90 (3H, s), 4.14 (4H, t, J = 5.2 Hz), 6.70 (1H, t, J = 2.4 Hz), and 7.19 (4H, d, J = 2.4 Hz).

Bis(5-carbomethoxy-1,3-phenylene)-32-crown-10 (20). To a 2 L three necked round bottom flask equipped with a mechanical stirrer, N_2 inlet and a thermometer were added DMF (1.5 L), nBu$_4$NI (100 mg) and CsF (43.6 g, 287 mmol) and the mixture was brought to 110°C. To this were added a solution of **19** (13.2 g, 23.7 mmol) and **7** (3.99 g, 23.7 mmol) in DMF (39 mL) *via* syringe pump at the rate of 0.75 mL/h. After the completion of the addition, the reaction mixture was vigorously stirred for 3 days, cooled to 25°C, and filtered with the aid of Celite. The solvent was rotary evaporated to give a brown viscous liquid. This was preabsorbed onto silica gel and the product was continuously extracted with Et_2O using a Soxhlet extraction apparatus. After the solvent was removed

the resulting yellow solid was recrystallized from EtOH to give a white powder (3.02 g, 20% yield), mp 108-110°C (lit.[38] mp 106.5-107.5°C). ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.67-3.73 (16H, m), 3.84 (8H, t, *J* = 4.8 Hz), 3.87 (3H, s), 4.10 (8H, t, *J* = 4.8 Hz), 6.67 (2H, t, *J* = 2.4 Hz), and 7.15 (4H, t, *J* = 2.4 Hz).

Bis(5-hydroxymethyl-1,3-phenylene)-32-crown-10 (21). To a 1 L two necked round bottom flask equipped with a mechanical stirrer and a N_2 inlet were added **20** (7.26 g, 11.1 mmol) and anhydrous THF (350 mL). To this was added LAH (12.2 mL 1.0 M THF solution, 1.1 equiv.) *via* syringe and the mixture was vigorously stirred for 12 h at room temperature. A small amount of EtOAc was added to quench the reaction and the solvents were removed to give a white solid, which was suspended in H_2O and neutralized with 2M HCl. The solution was extracted with $CHCl_3$ and the organic layers were combined, dried over $MgSO_4$ and concentrated to give a white solid, which was subsequently recrystallized from EtOH to afford a white solid (6.20 g, 93% yield), mp 96-98°C (lit.[38] mp 99.5-100.4°C). ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.66-3.72 (16H, m), 3.82 (8H, t, *J* = 5.2 Hz), 4.04 (8H, t, *J* = 5.2 Hz), 4.56 (4H, s), 6.35 (2H, t, *J* = 2.4 Hz), and 6.50 (4H, d, *J* = 2.4 Hz).

2.5. References

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