Difunctional derivatives of bis(*m*-phenylene)-32-crown-10

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Abstract: Optimization studies of the condensation of methyl 3,5-dihydroxybenzoate (**1**) with tetra(ethylene glycol) dichloride (**3**) resulted in improvement of the yield of the 1+1 cyclization product, 5-carbomethoxy-*m*-phenylene-16-crown-5 (**5**), to 67% (HPLC), but no improvement in the yield (28%, HPLC) of the desired 2+2 product, bis(5-carbomethoxy-*m*-phenylene)-32-crown-10 (**4**). However, after optimization, a two-step procedure provided improved yields of **4** and this procedure was generalized to afford other difunctional monomers. Condensation of substituted resorcinols with **3** and subsequent transformations yielded substituted (R) 3,5-bis(11-chloro-3,6,9-trioxaundecyl-oxy)benzenes (**7**, **9**–**14**). Reaction of dihalides **7** (R = $COOCH_3$), **13** (R = CHO), and **12** (R = $CH_2OSi(Me)_2$-*t*-Bu) with methyl 3,5-dihydroxybenzoate (**1**) produced bis(5-carbomethoxy-*m*-phenylene)-32-crown-10 (**4**) (43%), 5-carbomethoxy-*m*-phenylene-5′-formyl-*m*′-phenylene-32-crown-10 (**15**) (32%), and the lactone (**16a**) (18%, derived from the initially formed 5-hydroxymethyl-*m*-phenylene-5′-carbomethoxy-*m*′-phenylene-32-crown-10 (**16**)), respectively. Subsequent reactions gave the corresponding diacid (**17**), bis(hydroxymethyl) (**19**), bis(bromomethyl) (**20**), diacetyl (**18**), diformyl (**21**), bis(*p*-nitrophenoxymethyl) (**22**), and di(acetoxymethyl) (**23**) derivatives.

Key words: cyclization, functionalized bis(*m*-phenylene) crown ethers.

Résumé : Des études d'optimisation de la condensation du 3,5-dihydroxybenzoate de méthyle (**1**) avec le dichlorure de tétra(éthylèneglycol) (**3**) ont conduit à une amélioration du rendement du produit de cyclisation 1+1, 5-carbométhoxy-*m*-phénylène-16-couronne-5 (**5**) (à 67% selon la CLHP), sans amélioration du rendement (28% selon la CLHP) du produit désiré 2+2, bis(5-carbométhoxy-*m*-phénylène)-32-couronne-10 (**4**). Toutefois, après optimisation, une méthode en deux étapes a permis d'obtenir de meilleurs rendements de **4**; on a généralisé cette méthode pour obtenir d'autres monomères difonctionnels. La condensation de résorcinols substitués avec le composé **3** et des transformations subséquentes ont conduit aux 3,5-bis(11-chloro-3,6,9-trioxaundécyloxy)benzènes substitués (R) (**7**, **9**–**14**). La réaction des dihalogénures **7** (R = $COOCH_3$), **13** (R = CHO) et **12** (R = $CH_2OSi(Me)_2$-*t*-Bu) avec le 3,5-dihydroxybenzoate de méthyle (**1**) fournissent respectivement du bis(5-carbométhoxy-*m*-phénylène)-32-couronne-10 (**4**) (43%), du 5-carbométhoxy-*m*-phénylène-5′-formyl-*m*′-phénylène-32-couronne-10 (**15**) (32%) et la lactone (**16a**) (18%, dérivée de la 5-hydroxyméthyl-*m*-phénylène-5′-carbométhoxy-*m*′-phénylène-32-couronne-10 (**16**) formée initialement). Des réactions subséquentes ont permis d'obtenir les dérivés diacide (**17**), bis(hydroxyméthyle) (**19**), bis(bromométhyle) (**20**), diacétyle (**18**), diformyle (**21**), bis(*p*-nitrophénoxyméthyle) (**22**) et di(acétoxyméthyle) (**23**) correspondants.

Mots clés : cyclisation, éthers couronnes bis(*m*-phénylène) fonctionnalisées.

[Traduit par la rédaction]

Introduction

The ability of crown ethers to complex with alkali and alkaline earth metal ions was recognized by Pedersen when he discovered crown ethers (1) and has subsequently been studied in detail (2). This area, the seminal point for host–guest or supramolecular chemistry (3), has fascinated a great number of chemists worldwide and has led to important discoveries in a number of areas.

Work in our laboratory has been directed to the synthesis of aliphatic crown ethers ranging from 21- to 60-membered rings (4). Threading of these and bisphenylene crown ethers by aliphatic and aromatic linear species has provided rotaxanes (5, 6), catenanes (5, 6*c*, 7), and polyrotaxanes (5, 8). We reported earlier that the one-pot reaction of methyl 3,5-dihydroxybenzoate (**1**) and tetra(ethylene glycol) dichloride (**3**) gave only a 9% yield of bis(5-carbomethoxy-*m*-phenylene)-32-crown-10 (**4**) along with a 15% yield of 5-(carbomethoxy-*m*-phenylene)-16-crown-5 (**5**) (Scheme 1) (9).

The present article reports the optimization of the synthesis of diester crown ether **4** and its generalization to produce a variety of functionally substituted derivatives of bis(*m*-phenylene)-32-crown-10. Coupled with standard functional group conversions, this approach provides acceptable yields of an array of useful crown ethers.

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Results and discussion

A. Optimization of one-step approach

1. HPLC analysis

The first phase of this research involved the implementation of HPLC to detect and estimate the product distribution. Several

Table 1. Optimization of one-step synthesis of bis(5-carbomethoxy-*m*-phenylene)-32-crown-10 (**4**) by reaction of **1** and **3** in DMF.

Expt.	Final conc. (mM)	Base	Added salt (equiv.)	Temp. (°C)	Time (days)	HPLC products (%)			
						1	**5**	**6**	**4**
1	64.3	NaH[a]	—	85	3	3.2	37.2	13.9	0
2	32.1	NaH[a]	—	85	3	9.5	50.1		11.7
3	18.4	NaH[a]	—	85	3	30.6	57.6	0	3.0
4	18.5	NaH[a]	CsCl(3)	85	3	26.4	52.4	4.2	6.9
5	32.1	NaH[a]	CsCl(3)	85	3	27.5	40.0	5.1	4.5
6	32.1	NaH[a]	$(n\text{-Bu})_4$NI(2)	85	3	27.4	41.1	2.9	8.1
7	23.9	NaH[b]	—	85	3	0	51.1	20.9	11.7
8	46.9	NaH[b]	—	85	3	18.9	46.9	10.6	3.3
9	59.4	NaH[b]	—	85	3	0	52.9	4.4	24.0
10	79.8	NaH[b]	—	85	3	4.9	59.7	7.4	16.0
11	95.2	NaH[b]		85	3	0	61.4	12.8	13.7
12	103	NaH[b]	$(n\text{-Bu})_4$NI(1)	85	3	1.0	55.5	0	20.0
13	119	NaH[b]	—	85	3	0	53.9[c]	0	28.1[c]
14	120	NaH[b]	CsCl(3)	85	3	18.9	45.8	12.0	9.1
15	159	NaH[b]	—	85	3	4.0	60.7	7.5	17.5
16	119	NaH[b]	—	110	3	3.3	57.0	0	22.6
17	119	NaH[b]	—	130	3	11.8	56.8	0	21.1
18	119	NaH[b]	—	153	3	15.9	60.7	0	10.5
19	519	NaH[d]	—	110	4	0	53.3	0	25.0
20	519	K_2CO_3[d]	—	110	4	0	63.3	0	24.4
21	519	Cs_2CO_3	—	110	4	0	67.3	0.6	9.2

[a]Method A: Na salt of **1** (made with NaH at 25°C) added to 1 equiv. of **3**; 1/2 equiv. over 4 h, stirred 10 h, diluted 3×, add 1/2 equiv. quickly.
[b]Method B: **3** quickly added to 1 equiv. of Na salt of **1** (made with NaH at 85°C).
[c]Isolated yield of **4**: 7%; **5**: 15% (9).
[d]Method C: equivalent amounts of **1** and **3** and base mixed together in DMF.

solvent systems were examined; a combination of chloroform and isopropanol (94:6) was found to work the best. The small and the large macrocycles (**4** and **5**) were well resolved. Detection by UV absorption and integration of peak areas was found to give accurate percentage compositions of synthetic mixtures. The dichloro intermediate **7**, the monochloro intermediate **6**, and starting material **1** were also resolved. A peak of longer retention time was attributed to intermediate **8**. Other unidentified peaks were attributed to linear oligomers.

2. Summary

As a result of variation of concentration, temperature, the nature of the base, and order of addition (Table 1) the yield of desired macrocycle **4** was not improved relative to our earlier work (9) (expt. 13), although high yields (67%) of the smaller macrocycle **5** were obtained (expt. 21). We thus turned our attention to other routes to **4**.

B. Optimization of a two-step approach

1. Precursor synthesis: methyl 3,5-bis(11-chloro-3,6,9-trioxaundecycloxy)benzoate (7)

Production of bis(5-carbomethoxy-*m*-phenylene)-32-crown-10 (**4**) and 5-carbomethoxy-*m*-phenylene-16-crown-5 (**5**) depends on the intermediates methyl 3,5-bis(11-chloro-3,6,9-trioxaundecycloxy)benzoate (**7**) and methyl 3-(11-chloro-3,6,9-trioxaundecyloxy)-5-hydroxybenzoate (**6**), respectively (Scheme 1). The use of dichloride **7** as a starting material eliminates the possibility of forming **5** and should result in improved yields of **4**.

Tetra(ethylene glycol) was converted to its monochloride, using toluene as a diluent and slow thionyl chloride addition (67% yield, see Experimental). However, its reaction with **1** afforded only 29% of the desired diol, methyl 3,5-bis(11-hydroxy-3,6,9-trioxaundecycloxy) benzoate (see Experimental), so this approach was abandoned.

The synthesis of **7** from **1** was achieved using a 10 equiv. excess of tetra(ethylene glycol) dichloride (**3**) and by use of a variety of bases (Table 2, Scheme 2). In the best method the disodium salt solution of methyl 3,5-dihydroxybenzoate (**1**) was prepared at 110°C using sodium hydride as a base. The reaction after 2 h was cooled to room temperature and stirred with excess tetra(ethylene glycol) dichloride. Excess **3** was removed by vacuum distillation. The crude material was only partially soluble in cold or hot hydrocarbon solvents such as toluene, hexane, and petroleum ether (39–59°C), which was found to be the most selective solvent. Its use in continuous liquid–liquid extraction of the crude material gave methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (**7**) in 68% yield. Alternatively, column chromatography gave a 70% yield.

2. Cyclization

Cyclization is greatly dependent on the nature of the metal ion (3*b*, 10) and the ring size. In addition, by increasing the dilution the fraction of cyclic components can be increased at the

Scheme 1.

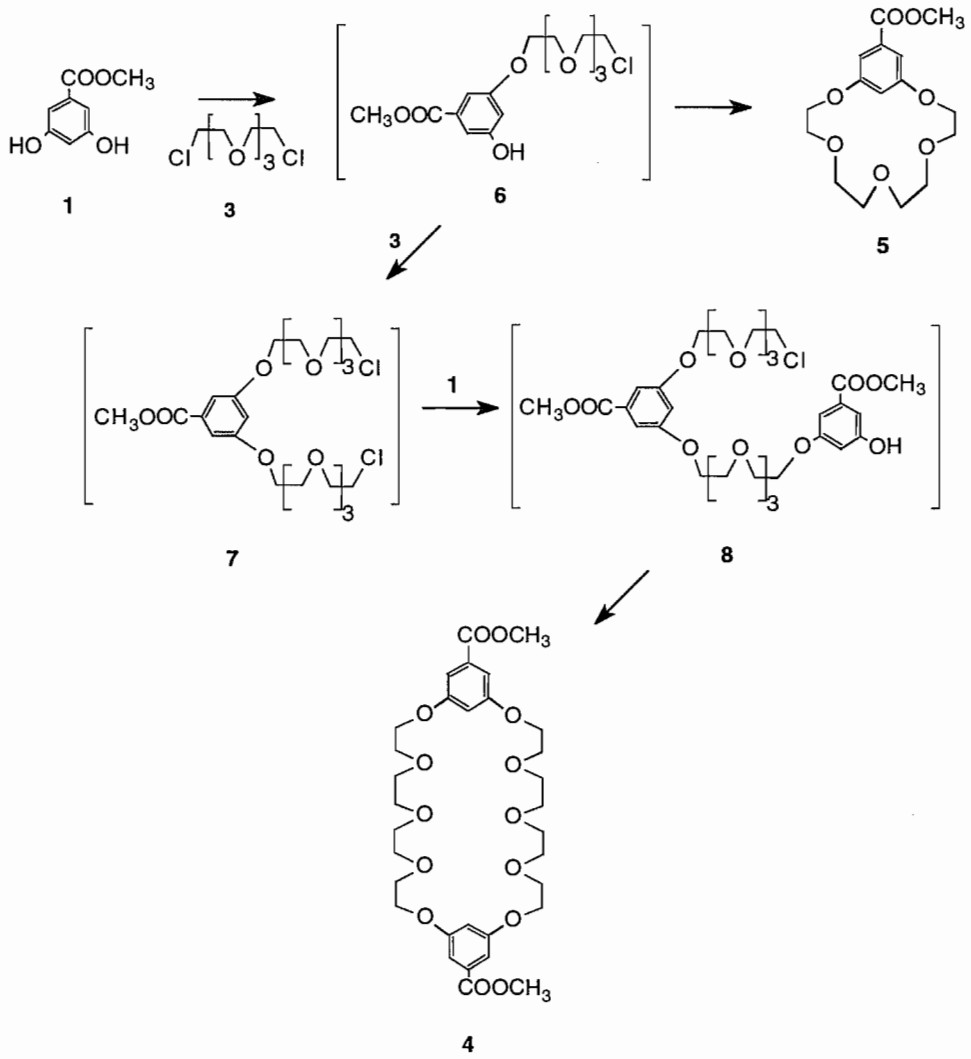


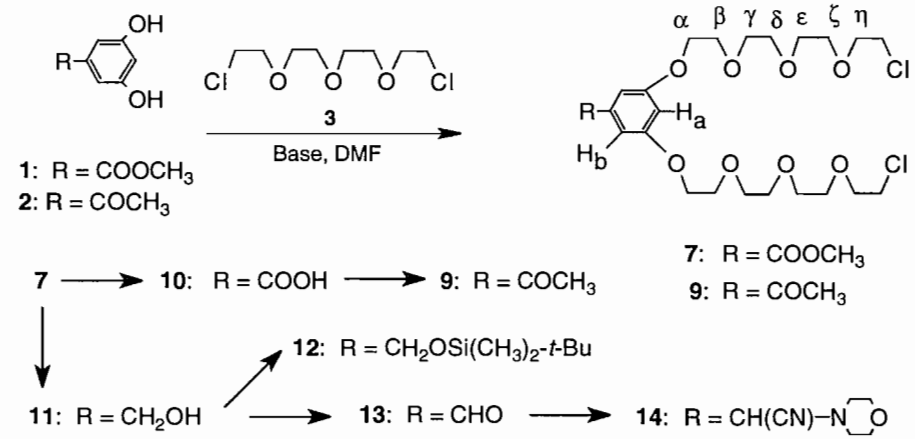
Table 2. Optimization of synthesis of methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (**7**).[a]

Expt.	Base	Temp. (°C)	Time (h)	Conc. (mM)	Product distribution via HPLC (%)		
					1	**6**	**7**
1	NaH	110	2	285	7.0	21.0	51.6
2	NaH	RT	18	285	0	11.5	81.5[b]
3	K_2CO_3	RT	96	238	51.1	31.7	10.6
4	K_2CO_3	110	24	284	0	28.5	71.5
5	Cs_2CO_3	110	30	227	10.8	28.2	57.6

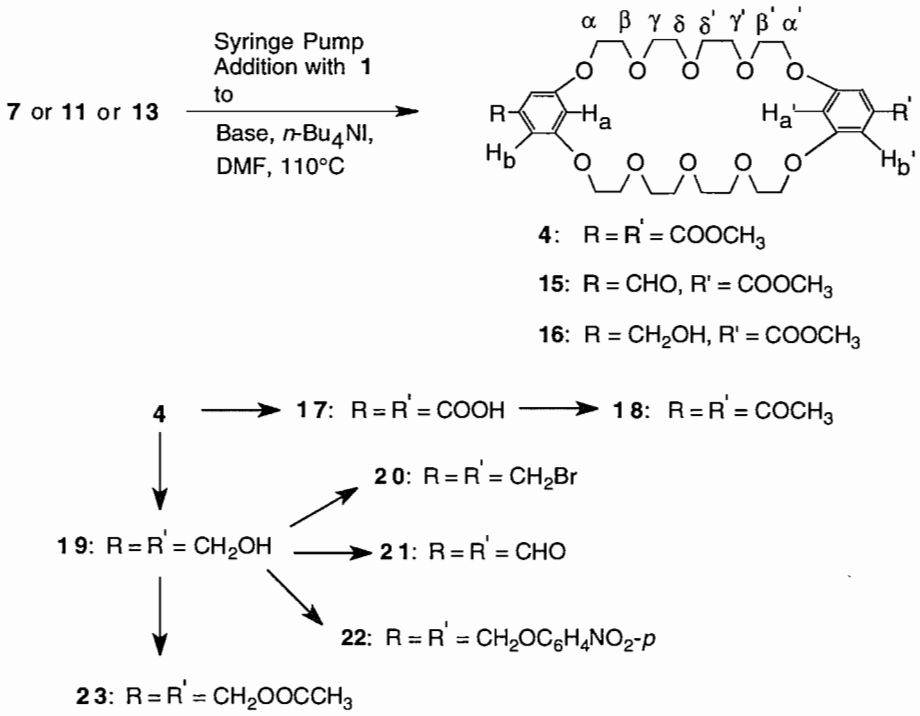
[a]By reaction of preformed anion of **1** with 10 equiv. of **3**.
[b]Isolated yield of compound **7**: 70%.

expense of linear oligomers; the maximum concentration that favors the intramolecular versus intermolecular reaction is generally of the order of 10^{-3} mol/L (3*b*, 11). Higher temperatures generally favor cyclization (3*b*, 12). Cesium-assisted cyclization reactions have been used quite successfully in recent years. Stoddart and co-workers (13) synthesized a 68-membered macrocycle in 62% yield by employing a combination of a high-dilution reaction in DMF at high temperature

Scheme 2.



Scheme 3.



(110°C) with the cesium effect (14) and a phase transfer catalyst. Considering all of the above factors, we performed the cyclization by syringe pump addition of a solution of either (*i*) **7** or (*ii*) both **7** and **1** to a stirred mixture of base and *n*-Bu_4NI (TBAI, phase transfer agent) (and **1** in case (*i*)) in DMF (Scheme 3).

F^- is basic enough to cause deprotonation of weak acids in dipolar aprotic solvents (15); the driving force is believed to be the formation of the stable H—F bond (569 kJ/mol) (16). Use of the weaker bases and addition of both **1** and **7** gave better yields than with NaH by addition of **7** only to the preformed dianion of **1** (Table 3). CsF and K_2CO_3 provided nearly identical yields of **4** (42 and 43%) in spite of the difference in the sizes of the metal ions. The ionic radius of K^+ (1.33 Å), although much smaller than Cs^+ (1.65 Å), may be involved in multiple complexations with the oxyethylene side chain. Such multiple complexation behavior is indeed quite well known (*3b*, 17) and holds especially true for crown ethers greater than 27-membered. Furthermore, the yield of the macrocycle **4** is lower with Cs_2CO_3 than with CsF.

C. Synthesis of other derivatives using optimized procedures

1. Dichloro precursors

Several derivatives of **7** were synthesized by functional group conversions (Scheme 2). Acetophenone derivative **9** was synthesized directly in 53% yield utilizing excess tetra(ethylene glycol) dichloride (**3**) and 3,5-dihydroxyacetophenone (**2**), using NaH as base at 50°C.

Table 3. Synthesis of bis(5-carbomethoxy-*m*-phenylene)-32-crown-10 (**4**) from **1** and **7** at 110°C.

Base	% Yield
NaH	18[a]
K_2CO_3	43[b]
Cs_2CO_3	37[b]
CsF	42[b]

[a] **7** added to dianion of **1** by syringe pump.
[b] **1** and **7** added to base by syringe pump.

Hydrolysis of ester **7** with KOH in ethanol (EtOH) gave the acid **10** in 98% yield. Reduction of **7** with lithium aluminum hydride (LAH) gave 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzyl alcohol (**11**) in 94% yield. The alcohol **11** was converted to the silyl ether **12** (97%) by treatment with *tert*-butyldimethylsilyl chloride (*t*-BDMSCl). Oxidation of the alcohol **11** with pyridinium chlorochromate (PCC) in dichloromethane (DCM) gave, after column chromatography, an 86% yield of 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzaldehyde (**13**). Reaction of aldehyde **13** with morpholine and trimethylsilyl cyanide (TMSCN) in DCM produced a 92% yield of aminonitrile **14**. The use of methyllithium (MeLi) to convert carboxylic acids to methyl ketones is a well-known general method (18); the major side reaction, the formation of tertiary alcohol (18, 19), can be eliminated by the use of excess chlorotrimethylsilane (TMSCl) to quench the dilithiated intermediate (20). Thus sequential treatment of the acid **10** with MeLi in tetrahydrofuran (THF) at 0°C, followed by quenching with TMSCl, produced 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)acetophenone (**9**) in 66% yield.

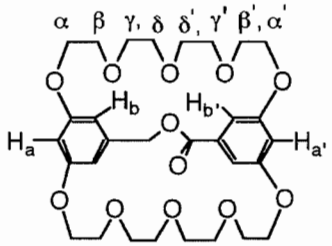
*2. Cyclization to other difunctional bis(*m*-phenylene)-32-crown-10 derivatives*

Reaction of dichloride **13** with **1** using CsF as the base afforded a 32% yield of 5-carbomethoxy-*m*-phenylene-5′-formyl-*m*′-phenylene-32-crown-10 (**15**) (Scheme 3).

Condensation of silyl ether **12** with **1** using Cs_2CO_3 was expected to produce the alcohol/ester **16** through hydrolysis of the intermediate silyl ether during work-up. However, the related lactone **16a** was isolated in 18% yield. Its structure is supported by the lack of a methoxy signal in its ^1H NMR spectrum (integration), the lack of the ^{13}C NMR signal at ca. 52 ppm as seen in methyl esters **4**, **7**, and **15**, and by the MS data, all of which fit the lactone structure well. Furthermore, there are significant downfield shifts of the α and α′ signals (4.0–4.4 ppm), $H_{b'}$ (7.29 ppm), and the benzylic methylene protons (5.29 ppm), relative to monocyclic analogs (α and α′ average: 4.09 ppm in **4**, **15**, **17**-**22**; H_b average: 7.15 in **4** and **15**; $ArCH_2$ 4.99 ppm in **23**); this is due to the change in conformation of the cryptand **16a** in comparison to the crown ethers. **16a** apparently forms by intramolecular transesterification of **16**, either during the reaction itself or in work-up and (or) purification.

3. Difunctional derivatives by functional group conversions

Several other derivatives of bis(*m*-phenylene)-32-crown-10 were synthesized via classical organic functional group conversions. The diacid **17** was synthesized in 93% yield by hydrolysis of the diester **4** in aqueous NaOH – EtOH. We also synthesized diacetyl macrocycle **18** from the diacid **17** in 45% yield by treatment with MeLi in THF, followed by quenching with TMSCl and aqueous work-up.



16a

Bis(5-hydroxymethyl-*m*-phenylene)-32-crown-10 (**19**) was synthesized in 95% yield via LAH reduction of the diester **4**. Treatment of **19** with PBr_3 gave bis(5-bromomethyl-*m*-phenylene)-32-crown-10 (**20**) in 88% yield. The oxidation of diol **19** with PCC afforded bis(5-formyl-*m*-phenylene)-32-crown-10 (**21**) in 85% yield. Treatment of diol **19** first with NaH and then with *p*-fluoronitrobenzene in THF provided a 100% yield of bis(*p*-nitrophenyl ether) **22**. The diacetate **23** was prepared in 98% yield by treatment of diol **19** with acetyl chloride in THF, with catalysis by pyridine.

Conclusions

A two-step strategy involving the synthesis of intermediates **7**, **9**–**14** in the first step followed by cyclization with methyl 3,5-dihydroxybenzoate (**1**) using a syringe pump to maintain pseudo-high-dilution conditions afforded bis(*m*-phenylene)-32-crown-10 derivatives **4** (43%), **15** (32%), and **16a** (18%). Thus, a significant yield improvement over our previously reported procedure (9%) (9) was realized for **4**. Several other new derivatives of bis(*m*-phenylene)-32-crown-10 were synthesized by functional group conversions; these include diketone **18**, diol **19**, dihalide **20**, dialdehyde **21**, bis(*p*-nitrophenyl ether) **22** (a diamine precursor), and diacetate **23**.

The use of these new difunctional crown ethers in the syntheses of polymers containing macrocycles in the backbones (i.e., poly(macrocycle)s) and supramolecular structures by self assembly is currently being explored. These studies will be reported in due course.

Experimental

Materials

Unless specified otherwise, reagent grade reactants and solvents were used as received from chemical suppliers. THF was distilled over sodium–benzophenone. Tetra(ethylene glycol) dichloride (**3**) (*1b*) and methyl 3,5-dihydroxybenzoate (**1**) (*9a*) were synthesized according to literature procedures.

Measurements

HPLC analyses were performed on an ISCO dual pump system comprising two model 2350 pumps and the V[4] variable wavelength UV/VIS detector set at 274 nm. $CHCl_3$:i-PrOH (94:6, v:v) was used for elution of products on a 4.6 × 250 mm

5 μm silica column at a flow rate of 1 mL/min. The system was interfaced with the ISCO ChemResearch chromatographic data management system, used for data analyses. A Harvard syringe infusion pump model 22 was used in the cyclization reactions. Melting points were taken in capillary tubes with a Haake–Buchler melting point apparatus and have been corrected. ^{1}H and ^{13}C NMR spectra were obtained at ambient temperature on Varian Unity 400 MHz and Bruker 270 MHz spectrometers using acetone-d_6 or $CDCl_3$ as solvents with tetramethylsilane (δ = 0) as internal standard. Infrared spectra (KBr pellets, unless otherwise noted) were recorded on a Nicolet MX-1 FTIR spectrometer. Mass spectra (MS) were measured at the Nebraska Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, Lincoln, Nebr., and at the Center for Mass Spectrometry at Washington University, St. Louis, Mo.; fast atom bombardment (FAB) MS utilized 3-nitrobenzyl alcohol as the matrix; EI = electron impact; HR = high resolution. Elemental analyses were performed by Atlantic Microlab, Norcross, Ga.

HPLC analyses

A synthetic mixture comprising 40.5:59.5 (w:w) macrocycles **5**:**4** was subjected to quantitative analysis using integrated peak areas with the following results: 40.6% **5**, 59.4% **4** (avg. of 2 determinations). Elution times: **4** @ 6.0 min, **5** @ 3.4 min, methyl 3,5-dihydroxybenzoate (**1**) @ 5.0 min, **7** @ 3.5 min; from the synthesis of **7** using K_2CO_3 (Table 2) the kinetic evolution of the products indicated that the compound with elution time 4.0 min was monochloride **6**. The peak with elution time 8.0 min was attributed to precursor **8**, and higher oligomers eluted @ 9.5 min. All percentages are based on integrated peak areas.

Optimization of synthesis of 4 via one-step method

Method A

NaH (0.20 g, 8.3 mmol) was added to a stirred solution of methyl 3,5-dihydroxybenzoate (**1**, 0.54 g, 3.2 mmol) in DMF (25 mL). The mixture was stirred at room temperature for 2 h. The resulting brown solution was diluted with DMF (25 mL) and added slowly to neat tetra(ethylene glycol) dichloride (**3**, 1.49 g, 6.45 mmol) over a period of 0.5 h at 85°C. The resulting mixture was stirred for 10 h at 85°C, diluted with DMF (100 mL), and the second portion of the disodium salt of methyl 3,5-dihydroxybenzoate (**1**, 0.54 g (3.2 mmol) in DMF (50 mL)) was added quickly. The resulting mixture was stirred for 2 days at 85°C. The cooled reaction mixture was filtered and DMF was stripped to give a brown gummy product. The crude product (15–17 mg in 10 mL DCM) was subjected to HPLC analysis.

Method B

NaH (0.87 g, 36 mmol) was added to a stirred solution of methyl 3,5-dihydroxybenzoate (**1**, 2.39 g, 14.2 mmol) in DMF (57 mL). The resulting mixture was stirred for 2 h at 85°C. A solution of tetra(ethylene glycol) dichloride (**3**, 3.29 g, 14.2 mmol) in DMF (62.5 mL) was added quickly and the mixture was stirred vigorously at 85°C for 48 h under a blanket of nitrogen. The mixture was cooled, filtered, and the DMF was stripped to give a crude product. The crude product (15–17 mg in DCM (10 mL)) was subjected to HPLC analysis.

2-{2′-[2″-(2‴-Chloroethoxy)ethoxy]ethoxy}ethanol

$SOCl_2$ (11.5 mL, 0.158 mol) was added over a period of 5 h to a solution of tetra(ethylene glycol) (30.54 g, 157 mmol), toluene (250 mL), and pyridine (12.2 mL, 151 mmol). The reaction was exothermic. The solution was refluxed for 36 h, cooled, and evaporated. The crude product was dissolved in H_2O (75 mL) and tetra(ethylene glycol) dichloride (**7**) was removed by extraction with toluene (3 × 50 mL). The aqueous layer was evaporated. The mixture was diluted with saturated NaCl (75 mL) and extracted with Et_2O (3 × 100 mL). Pure product (22.5 g, 67.4%) was obtained via vacuum distillation, bp 132–133°C/1.25 Torr (1 Torr = 133.3 Pa) (lit. (21) bp 134.6–136°C/0.094 Torr); (22) bp 123–125°C/2.0 Torr). IR (neat): 3450 (OH), 2860 (CH), 1085 (COC) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.72 (br s, 1H, OH), 3.57–3.67 (m, 4H, CH_2Cl and OCH_2), 3.68 (s, 8H, OCH_2), 3.69–3.79 (m, 4H, OCH_2).

Methyl 3,5-bis(11-hydroxy-3,6,9-trioxa-1-undecyloxy)-benzoate

A mixture of methyl 3,5-dihydroxybenzoate (**1**, 2.01 g, 12 mmol) and NaH (0.74 g, 31 mmol) in anhydrous DMF (25 mL) was heated for 2 h at 85°C. To the brown-colored mixture was added 2-{2′-[2″-(2‴-chloroethoxy)ethoxy]ethoxy}ethanol (5.11 g, 24.0 mmol) and the mixture was stirred vigorously for 2 days. The cooled solution was filtered and the DMF removed to give a crude product. Column chromatography with EtOH as eluent gave methyl 3,5-bis(11-hydroxy-3,6,9-trioxa-1-undecyloxy)benzoate (1.80 g, 29%), an oil. IR (neat): 3446 (OH), 2865 (-CH), 1716 (C═O), 1600 (C═C), and 1135 (C-O-C). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.12 (br s, 2H, OH), 3.6–3.7 (m, 24H, γ-η-OCH_2), 3.82 (t, J = 4.7 Hz, 4H, β-CH_2), 3.86 (s, 3H, OCH_3), 4.12 (t, J = 4.7 Hz, 4H, α-CH_2), 6.68 (t, J = 2.3 Hz, 1H, H_a), and 7.16 (d, J = 2.3 Hz, 2H, H_b). MS (EI): 520 (M^+, 11%), 489 [$(M - OCH_3)^+$, 2%], 445 [$(M - OCH3 - CH_2CH_2O)^+$, 3%], 344 {$[M - (OCH_2CH_2)_4]^+$, 9%], 194 (31%), 163 (50%), 89 (100%).

Methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)-benzoate (7)

NaH (9.37 g, 312 mmol, 80% in mineral oil, 2.1 equiv.) was added to a solution of methyl 3,5-dihydroxybenzoate (**1**, 25.0 g, 149 mmol) in DMF (150 mL). The mixture was stirred for 3 h at 110°C and cooled to room temperature (RT). The resulting suspension of dianion was added to a mixture containing tetra(ethylene glycol) dichloride (**3**, 343.6 g, 1.487 mol, 10 equiv.) in DMF (100 mL) over a period of 6 h and then the mixture was stirred for 5 days at 50°C. The mixture was filtered and DMF was removed on a rotary evaporator. Excess **3** (280 mL) was removed via vacuum distillation. A continuous liquid–liquid extraction with petroleum ether gave 47.2 g (68%) of **7**, an oil. Alternatively, silica gel column chromatography with EtOAc afforded a 70% yield. IR (neat): 3064 (C═C-H), 2877 (-CH), 1729 (C═O), 1596 (C═C), 1118 (C-O-C), and 733 (-CH_2Cl) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.55–3.65 (m, 4H, CH_2Cl), 3.65–3.75 (m, 20H, γ-η-CH_2), 3.86 (t, J = 4.8 Hz, 4H, β-CH_2), 3.89 (s, 3H, CH_3), 4.15 (t, J = 4.8 Hz, 4H, α-CH_2), 6.70, (t, J = 2.3 Hz, 1H, H_a), and 7.19 (d, J = 2.3 Hz, 2H, H_b). ^{13}C NMR δ (ppm): 42.68, 52.19, 67.69, 69.54, 70.59, 70.61, 70.64, 70.80, 71.30, 106.84, 107.95, 131.83, 159.70, and 166.70 (14 peaks as required). MS (EI) *m/z* (rel. int.): 558 [$M(^{35}Cl_1{}^{37}Cl_1)]^+$ (3%),

556 $[M(^{35}Cl_2)]^+$ (5%), 527 $[M(^{35}Cl_1{}^{37}Cl_1) - OCH_3]^+$ (0.8%), 525 $[M(^{35}Cl_2 - OCH_3]^+$ (1%), and 63 $[C_2H_3Cl]$ (100%). HRFAB, calcd. for $C_{24}H_{38}{}^{35}Cl_2O_{10}$: $[M]^+$ *m/z* 556.1842; found: 556.1818 (error 3.0 ppm).

Optimization of synthesis of bis(5-carbomethoxy-*m*-phenylene)-32-crown-10 (4) by cyclization of 1 and 7 (see Table 3)

$CsCO_3$

A mixture of methyl 3,5-dihydroxybenzoate (**1**, 0.17 g, 1.0 mmol) and methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (**7**, 0.56 g, 1.0 mmol) in DMF (10 mL) was added using a syringe pump (1.67 mL/h) to a suspension containing Cs_2CO_3 (3.30 g, 1.0 mmol), CsCl (0.35 g, 2.0 mmol), and TBAI (10 mg) in DMF (40 mL) at 110°C. The mixture was stirred vigorously for 3 days at 110°C, cooled, and filtered. DMF was removed and the crude product was purified via column chromatography using EtOAc as solvent to afford pure **4** (0.24 g, 37%). The product was recrystallized from acetone, mp 107.8–108.5°C (lit. (*9a*) mp 106.5–107.5°C).

NaH

A solution of methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (**7**, 0.558 g, 1.0 mmol) in DMF (10 mL) was added via a syringe pump (1.67 mL/h) to a mixture initially containing methyl 3,5-dihydroxybenzoate (**1**, 0.17 g, 1.0 mmol), NaH (64.3 mg, 2.68 mmol), CsCl (0.87 g, 5.3 mmol), and TBAI (10 mg) in DMF (40 mL) at 110°C. The mixture was stirred vigorously for 3 days at 110°C, cooled, and filtered. DMF was removed and the crude product was purified via column chromatography using EtOAc as a solvent, which gave pure **4** (0.12 g, 18%). The product was recrystallized from acetone, mp 107.8–108°C (lit. (*9a*) mp 106.5–107.5°C).

K_2CO_3 (optimized method)

A mixture containing methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (**7**, 7.66 g, 13.7 mmol) and methyl 3,5-dihydroxybenzoate (**1**, 2.33 g, 13.9 mmol) in DMF (total volume 22 mL) was added via a syringe pump at 0.75 mL/h to a suspension containing K_2CO_3 (19.04 g, 137.7 mmol) and TBAI (20 mg) in DMF (670 mL) at 110°C. After complete addition, the mixture was stirred at 110°C for 5 days. The cooled reaction mixture was evaporated to remove DMF, treated with DCM, and filtered. Removal of DCM followed by flash column chromatography using Et_2O as eluent gave pure **4** (3.89 g, 43%), mp 107.2–108.7°C (lit. (*9a*) mp 106.5–107.5°C). IR: 1717 (C=O), 1600 (C=C), 1067–1137 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 3.65–3.75 (m, 16H, γ, δ-CH_2), 3.84 (t, *J* = 4.5 Hz, 8H, β-CH_2), 3.87 (s, 6H, CH_3), 4.10 (t, *J* = 4.6 Hz, 8H, α-CH_2), 6.67 (t, *J* = 2.0 Hz, 2H, H_a), and 7.15 (d, *J* = 2.0 Hz, 4H, H_b). ^{13}C NMR ($CDCl_3$) δ (ppm): 52.10, 67.76, 69.48, 70.77, 70.83, 106.73, 107.91, 131.73, 159.65, and 166.63 (10 peaks as required).

CsF

A mixture containing methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (**7**, 18.62 g, 3.34 mmol) and methyl 3,5-dihydroxybenzoate (**1**, 5.65 g, 3.36 mmol) in DMF (total volume 55 mL) was added via a syringe pump (0.75 mL/h) to a suspension containing CsF (50.86 g, 3.35 mmol) and TBAI (50 mg) in DMF (1650 mL) at 110°C. After complete addition, the mixture was stirred vigorously at 110°C for 5 days. The cooled reaction mixture was evaporated to remove DMF and filtered to remove all salts using DCM. Removal of DCM followed by flash column chromatography using Et_2O as eluent gave pure **4** (9.10 g, 41.8%), mp 107.3–108.6°C (lit. (*9a*) mp 106.5–107.5°C).

3,5-Bis(11-chloro-3,6,9-trioxaundecyloxy)acetophenone (9)

Method A

NaH (1.05 g, 35.0 mmol, 80% in mineral oil) was added to a solution of 3,5-dihydroxyacetophenone (**2**, 2.525 g, 16.6 mmol) in DMF (25 mL). The mixture was stirred for 3 h at 110°C and brought to 50°C before adding excess tetra(ethylene glycol) dichloride (**3**, 40.05 g, 173.3 mmol, 10 equiv.). The mixture was stirred for 5 days at 50°C and filtered. After removal of DMF, the excess **3** was removed via vacuum distillation. Silica gel column chromatography with Et_2O as eluent gave pure **9** (4.72 g, 53%), an oil. ^1H NMR ($CDCl_3$) δ (ppm): 2.56 (s, 3H, CH_3), 3.63 (t, *J* = 5.8 Hz, 4H, CH_2Cl), 3.65–3.75 (m, 20H, γ-η-CH_2), 3.87 (t, *J* = 4.8 Hz, 4H, β-CH_2), 4.15 (t, *J* = 4.8 Hz, 4H, α-CH_2,), 6.70 (t, *J* = 2.4 Hz, 1H, H_a), and 7.11 (d, *J* = 2.4 Hz, 2H, H_b). ^{13}C NMR ($CDCl_3$) δ (ppm): 42.68, 52.19, 67.69, 69.54, 70.59, 70.61, 70.64, 70.80, 71.30, 106.84, 107.95, 131.83, 159.70, and 166.70 (14 peaks as required). MS FAB *m/z* (rel. int.): 565.1 $[M(^{37}Cl_1{}^{35}Cl_1) + Na]^+$ (70%), 563.1 $[M(^{35}Cl_2) + Na]^+$ (100%); HRFAB, calcd. for $C_{24}H_{38}Cl_2O_9Na$: $[M + Na]^+$ 565.1761 ($^{37}Cl_1$ $^{35}Cl_1$) and 563.1791 ($^{35}Cl_2$); found: 565.1759 (error 0.3 ppm) and 563.1782 (error 1.5 ppm).

Method B

To a solution of 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)-benzoic acid (**10**, 3.76 g, 6.92 mmol) in dry THF (100 mL) at 0°C was added MeLi (20 mL, 1.4 M, 2.8 mmol). Stirring was continued at 0°C for 3.5 h; then TMSCl (18.0 mL, 141 mmol) was added and stirring was continued for 2 h. The solution was allowed to warm to RT and quenched with 25 mL 1 N HCl. The mixture was stirred for 12 h and extracted with Et_2O. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to afford 2.47 g (66%) of **9** as a slightly reddish oil with the same spectral characteristics as a sample made by Method A above. Anal. calcd. for $C_{24}H_{38}Cl_2O_9$: C 61.45, H 7.47; found: C 61.59, H 7.42.

3,5-Bis(11-chloro-3,6,9-trioxaundecyloxy)benzoic acid (10)

A solution of methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (**7**, 10.32 g, 18.5 mmol), 3.21 g (48.6 mmol) of KOH, 60 mL of EtOH, and 30 mL of H_2O was heated at reflux for 3 h, cooled, and neutralized with 2 N HCl. The solvents were removed in vacuo and the residue was extracted with DCM. The solution was dried (Na_2SO_4) and evaporated to give 10.06 g (98%) of **10**, which after purification by elution through silica gel with Et_2O remained an oil. ^1H NMR ($CDCl_3$) δ (ppm): 3.65–3.75 (m, 24H, γ-η-CH_2 + CH_2Cl), 3.87 (t, *J* = 4.6 Hz, 4H, β-CH_2,), 4.16 (t, *J* = 4.6Hz, 4H, α-CH_2), 6.73 (t, *J* = 2.0 Hz, 1H, H_a), and 7.25 (d, *J* = 2.0 Hz, 2H, H_b). ^{13}C NMR ($CDCl_3$) δ (ppm): 42.69, 67.73, 69.57, 70.60, 70.62, 70.66, 70.81, 71.32, 107.55, 108.47, 131.09, 159.75,

170.61 (13 peaks as required). MS (FAB) *m/z* (rel. int.): 567.1 [M($^{35}Cl_1{}^{37}Cl_1$) + Na]$^+$, 45%}, 565.1{[M($^{35}Cl_2$) + Na)$^+$, 100%]; HRFAB, calcd. for $C_{22}H_{36}Cl_2O_{10}$: [M + Na]$^+$ *m/z* 565.1583 ($^{35}Cl_2$) and 567.1554 ($^{35}Cl_1{}^{37}Cl_1$); found: 565.1581 (error 0.4 ppm) and 567.1548 (error 0.9 ppm) .

3,5-Bis(11-chloro-3,6,9-trioxaundecyloxy)benzyl alcohol (11)

A solution of LAH (15.0 mL, 15 mmol, 1.0 M) in THF was added to a solution of methyl 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzoate (**7**, 15.55 g, 27.9 mmol) in THF (300 mL) at RT. After the mixture had stirred for 15 h at RT, excess LAH was destroyed using EtOAc. The solution was diluted with H_2O and acidified with 2 N HCl. The product was extracted with Et_2O (3 × 75 mL). The combined organic layer was washed with H_2O and saturated NaCl. Evaporation of the solvent after drying (Na_2SO_4) gave **11** (13.84 g, 94%), an oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.65–3.75 (m, 24H, γ-η-CH_2 + CH_2Cl), 3.83 (t, *J* = 4.8 Hz, 4H, β-CH_2), 4.10 (t, *J* = 4.8 Hz, 4H, α-CH_2), 4.59 (s, 2H, CH_2O), 6.40 (t, *J* = 2.0 Hz, 1H, H_a), and 6.53 (d, *J* = 2.0 Hz, 2H, H_b). ^{13}C NMR ($CDCl_3$) δ (ppm): 42.66, 65.04, 67.42, 69.64, 70.53, 70.57, 70.61, 70.72, 71.27, 100.77, 105.36, 143.44, and 159.98 (13 peaks as required). MS (FAB) *m/z* (rel. int.): 553.1 [M($^{35}Cl_1{}^{37}Cl_1$) + Na]$^+$ (9%), 551.0 [M($^{35}Cl_2$) + Na]$^+$ (13%), 530.0 [M($^{35}Cl_1{}^{37}Cl_1$)]$^+$ (15%), 528.1 [M($^{35}Cl_2$]$^+$ (21%), 154 (100%); HRFAB, calcd. for $C_{23}H_{38}Cl_2O_9$: [M($^{35}Cl_2$)]$^+$ *m/z* 528.1893; found: 528.1898 (error 0.9 ppm).

3,5-Bis(11-chloro-3,6,9-trioxaundecyloxy)benzyl *tert*-butyldimethylsilyl ether (12)

To a solution of **11** (7.54 g, 14.1 mmol), imidazole (1.05 g, 1.1 equiv.), and 70 mL of DMF was added 2.22 g (1.05 equiv.) of *t*-BDMSCl and the solution was stirred at RT for 12 h, then at 70°C for 6 h. H_2O was added and the resulting mixture was extracted with Et_2O. The extract was washed with H_2O and brine, dried (Na_2SO_4), and evaporated to afford 8.87 g (98%) of **12**. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.08 (s, 6H, $SiCH_3$), 0.89 (s, 9H, C-CH_3), 3.65–3.75 (m, 24H, γ-η-CH_2 + CH_2Cl), 3.82 (t, *J* = 4.8 Hz, 4H, β-CH_2), 4.08 (t, *J* = 4.8 Hz, 4H, α-CH_2), 4.64 (s, 2H, CH_2O), 6.35 (t, *J* = 2.0 Hz, 1H, H_a), and 6.47 (d, *J* = 2.0 Hz, 2H, H_b). MS (FAB) *m/z* (rel. int.): 667.4 [M($^{35}Cl_1{}^{37}Cl_1$) + Na]$^+$ (3%), 665.4 [M($^{35}Cl_2$) + Na]$^+$ 4%), 644.4 [M($^{35}Cl_1{}^{37}Cl_1$)]$^+$ (4%), 642.4 [M($^{35}Cl_2$)]$^+$ (5%), 509.3; HRFAB, calcd. for $C_{29}H_{52}SiCl_2N_2O_9$: [M($^{35}Cl_2$)]$^+$ *m/z* 642.2757; found: 642.2730 (error 4.3 ppm).

3,5-Bis(11-chloro-3,6,9-trioxaundecyloxy)benzaldehyde (13)

PCC (5.16 g, 23.9 mmol) was added to a solution of 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzyl alcohol (**11**, 11.55 g, 21.8 mmol) in DCM (150 mL). After 15 h at RT, the mixture was filtered and the solid was washed with DCM. The solution after concentration was passed through a short silica gel column with Et_2O as eluent. The fractions were dried (Na_2SO_4) and evaporated to give pure **13** (9.89 g, 86%), an oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.55–3.65 (m, 24H, γ-η-CH_2 + CH_2Cl), 3.87 (t, *J* = 4.8 Hz, 4H, β-CH_2), 4.17 (t, *J* = 4.8 Hz, 4H, α-CH_2), 6.76 (t, *J* = 2.2 Hz, 1H, H_a), 7.02 (d, *J* = 2.2 Hz, 2H, H_b), and 9.89 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 42.67, 67.81, 69.51, 69.76, 70.60, 70.62, 70.66, 70.82, 71.31, 107.94, 108.26, 138.27, 160.35, and 191.77 (14 peaks as required). MS (FAB) *m/z* (rel. int.): 551.1 [M($^{35}Cl_1{}^{37}Cl_1$) + Na]$^+$ (69%), 549.1 [M($^{35}Cl_2$) + Na]$^+$ (100%), 515.2 [M($^{35}Cl_2$) + Na − ^{35}Cl] (35%); HRFAB, calcd. for $C_{23}H_{36}Cl_2O_9Na$: [M($^{35}Cl_1{}^{37}Cl_1$) + Na]$^+$ *m/z* 551.1605 and [M($^{35}Cl_2$) + Na]$^+$ *m/z* 549.1634; found: 551.1595 (error 1.7 ppm) and 549.1629 (error 0.9 ppm).

α-Morpholino-3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)-benzyl cyanide (14)

TMSCN (0.32 mL, 2.4 mmol) was added to a mixture of 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzaldehyde (**13**, 1.10 g, 2.09 mmol), $ZnCl_2$ (10 mg), and DCM (10 mL). The mixture was stirred at RT for 3 days, heated at reflux for 2 days, and poured into 50 mL of ice. The organic phase was washed with H_2O and evaporated to give 1.30 g (97%) of an oil. Silica gel chromatography using Et_2O afforded 1.2 g (92%) of **14**, an oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.5–2.7 (m, morpholino), 3.65–3.75 (m, 24H, γ-η-CH_2 + CH_2Cl), 3.86 (t, *J* = 4.8 Hz, 4H, β-CH_2), 4.11 (t, *J* = 4.8 Hz, 4H, α-CH_2), 4.72 (s, 1H, CHCN), 6.49 (t, *J* = 2.0 Hz, 1H, H_a), and 6.71 (d, *J* = 2.0 Hz, 2H, H_b). ^{13}C NMR ($CDCl_3$) δ (ppm): 42.71, 49.96, 66.64, 67.62, 69.59, 69.78, 70.61, 70.64, 70.67, 70.82, 71.34, 101.86, 106.85, 115.06, 134.65, 160.21 (16 peaks as required). MS (FAB) *m/z* (rel. int.): 623.4 [M($^{35}Cl_1{}^{37}Cl_1$) − H]$^+$ (8%), 621.4 [M($^{35}Cl_2$) − H]$^+$ (9%), 598.4 [M($^{35}Cl_1{}^{37}Cl_1$) − CN] (37%), 596.4 [M($^{35}Cl_2$) − CN]$^+$ (57%), 564.5 [M($^{35}Cl_1{}^{37}Cl_1$) + H − CN − ^{35}Cl] (37%), 562.5 [M($^{35}Cl_2$) + H − CN − ^{35}Cl]$^+$ (100%), 528.5 (62%); HRFAB (3-NBA/GLY/TFA), calcd. for $C_{28}H_{43}{}^{35}Cl_2N_2O_9$: [M − H]$^+$ *m/z* 621.2346; found: 621.2340 (error 0.9 ppm).

5-Carbomethoxy-*m*-phenylene-5′-formyl-*m*′-phenylene-32-crown-10 (15)

A solution containing 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzaldehyde (**13**, 6.00 g, 11.4 mmol) and methyl 3,5-dihydroxybenzoate (**1**, 1.91 g, 11.4 mmol) in DMF (total volume 18 mL) was added via a syringe pump at 0.75 mL/h to a suspension containing CsF (18.11 g, 119.2 mmol) and TBAI (20 mg) in DMF (550 mL) at 110°C. After complete addition, the mixture was stirred at 110°C for 5 days. The cooled reaction mixture was evaporated, treated with DCM, and filtered. Removal of DCM followed by flash silica gel column chromatography using Et_2O as eluent gave pure **15** (2.26 g, 32%) as an oil that crystallized upon standing, mp 70.2–72.0°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.65–3.75 (m, 16H, γ, γ′, δ, δ′-CH_2), 3.85–3.95 (m, 8H, β,β′-CH_2), 3.87 (s, 3H, CH_3), 4.05–4.15 (m, 8H, α,α′-CH_2), 6.67 (t, *J* = 2.4 Hz, 1H, $H_{a'}$), 6.73 (t, *J* = 2.4 Hz, 1H, H_a), 6.98 (d, *J* = 2.4 Hz, 2H, H_b), 7.14 (d, *J* = 2.4 Hz, 2H, $H_{b'}$), and 9.84 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 52.17, 67.77, 67.87, 69.49, 69.52, 70.77, 70.79, 70.84, 106.78, 107.93, 108.18, 131.77, 138.17, 159.67, 160.31, 166.68, and 191.86 (17 peaks; theory 18). MS (FAB) *m/z* (rel. int.): 623.2 [M + H]$^+$ (100%), 591.3 (M$^+$ − OCH_3) (44%); HRFAB, calcd. for $C_{31}H_{43}O_{13}$: [M + H]$^+$ *m/z* 623.2703; found: 623.2681 (error 3.5 ppm).

Lactone (16a) from 5-hydroxymethyl-*m*-phenylene-5′-carbomethoxy-*m*′-phenylene-32-crown-10 (16)

To a stirred suspension of Cs_2CO_3 (38.51 g, 118 mmol) and TBAI (20 mg) in DMF (560 mL) at 110°C was added a solu-

tion of 3,5-bis(11-chloro-3,6,9-trioxaundecyloxy)benzyl *tert*-butyldimethylsilyl ether (**12**) (7.56 g, 11.7 mmol) and methyl 3,5-dihydroxybenzoate (**1**) in DMF (20 mL) at a rate of 0.75 mL/h. The mixture was stirred for 4 days at 110°C, cooled, and filtered throught Celite, which was rinsed with DCM. The filtrate was rotary evaporated to yield a dark brown oil, 11 g, which was subjected to silica gel column chromatography with 7/1 EtOAc/EtOH to afford pure **16a**, an oil, 1.56 g (18%). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.7–3.9 (m, 24H, β, γ, δ, β′, γ′, δ′-CH_2), 4.0–4.4 (m, 8H, α,α′-CH_2), 5.29 (s, 2H, CH_2), 6.41 (t, J = 2.0 Hz, 1H, H_a), 6.59 (t, J = 2.0 Hz, 1H, H_b), 6.73 (d, J = 2.0 Hz, 1H, $H_{a'}$), and 7.29 (d, J = 2.0 Hz, 1H $H_{b'}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 66.62, 67.85, 67.98, 69.45, 69.83, 70.45, 70.55, 70.62, 70.86, 103.43, 108.05, 108.94, 109.29, 132.06, 138.38, 159.63, 159.65, 165.68 (18 peaks; 19 peaks theory). MS (FAB) *m/z* (rel. int.): 615.2 $[M + Na]^+$ (100%), 483.2 $[M + Na - (OCH_2CH_2)_3]^+$ (14%), 176.0 $[(OCH_2CH_2)_4]^+$ (44%); HRFAB, calcd. for $C_{30}H_{40}O_{12}Na$ (lactone, i.e., **16a** + Na^+): $[M]^+$ *m/z* 615.2417; found: 615.2425 (error 1.2 ppm).

Bis(5-carboxy-*m*-phenylene)-32-crown-10 (17)

Aqueous NaOH (27 mL, 4 M) was added to a solution of diester crown **4** (1.26 g, 1.93 mmol) in absolute EtOH (120 mL). The mixture was refluxed for 48 h, cooled to RT, acidified with 4 M HCl, diluted with H_2O, and extracted with DCM (3 × 50 mL). The organic extract was concentrated and the crude solid was purified by recrystallization from EtOH to give **17** (1.12 g, 93%), mp 171.1–171.5°C (lit. (9*a*) mp 169.5–170.5°C). IR: 3501 (-OH), 1696 (C=O), 1600 (C=C), 1129 (C-O-C) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 3.55–3.65 (m, 16H, γ,δ-CH_2), 3.65–3.75 (m, 8H, β-CH_2), 4.09 (t, J = 4.4 Hz, 8H, α-CH_2), 6.75 (t, J = 2.2 Hz, 2H, H_a), and 7.02 (d, J = 2.2 Hz, 4H, H_b). ^{13}C NMR (DMSO-d_6) δ (ppm): 67.51, 68.83, 70.01, 70.02, 105.65, 107.51, 132.73, 159.54, and 166.90 (9 peaks; theory 9).

Bis(5-acetyl-*m*-phenylene)-32-crown-10 (18)

MeLi in Et_2O (28.0 mL, 1.4 M, 38.4 mmol, 15.9 equiv.) was added to an ice cold solution of bis(5-carboxy-*m*-phenylene)-32-crown-10 (**17**, 1.51 g, 2.42 mmol) in THF (100 mL). After 3 h at 0°C, TMSCl (25.6 mL, 202 mmol) was rapidly added while stirring continued. After 30 min at 0°C, the mixture was allowed to come to RT at which point 1 N HCl (25 mL) was added. The resulting two-phase system was stirred at RT for 2 h and the product was extracted with Et_2O (3 × 50 mL). The organic layer was washed with H_2O and dried (Na_2SO_4). The pure product **18** (0.67 g, 45%), mp 95.2–96.1°C, a white powder, was obtained via silica gel column chromatography with EtOAc as eluent. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.53 (s, 6H, CH_3), 3.65–3.75 (m, 16H, γ,δ-CH_2), 3.85 (t, J = 4.6 Hz, 8H, β-CH_2), 4.10 (t, J = 4.6 Hz, 8H, α-CH_2), 6.67 (t, J = 2.2 Hz, 2H, H_a), and 7.07 (d, J = 2.2 Hz, 4H, H_b). ^{13}C NMR ($CDCl_3$) δ (ppm): 26.70, 67.80, 69.57, 70.85, 70.86, 106.34, 107.00, 138.83, 159.92, and 197.67 (10 peaks as required). MS (FAB) *m/z* (rel. int.): 621.5 $[M + H]^+$ (100%); HRFAB, calcd. for $C_{32}H_{44}O_{12}$: $[M + H]^+$ *m/z* 621.2911; found: 621.2915 (error 0.6 ppm).

Bis(5-hydroxymethyl-*m*-phenylene)-32-crown-10 (19)

LAH in THF (3.6 mL, 1.0 M, 3.6 mmol, 1.11 equiv.) was added to a solution of bis(5-carbomethoxy-*m*-phenylene)-32-crown-10 (**4**, 2.11 g, 3.23 mmol) in anhydrous THF (100 mL) at RT. The mixture was stirred for 12 h, excess LAH was destroyed with EtOAc, and the mixture was diluted with H_2O (30 mL). Upon neutalization with 2 N HCl the mixture was extracted with Et_2O (3 × 30 mL). The organic layer was dried (Na_2SO_4) and evaporated. Recrystallization from acetone gave pure **19** (1.82 g, 94%), mp 99.5–100.4°C. IR: 3435 (-OH), 2924 (-CH), 1602 (C=C), and 1122 (C-O-C) cm^{-1}. ^{1}H NMR (CD_3COCD_3) δ (ppm): 3.55–3.65 (m, 16H, γ,δ-CH_2), 3.79 (t, J = 4.6 Hz, 8H, β-CH_2), 4.06 (t, J = 4.6 Hz, 8H, α-CH_2), 4.16 (t, J = 6.0 Hz, 2H, OH), 4.54 (d, J = 6.0 Hz, 4H, CH_2), 6.37 (t, J = 2.2 Hz, 2H, H_a), and 6.52 (d, J = 2.2 Hz, 4H, H_b). ^{13}C NMR (CD_3COCD_3) δ (ppm): 64.59, 68.33, 70.32, 71.46, 71.44, 104.88, 105.76, 145.78, and 161.01 (9 peaks as required). MS (FAB) *m/z* (rel. int.): 596.3 $(M + H)^+$ (100%), 561.3 $(M^+ - 2OH)$ (32%), and 534.9 $(M^+ - 2CH_2OH)$ (12.5%); HRFAB, calcd. for $C_{30}H_{44}O_{12}$: $[M + H]^+$ *m/z* 596.2833; found: 596.2848 (error 2.5 ppm).

Bis(5-bromomethyl-*m*-phenylene)-32-crown-10 (20)

PBr_3 (1.60 mL, 16.9 mmol, 5.20 equiv.) was added to a solution of bis(5-hydroxymethyl-*m*-phenylene)-32-crown-10 (**19**, 1.92 g, 3.22 mmol) in a mixture of Et_2O (250 mL) and EtOAc (30 mL). The mixture was stirred for 36 h at RT. The resulting white solid was filtered and washed several times with Et_2O. Pure **20** (2.04 g, 88%), mp 108.5–110.1°C, was obtained by recrystallization from EtOAc. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.65–3.75 (m, 16H, γ,δ-CH_2), 3.83 (t, J = 4.6 Hz, 8H, β-CH_2), 4.05 (t, J = 4.6 Hz, 8H, α-CH_2), 4.37 (s, 4H, CH_2), 6.40 (t, J = 2.2 Hz, 2H, H_a), and 6.53 (d, J = 2.2 Hz, 4H, H_b). ^{13}C NMR ($CDCl_3$) δ (ppm): 33.61, 67.60, 69.59, 70.81, 70.84, 101.59, 107.87, 139.55, and 159.96 (9 peaks as required). MS (FAB) *m/z* (rel. int.): 721.2 $[M + H]^+$ (100%); HRFAB, calcd. for $C_{30}H_{42}Br_2O_{10}$: $[M + H]^+$ *m/z* 721.1222; found: 721.1214 (error 1.1 ppm).

Bis(5-formyl-*m*-phenylene)-32-crown-10 (21)

PCC (1.16 g, 5.38 mmol, 2.21 equiv.) was added to a solution of bis(5-hydroxymethyl-*m*-phenylene)-32-crown-10 (**19**, 1.45 g, 2.43 mmol) in DCM (20 mL). After 2 h the mixture was filtered and the solid washed with DCM. The solution upon concentration was passed through a short silica gel column with EtOAc as eluent to give a white solid. Recrystallization from acetone gave pure **21** (1.22 g, 85%), mp 92.3–95.8°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.65–3.75 (m, 16H, γ,δ-CH_2), 3.86 (t, J = 4.6 Hz, 8H, β-CH_2), 4.12 (t, J = 4.6 Hz, 8H, α-CH_2), 6.73 (t, J = 2.2 Hz, 2H, H_a), 6.98 (d, J = 2.2 Hz, 4H, H_b), and 9.85 (s, 2H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 67.90, 69.52, 70.81, 70.88, 107.95, 108.24, 138.22, 160.33, and 191.84 (9 peaks as required). MS (FAB) *m/z* (rel. int.): 593.6 $[M + H]^+$ (100%); HRFAB, calcd. for $C_{30}H_{40}O_{12}$: $[M + H]^+$ *m/z* 593.2598; found: 593.2577 (error 3.5 ppm).

Bis[5-(*p*-nitrophenoxymethyl)-*m*-phenylene]-32-crown-10 (22)

NaH (0.108 g, 60%, 2.70 mmol) was added to a solution of bis(5-hydroxymethyl-*m*-phenylene)-32-crown-10 (**19**, 0.718 g, 1.20 mmol) in dry THF (20 mL). The mixture was heated at reflux for 3 h, cooled, treated with *p*-fluoronitrobenzene (0.30 mL, 2.8 mmol), and stirred at RT for 24 h. After solvent removal the residue was extracted with $CHCl_3$, evaporation of which gave crude **22**, a yellow solid, 1.0 g (100%). After silica gel column chromatography, using first Et_2O and then EtOAc

followed by recrystallization from acetone, pure **22**, mp 133.1–134.0°C, was obtained. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.65–3.75 (m, 16H, γ, δ-CH_2), 3.83 (t, J = 4.8 Hz, 8H, β-CH_2), 4.06 (t, J = 4.8 Hz, 8H, α-CH_2,), 5.04 (s, 4H, CH_2), 6.43 (t, J = 2.0 Hz, 2H, H_a), 6.54 (d, J = 2.0 Hz, 4H, H_b), 6.98 (d, J = 9.1 Hz, 4H, Ar), and 8.17 (d, J = 9.1Hz, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 67.63, 69.61, 70.44, 70.85, 101.09, 106.03, 114.86, 125.89, 137.77, 141.65, 160.28, 163.53 (12 peaks, 13 peaks theory). Anal. calcd. for $C_{42}H_{50}N_2O_{16}$: C 60.14, H 6.01, N 3.34; found: C 59.87, H 6.03, N 3.26.

Bis(5-acetoxymethyl-*m*-phenylene)-32-crown-10 (23)

To a solution of bis(5-hydroxymethyl-*m*-phenylene)-32-crown-10 (**19**, 0.581 g, 0.974 mmol) and pyridine (0.17 mL) in dry THF (75 mL) was added acetyl chloride (0.080 mL, 1.1 mmol) and the mixture was stirred at RT for 30 h. After filtration the solvent was evaporated. The residue was taken up in Et_2O. The solution was washed with H_2O (2 × 50 mL), 2 N HCl (30 mL), and H_2O, dried (Na_2SO_4), and rotary evaporated to give **23**, 0.65 g (98%), an oil that subsequently crystallized, mp 68.9–70.1°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.05 (s, 3H, CH_3), 3.58–3.68 (m, 16H, γ, δ-CH_2), 3.79 (t, J = 4.8 Hz, 8H, β-CH_2), 4.07 (t, J = 4.8 Hz, 8H, α-CH_2), 4.99 (s, 4H, CH_2O), 6.45 (t, J = 2.0 Hz, 2H, H_a), and 6.52 (d, J = 2.0 Hz, 4H, H_b). ^{13}C NMR ($CDCl_3$) δ (ppm): 29.77, 66.23, 68.46, 70.27, 71.44, 71.47, 101.39, 107.33, 139.58, 161.14, 170.78 (11 peaks as required). MS (FAB) *m/z* (rel. int.): 680.4 $[M]^+$ (13%); HRFAB, calcd. for $C_{34}H_{48}O_{14}$: $[M]^+$ *m/z* 680.3044; found: 680.3022 (error 3.2 ppm).

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