Novel Benzene-Bridged Macrobi- and Macrotricyclic Polyethers

Haoyun An,‡ Jerald S. Bradshaw,*,† Krzysztof E. Krakowiak,‡ Bryon J. Tarbet,‡ N. Kent Dalley,† Xiaolan Kou,† Chengyue Zhu,† and Reed M. Izatt†

Department of Chemistry, Brigham Young University, Provo, Utah 84602, and IBC Advanced Technologies, Inc., 505 East 1860 South, Provo, Utah 84606

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Novel three-dimensional benzene-bridged macrobicyclic polyether **1** and macrotricyclic polyether **2** have been prepared. Macrobicyclic triply bridged cyclophane crown compound **1** was synthesized by a tripode–tripode coupling of 1,3,5-tris[7′-(tosyloxy)-2′,5′-dioxa-1′-heptyl]benzene (**19**) with 1,3,5-tris(hydroxymethyl)benzene (**5**). Macrotricyclic quadruply bridged cyclophane crown ether **2** was obtained by a quadrupode–quadrupode coupling of 1,2,4,5-tetrakis(7′-tosyloxy-2′,5′-dioxa-1′-heptyl)-benzene (**20**) with 1,2,4,5-tetrakis(hydroxymethyl)benzene (**6**). These ligands could have suitable rigidity and cavity sizes for the coordination of metal cations. They appear to have selectivities for cesium over sodium and lead ions, and **2** shows a log K value of 3.50 for interaction with cesium ion in 80% CH_3OH/20% water (v/v). Macrotricyclic polyether **2** containing benzene bridgeheads is a new type of ligand, and its structure was confirmed by an X-ray crystallographic study.

Introduction

There is great interest in the design, synthesis, and use of various macropolycyclic host receptors capable of the selective recognition of metal cations and other species. In addition to the well known monocyclic crown ethers and bicyclic cryptands,[1–7] more preorganized supramolecules including macropolycyclic polyethers,[8–10] spherands,[11] channel-type molecules,[12] and knot[13] and cyclophane[14] type receptors have been studied. Because of their strong interaction with and high selectivity for a variety of metal cations, the three-dimensional cryptands have been used in various separation, transport, and detection areas. Some cryptands with carbon bridgehead atoms were found to have high log K values and good selectivities for sodium over potassium ions.[15] More rigid ligands could possibly have higher selectivities and, therefore, would be important for certain separation processes which demand extremely high selectivity.

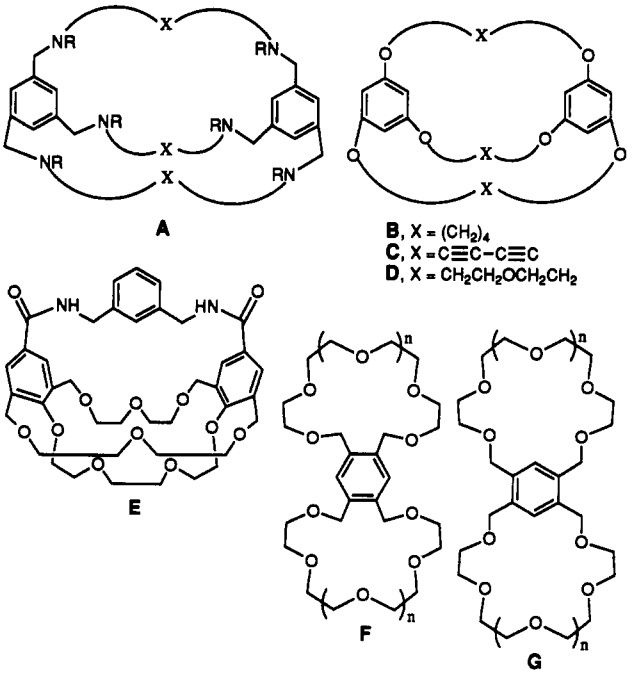

Figure 1. Known benzene-bridged macropolycycles.

A number of rigid cryptand-like compounds containing benzene bridgeheads (**A** in Figure 1), the benzene-bridged cyclophane type crown compounds, have been synthesized.[16–18] Some of them exhibit very interesting complexation properties, for example, selective recognition of trihydroxybenzene or as anion receptors.[17,19] The aromatic structural units in the cyclophane hosts ensure the necessary structural rigidity and thereby improve the preorganization of the coordination sites for cooperative binding of the guests. Seel and Vögtle summarized the synthetic strategies for these kinds of triply bridged cyclophane hosts.[17] Most of the cyclophane-type ligands with nitrogen donor atoms were synthesized by amide bond

† Brigham Young University.
‡ IBC Advanced Technlologies, Inc.
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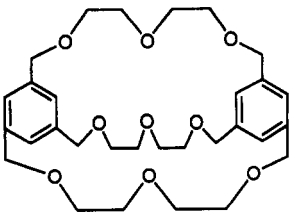
formation in the cyclization step because of the high reactivity of acyl chlorides. Similar triply branched hexaester macrobicyclic polyethers with benzene bridgeheads were also prepared by the esterification of glycols with diacyl dichloride derivatives.[20] Nitrogen-containing ligands can have limited use, especially under acidic conditions, and ester bond-containing hosts have limited use because they are easily hydrolyzed. Cyclophane ligands containing only ether bonds, e.g. **B**,[21] **C**[22] (Figure 1), and others,[23-25] have been synthesized, but they are not good complexing agents for metal cations because they do not have enough donor atoms in their bridges. Macrobicycle **D**, containing more donor atoms and an appropriate cavity size, was proposed but not synthesized.[21]

Benzene-bridged macrotricyclic polyethers, the macrotricyclic quadruply bridged cyclophane crown compounds, are very rare. To the best of our knowledge, only unsymmetrical macrotricyclic polyether diamide **E** (Figure 1) has been synthesized using many steps.[26] A cyclohexane-bridged macrotricyclic polyether with a large and flexible cavity has also been reported.[27] Most of the benzene-bridged macrobi- and tricyclic ligands were synthesized by multistep processes. A few of the macrobicycles were obtained in low yields by a one-step 2:3 cyclization route.[17,23] These latter macrobicycles required highly reactive groups for cyclization. When 1,2,4,5-tetra(bromomethyl)benzene was treated with the polyethylene glycols in base, only 1:2 cyclization products, the bis-*o*-xylyl crowns **F** and bis-*m*-xylyl crowns **G** were obtained.[28]

In order to explore ligand geometries and find macropolycyclic ligands with suitable rigidity and cavity sizes to have high selectivity for certain metal cations, we have prepared two novel three-dimensional benzene-bridged macropolycyclic ligands **1** and **2** (Figure 2). Ligand **1** is a triply bridged (1,3,5)-cyclophane molecule and **2** is a quadruply bridged (1,2,4,5)-cyclophane molecule. These ligands could have rigid and large cavities such that they could have high affinities for cesium ions in water–methanol mixtures. The crystal structure of free macrotricyclic ligand **2** is also reported.

Results and Discussion

As mentioned above, only a few cyclophane macrobicyclic ligands containing large cavities have been synthesized by a one step 2:3 cyclization process. These were obtained by cyclic diamide formation or by the reaction of phenolic and benzyl bromide moieties. An attempt to prepare benzene-bridged macrobicycle **1** in one-step by treating 1,3,5-tris(hydroxymethyl)benzene (**5**) with diethylene glycol ditosylate in base was not successful. The one-step 2:3 and 2:4 cyclizations of 1,3,5-tris(bromomethyl)benzene and 1,2,4,5-tetrakis (bromomethyl)benzene with diethylene glycol were not attempted because only



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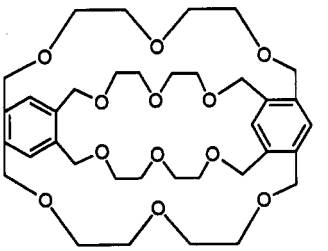

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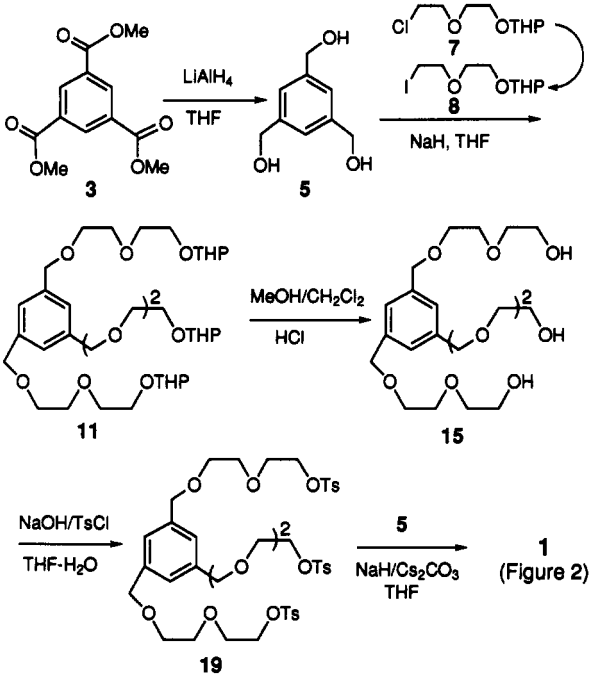
Figure 2. New benzene-bridged macrobi- and macrotricyclic polyethers **1** and **2**.

Scheme I. Synthesis of Benzene-Bridged Macrobicyclic Polyether 1



biscrowns **F** and **G** (Figure 1) were obtained in this type of reaction.[28]

Stepwise methods were used for the construction of macrobicyclic and macrotricyclic ligands **1** and **2** (Schemes I and II). Trimethyl 1,3,5-benzenetricarboxylate (**3**) was first reduced to give 1,3,5-tris(hydroxymethyl)benzene (**5**) (Scheme I). 2-(2′-Chloroethoxy)ethyl 2″-tetrahydropyranyl ether (**7**) was not reactive enough to react with triol **5**; therefore, **7** was converted into its iodo derivative **8** by the halogen exchange reaction with NaI in acetonitrile. Iodo derivative **8**, without isolation, was treated with **5** to give tris(tetrahydropyranyl)-protected ether **11**. Deprotection of **11** under acidic conditions gave trialcohol **15** which was then converted to its tritosylate **19** in a 97% yield by reaction with tosyl chloride in a THF/H_2O solvent system using NaOH as the base. The tripode–tripode coupling of tritosylate **19** with trialcohol **5** provided benzene-bridged macrobicyclic polyether **1**. This com-

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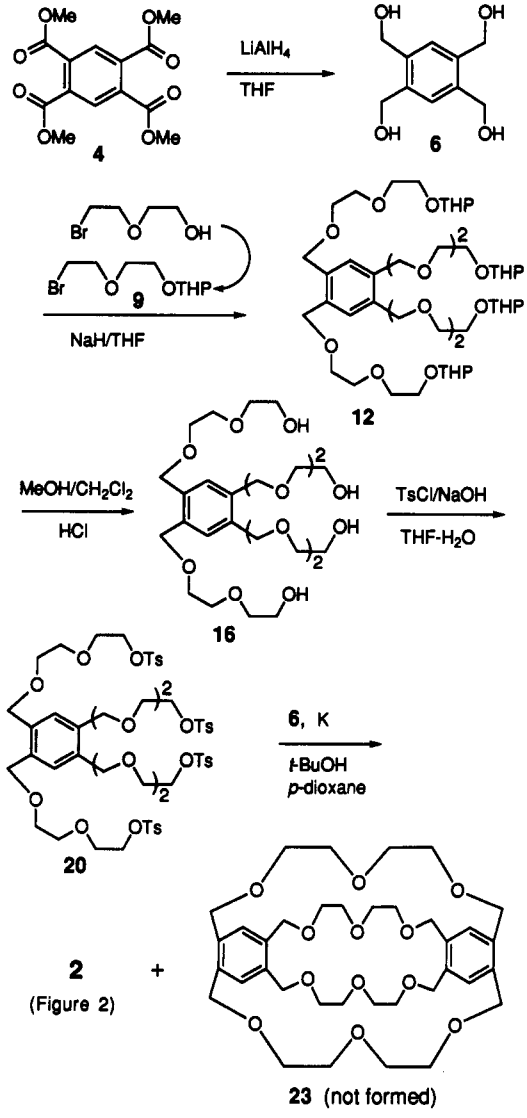
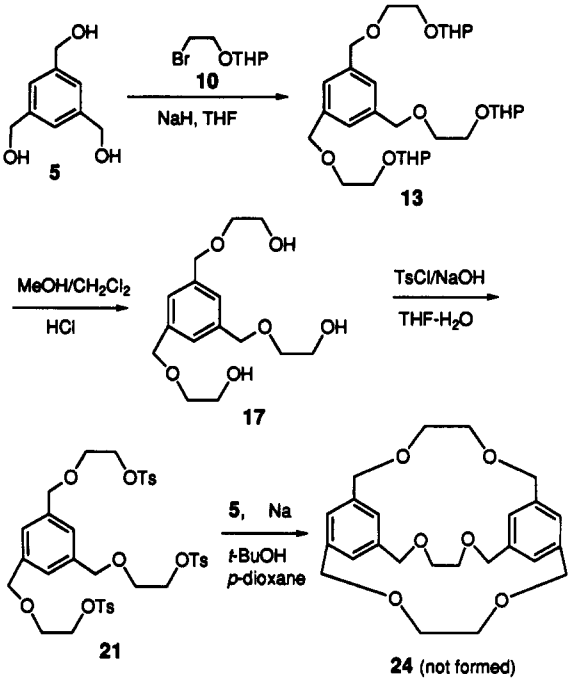
Scheme II. Synthesis of Benzene-Bridged Macrotricyclic Polyether 2



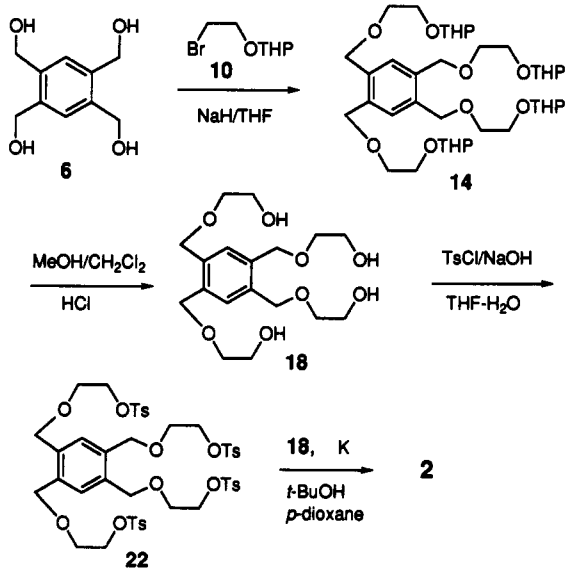
pound could also be called a benzene-bridged cryptand or a macrobicyclic triply bridged cyclophane ligand. Three-dimensional ligand 1 could have suitable rigidity and cavity size for the encapsulation of the large metal cations.

The synthesis of benzene-bridged macrotricyclic polyether 2 is shown in Scheme II. The reduction of tetramethyl 1,2,4,5-benzenetetracarboxylate (4) gave the corresponding 1,2,4,5-tetrakis(hydroxymethyl)benzene (6). 2-(2′-Bromoethoxy)ethanol is not available and was prepared by the bromination of excess diethylene glycol with phosphorus tribromide. Tetrahydropyranyl derivatives 9, 10[29] (Scheme III) and 7[30] (Scheme I) were obtained by the reaction of dihydropyran with the corresponding haloglycols. Tetraalcohol 6 was treated with an excess amount of bromide 9 using NaH as the base in THF to produce tetrakis(tetrahydropyranyl) derivative 12 in a 90% yield. Deprotection of 12 under acidic conditions gave tetraalcohol 16 which was then converted to the corresponding tetratosylate 20. A quadrupode–quadrupode coupling of this tetratosylate with tetraalcohol 6 using potassium dissolved in *tert*-butyl alcohol as the base gave

Scheme III. Attempted Preparation of Small Benzene-Bridged Macrobicyclic Polyether 24



Scheme IV. Another Method for the Preparation of 2



benzene-bridged macrotricyclic polyether 2. This is a new type of quadruply bridged macrotricyclic cyclophane ligand with two parallel benzene rings in a three-dimensional shape. The X-ray crystal structure confirmed the structure of 2 as shown and not the symmetrical isomer 23.

An attempt to prepare macrobicycle 24, a smaller analog of 1, was made starting from trialcohol 5 and tetrahydropyranyl bromoethyl ether 10 (Scheme III). Intermediates 13, 17, and 21 were all prepared in the same manner as 11, 15 and 19 (Scheme I). Macrobicycle 24 was not obtained by the tripode–tripode coupling of 21 with 5, possibly because of high strain in the small cavity.

Macrotricycle 2 was also prepared by a 1:1 coupling of 18 and 22 as shown in Scheme IV. Intermediates 14, 18, and 22 were synthesized in the same manner as 12, 16 and 20 (Scheme II). The quadrupode–quadrupode coupling

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Table I. Log K, ΔH, and ΔS Values for the Interaction of 1 and 2 with Several Metal Cations

		Log K^a	ΔH (kJ mol^{-1})^a	ΔS (J mol^{-1} K^{-1})^a
1	Cs^{+} [b]	2.20 (5)	−57.5 (7)	−150.9
	Na^{+} [c]	N/O[d]	–	–
	Pb^{2+} [c]	N/O[d]	–	–
2	Cs^{+} [b]	3.50 (2)	−53.6 (5)	−112.9
	Na^{+} [c]	N/O[d]	–	–
	Pb^{2+} [c]	N/O[d]	–	–

[a] The numbers in parentheses indicate the uncertainties of the values. [b] 80% MeOH–20% H_2O (v/v). [c] 50% MeOH–50% H_2O (v/v). [d] N/O = No observable heat, indicating little or no reaction.

of tetratosylate **22** with tetraalcohol **18** was done under similar conditions as the coupling of **20** and **6** shown in Scheme II. Unfortunately, most of the product was lost because a fraction collector stopped operating. A small amount of the product was collected. The R_f value in the TLC analysis of this product using two different solvent systems was the same as that for compound **2** obtained using the method shown in Scheme II.

All intermediates were characterized by their spectral analyses. Ligand **1** was characterized by its ^1H and ^{13}C NMR and IR spectra and MS and combustion analyses. Due to its symmetrical structure, **1** exhibited three types of protons in its ^1H NMR spectrum with three singlets and five types of carbons in its ^{13}C NMR spectrum. Ligand **2** was characterized by all of its spectra and by X-ray crystallography. Because of the high rigidity of ligand **2**, two benzyl methylene protons ($ArCH_aH_b$) on one carbon are not in the same chemical environment. Therefore one proton (H_a) couples with the other (H_b) resulting in two doublets (see Experimental Section).

The log K values in water–methanol mixtures for the interaction of **1** and **2** with Cs^+, Na^+, and Pb^{2+} (Table I) were measured using a titration calorimetric technique at 25 °C. The complexation results indicate that these three-dimensional ligands, especially **2**, probably have high selectivity for Cs^+ over Na^+ and Pb^{2+}. The measurements for Cs^+ were made in a different methanol–water mixture than those for Na^+ and Pb^{2+}. Therefore, direct comparison of selectivities is not possible. Macrotricyclic ligand **2** with an additional bridge shows a stronger interaction with Cs^+ than does macrobicyclic ligand **1**. The increased number of donor atoms, while otherwise maintaining the geometrical ligand structure, allows for the increase in log K for Cs^+.

The crystal structure of **2** is shown in Figure 3. The figure clearly establishes the structural formula of **2**. The compound exists as a three-dimensional cage with four $CH_2O(CH_2)_2O(CH_2)_2OCH_2$ branches linked by benzene groups. The benzenes form the top and the bottom of the cage and are nearly parallel. The dihedral angle between the least-square planes of the benzene rings is 17°. The nonsymmetrical isomer can be described by examining the rings formed by the ether branches and portions of the benzene rings. Branches joined by adjacent carbons of one benzene are attached to carbons on the other benzene which are also separated by one carbon. The result is illustrated in Figure 3 which shows that the line joining the carbons not bonded to branches in the bottom benzene, C2 and C5, is approximately perpendicular to the line joining similiar carbons in the top benzene, C18 and C21. Figure 3 also shows clearly that the potential host molecule is not preorganized. Several of the donor oxygen atoms point out of the cavity of the molecule. Without the organizing effect of the cation, the flexible

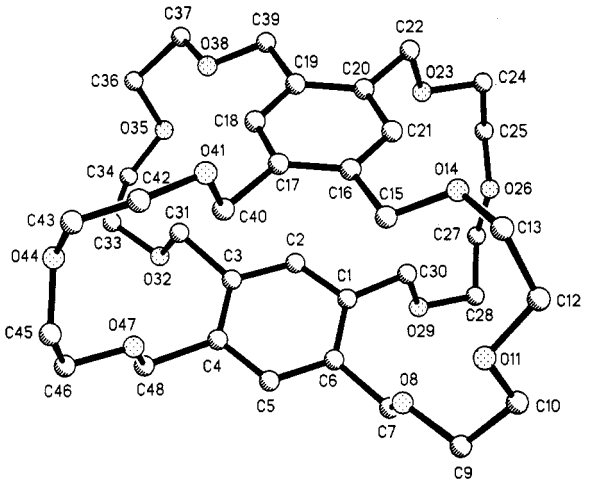

Figure 3. X-ray crystal stucture of macrotricyclic polyether **2**. Hydrogen atoms and disordered primed atoms are omitted for clarity.

branches are disordered. The disorder involving at least one atom of each branch could be resolved, i.e., C10, O23, O29, C30, O41, and O47, except for the O32–C39 branch. Other disorder, which can be identified by large thermal motions of atoms and unusually short bond lengths, could not be resolved. Unfortunately we have not crystallized the cation complexes of **2**. A summary of the experimental conditions and the structure determination are included in the supplementary material. Atomic positional and thermal parameters, bond lengths, and bond angles are also included in the supplementary materials.

Experimental Section

Proton and carbon NMR spectra were obtained at 200 MHz in $CDCl_3$. Molecular weights were determined by electron-impact HRMS unless otherwise indicated. Log K, ΔH, and ΔS values were measured by a titration calorimetric method.[31] The nitrate salts of Cs^+, Na^+ and Pb^{2+} and other starting materials were used as purchased. 2-Bromoethyl 2′-tetrahydropyranyl ether **10**[29] and 2-(2′-chloroethoxy)ethyl 2″-tetrahydropyranyl ether **7**[30] were prepared in the same manner as **9** (see below). Trimethyl 1,3,5-benzenetricarboxylate (**3**) and tetramethyl 1,2,4,5-benzenetetracarboxylate (**4**) were obtained by the esterification of the corresponding acids in 93 and 69% yields, respectively.[32,33] 1,3,5-Tris(hydroxymethyl)benzene (**5**)[34–37] and 1,2,4,5-tetrakis(hydroxymethyl)benzene (**6**)[38,39] were prepared as reported.

Preparation of 2-(2′-Bromoethoxy)ethanol. Phosphorus tribromide (300 g, 1.1 mol) was added slowly to stirred diethylene glycol (1000 g, 9.42 mol) at −5 °C. The temperature was increased until the reaction mixture refluxed gently. The mixture was distilled under reduced pressure and the material that was collected at 69–90 °C/1–2 mm was redistilled to give 347 g (62%) of a colorless liquid, bp 75–82 °C/1–2 mm; ^1H NMR δ 3.40–3.55 (m, 2 H), 3.60–3.70 (m, 2 H), 3.73–3.90 (m, 4 H), 4.80 (s, 1 H, disappeared in D_2O); IR 3400, 2800, 2900, 1100 cm^{-1}.

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Preparation of 2-(2′-Bromoethoxy)ethyl 2″-Tetrahydropyranyl Ether (9) (Scheme II). 3,4-Dihydro-2*H*-pyran (73 g, 0.86 mol) was added stepwise to stirred 2-(2′-bromoethoxy)ethanol (96 g, 0.57 mol) at rt. After 1 h, 2 g of $NaHCO_3$ was added. After evaporating the excess dihydropyran, the residue was distilled under reduced pressure to give 102 g (71%) of **9** as a colorless liquid: bp 85–90 °C/0.3–0.4 mm; ^{1}H NMR δ 1.40–1.85 (m, 6 H), 3.35–3.85 (m, 10 H), 4.55–4.62 (m, 1 H); ^{13}C NMR δ 99.34, 71.64, 70.95, 67.07, 62.59, 31.00, 30.71, 25.87, 19.89.

Tri(2′-tetrahydropyranyl) Ether of 1,3,5-Tris(7′-hydroxy-2′,5′-dioxa-1′-heptyl)benzene (11) (Scheme I). A mixture of **7** (17.7 g, 0.09 mol), NaI (16.2 g, 0.11 mol), and $NaHCO_3$ (10 g) in 200 mL of acetonitrile was refluxed for 12 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2. The solid was filtered and washed. The combined filtrate was evaporated to give iodo derivative **8** which was used without purification. To a mixture of NaH (2.5 g, 0.10 mol) and 40 mL of THF was added a solution of 1,3,5-tris(hydroxymethyl)benzene (**5**) (1.68 g, 0.01 mol) in 60 mL of THF. The mixture was refluxed for 2 h and the above iodo derivative **8** in 100 mL of THF was added dropwise at 60 °C for 1–2 h. The resulting mixture was refluxed for 3 days. The cooled reaction mixture was filtered and the solvent was evaporated. The residue was purified by chromatography on silica gel using toluene/THF 40/1, 10/1, and 5/1 as eluents to give 2.85 g (42%) of **11** as a colorless oil: ^{1}H NMR δ 1.48–1.90 (m, 18 H), 3.42–3.71 (m, 24 H), 3.80–3.93 (m, 6 H), 4.54 (s, 6 H), 4.59–4.66 (m, 3 H), 7.24 (s, 3 H); ^{13}C NMR δ 139.12, 126.67, 99.35, 73.57, 71.13, 71.06, 70.09, 67.14, 62.57, 31.05, 25.93, 19.94; IR 2939, 2867, 1454, 1351, 1125 cm^{-1}.

Tetra(2′-tetrahydropyranyl) Ether of 1,2,4,5-Tetrakis(7′-hydroxy-2′,5′-dioxa-1′-heptyl)benzene (12) (Scheme II). A mixture of NaH (1.6 g, 0.066 mol), 1,2,4,5-tetrakis(hydroxymethyl)benzene (**6**) (1.0 g, 0.005 mol), and 100 mL of THF was refluxed for 2 h. A solution of bromo derivative **9** (17.86 g, 0.07 mol) in 50 mL of THF was added dropwise at reflux temperature. The resulting mixture was refluxed for 7 days. The cooled mixture was filtered and the solvent was evaporated. The residue was purified by chromatography on silica gel using toluene/THF 10/1 and 5/1 as eluents to give 3.58 g (81%) of **12** as a colorless viscous oil: ^{1}H NMR δ 1.40–1.90 (m, 24 H), 3.40–3.71 (m, 32 H), 3.76–3.91 (m, 8 H), 4.71 (s, 12 H), 7.38 (s, 2 H); ^{13}C NMR δ 136.34, 129.94, 99.35, 71.07, 70.04, 67.14, 62.58, 31.03, 25.91, 19.93; IR 2939, 2860, 1455, 1351, 1121 cm^{-1}.

Tri(2′-tetrahydropyranyl) Ether of 1,3,5-Tris(4′-hydroxy-2′-oxa-1′-butyl)benzene (13) (Scheme III). **13** was synthesized as above for **11** from 3.4 g (0.02 mol) of triol **5**, 4.5 g (0.187 mol) of NaH, and 27.5 g (0.131 mol) of bromide **10** in 250 mL of THF by stirring the reaction mixture for 6 days at reflux temperature. Purification by chromatography on silica gel using toluene/THF 15/1 and 5/1 as eluents gave 7.0 g (63%) of **13** as a pale yellow viscous oil: ^{1}H NMR δ 1.43–1.91 (m, 18 H), 3.42–3.70 (m, 12 H), 3.80–3.97 (m, 6 H), 4.58 (s, 6 H), 4.62-4.70 (m, 3 H), 7.26 (s, 3 H).

Tetra(2′-tetrahydropyranyl) Ether of 1,2,4,5-Tetrakis(4′-hydroxy-2′-oxa-1′-butyl)benzene (14) (Scheme IV). **14** was synthesized as above for **12** from 1.0 g (0.005 mol) of triol **6**, 1.6 g (0.066 mol) of NaH, and 15 g (0.071 mol) of bromide **10** in 70 mL of THF by stirring the reaction mixture for 7 days at reflux temperature. Purification by chromatography on silica gel using toluene/THF 20/1, 10/1 and 3/1 as eluents gave 2.8 g (79%) of **14** as a pale yellow viscous oil: ^{1}H NMR δ 1.44–1.89 (m, 24 H), 3.41–3.67 (m, 16 H), 3.78–3.98 (m, 8 H), 4.64 (s, 8 H), 7.41 (s, 2 H).

1,3,5-Tris(7′-hydroxy-2′,5′-dioxa-1′-heptyl)benzene (15) (Scheme I). To a solution of **11** (2.85 g, 0.004 mol) in 50 mL of CH_3OH and 50 mL of CH_2Cl_2 was added 15 mL of concentrated HCl. The resulting mixture was stirred for 2–3 h (or overnight) at rt. Enough $NaHCO_3$ was added to neutralize the solution. The solid was filtered and washed with CH_3OH. After evaporation of the solvent, CH_3CN was added to dissolve the organic materials. The solid was filtered and washed with CH_3CN. After evaporation of the combined filtrate, the residue was purified by chromatography on silica gel using CH_3CN/C_2H_5OH 10/1 as eluent to give 1.1 g (64%) of **15** as a pale yellow oil: ^{1}H NMR (DMSO-d_6) δ 3.30–3.61 (m, 24 H), 4.49 (s, 6 H), 4.52–4.65 (b, 3 H, disappeared in D_2O), 7.21 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 138.79, 125.92, 72.63, 72.24, 70.00, 69.52, 60.52; IR 3416, 2866, 1455, 1350, 1089 cm^{-1}.

1,2,4,5-Tetrakis(7′-hydroxy-2′,5′-dioxa-1′-heptyl)benzene (16) (Scheme II). **16** was prepared as above for **15** from 8.54 g (0.0096 mol) of **12** and 40 mL of concentrated HCl in 150 mL of CH_3OH and 150 mL of CH_2Cl_2. Purification by chromatography on silica gel using CH_3CN/ethyl acetate 5/1 and then CH_3CN/C_2H_5OH 10/1 and 5/1 as eluents gave 4.70 g (89%) of **16** as colorless viscous oil: ^{1}H NMR δ 3.50–3.73 (m, 32 H), 4.64 (s, 8 H), 4.50–4.75 (b, 4 H, disappeared in D_2O), 7.39 (s, 2 H); ^{13}C NMR δ 136.43, 130.42, 73.07, 71.05, 71.00, 69.92, 62.07.

1,3,5-Tris(4′-hydroxy-2′-oxa-1′-butyl)benzene (17) (Scheme III). **17** was prepared as above for **15** from 7.0 g (0.012 mol) of **13** and 18 mL of concentrated HCl in 50 mL of CH_3OH and 50 mL of CH_2Cl_2. Purification by chromatography on silica gel using CH_3CN/ethyl acetate 10/1 as the eluent gave 2.3 g (60%) of **17** as a pale yellow oil: ^{1}H NMR δ 2.30 (b, 3 H, disappeared in D_2O), 3.55–3.65 (m, 6 H), 3.70–3.80 (m, 6 H), 4.56 (s, 6 H), 7.27 (s, 3 H); IR 3420, 2870, 1460, 1355, 1100 cm^{-1}.

1,2,4,5-Tetrakis(4′-hydroxy-2′-oxa-1′-butyl)benzene (18) (Scheme IV). **18** was prepared as above for **15** from 18 g (0.025 mol) of **14** and 15 mL of concentrated HCl in 100 mL of CH_3OH and 50 mL of CH_2Cl_2. Purification by chromatography on silica gel using CH_3CN/C_2H_5OH 2/1 and 1/1 as eluents gave 3.2 g (34%) of **18** as a white solid: mp 94–96 °C; ^{1}H NMR δ 2.35 (b, 4 H, disappeared in D_2O), 3.56–3.65 (m, 8 H), 3.68–3.78 (m, 8 H), 4.62 (s, 8 H), 7.38 (s, 2 H).

1,3,5-Tris[7′-(tosyloxy)-2′,5′-dioxa-1′-heptyl]benzene (19) (Scheme I). A solution of NaOH (2.0 g, 0.083 mol) in 15 mL of water and a solution of triol **15** (1.3 g, 0.003 mol) in 15 mL of THF were mixed. A solution of tosyl chloride (3.0 g, 0.015 mol) in 20 mL of THF was added dropwise to the above stirred mixture at 5–10 °C. The resulting mixture was stirred at rt for 2 h (or overnight) and poured into a cooled 10% HCl solution. The solution was extracted with benzene. The benzene extract was washed with water, dilute aqueous $NaHCO_3$, and then water. The benzene extract was dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel using CH_2Cl_2 and then CH_2Cl_2/ethyl acetate 5/1 as the eluents to give 2.62 g (97%) of tritosylate **19** as a colorless viscous oil: ^{1}H NMR δ 2.44 (s, 9 H), 3.53–3.76 (m, 18 H), 4.18 (t, 6 H), 4.54 (s, 6 H), 7.22 (s, 3 H), 7.32 (d, J = 8.2 Hz, 6 H), 7.78 (d, J = 8.2 Hz, 6 H); ^{13}C NMR δ 145.28, 139.10, 133.57, 130.35, 128.46, 126.75, 73.57, 71.26, 70.03, 69.79, 69.19, 22.14; IR 3008, 2867, 1597, 1451, 1355, 1306, 1244, 1177 cm^{-1}.

1,2,4,5-Tetrakis[7′-(tosyloxy)-2′,5′-dioxa-1′-heptyl]benzene (20) (Scheme II). Tetratosylate **20** was synthesized as above for **19** from 0.68 g (1.2 mmol) of tetraalcohol **16**, 1.5 g of NaOH, and 2.5 g (0.013 mol) of tosyl chloride in 15 mL of water and 35 mL of THF. Purification by chromatography on silica gel using CH_2Cl_2 as eluent gave 1.2 g (86%) of **20** as a colorless viscous oil: ^{1}H NMR δ 2.42 (s, 12 H), 3.50–3.61 (m, 16 H), 3.67 (t, J = 5.2 Hz, 8 H), 4.14 (t, J = 5.2 Hz, 8 H), 4.58 (s, 8 H), 7.29 (s, 2 H), 7.35 (d, J = 8.2 Hz, 8 H), 7.78 (d, J = 8.2 Hz, 8 H).

1,3,5-Tris[4′-(tosyloxy)-2′-oxa-1′-butyl]benzene (21) (Scheme III). Tritosylate **21** was synthesized as above for **19** from 1.91 g (0.006 mol) of triol **17**, 6.0 g (0.031 mol) of tosyl chloride, and 4.0 g of NaOH in 35 mL of water and 60 mL of THF. Purification by chromatography on silica gel using CH_2Cl_2 as eluent gave 4.1 g (84%) of **21** as a pale yellow viscous oil: ^{1}H NMR δ 2.42 (s, 9 H), 3.65 (t, J = 5.2 Hz, 6 H), 4.17 (t, J = 5.2 Hz, 6 H), 4.46 (s, 6 H), 7.25 (s, 3 H), 7.31 (d, J = 8.2 Hz, 6 H), 7.78 (d, J = 8.2 Hz, 6 H).

1,2,4,5-Tetrakis[4′-(tosyloxy)-2′-oxa-1′-butyl]benzene (22) (Scheme IV). Tetratosylate **22** was synthesized as above for **19** from 1.8 g (4.8 mmol) of tetraalcohol **18**, 6.0 g (0.031 mol) of tosyl chloride, and 4.0 g of NaOH in 30 mL of water and 60 mL of THF. Purification by chromatography on silica gel using $CHCl_3$/ethyl acetate 20/1, 10/1, and 5/1 as eluents gave 3.0 g (63%) of **22** as a white solid: mp 99–101 °C; ^{1}H NMR δ 2.42 (s, 12 H), 3.65 (t, J = 5.2 Hz, 8 H), 4.17 (t, J = 5.2 Hz, 8 H), 4.52 (s, 8 H), 7.26 (s, 2 H), 7.32 (d, J = 8.2 Hz, 8 H), 7.78 (d, J = 8.2 Hz, 8 H).

Benzene-Bridged Macrobicyclic Polyether 1 (Scheme I). To a mixture of NaH (0.8 g) in 100 mL of THF was added a solution of triol **5** (0.47 g, 2.8 mmol) in 100 mL of THF. The mixture was stirred and refluxed for 2 h. After 1.5 g of Cs_2CO_3

was added, a solution of tritosylate **19** (2.5 g, 2.8 mmol) in 200 mL of THF was added dropwise. The reaction mixture was stirred and refluxed for 4 days. The cooled mixture was filtered and the filtrate was evaporated. The residue was passed through a short alumina column using toluene/C_2H_5OH 30/1 as the eluent. Then it was purified by chromatography on silica gel using CH_3OH/30% NH_4OH 60/1 as eluent to give 0.14 g (9%) of **1** as a pale yellow viscous oil which solidified on standing: ^1H NMR δ 3.54 (s, 24 H), 4.39 (s, 12 H), 7.10 (s, 6 H); ^{13}C NMR δ 138.98, 127.42, 73.51, 71.07, 69.75; IR 2859, 1607, 1453, 1354, 1250, 1114 cm^{-1}. Anal. Calcd for $C_{30}H_{42}O_9$: C, 65.91; H, 7.74; MW 546.65. Found: C, 65.77; H, 7.70, MW 546.

Benzene-Bridged Macrotricyclic Polyether 2 (Scheme II). A mixture of 2.6 g (0.66 mol) of potassium metal in 500 mL of *tert*-butyl alcohol was refluxed until the potassium metal dissolved. Tetraalcohol **6** (2.73 g, 0.014 mol) in 300 mL of *tert*-butyl alcohol was added and the resulting mixture was refluxed for 2 h. A solution of 16.1 g (0.014 mol) of tetratosylate **20** in 300 mL of *p*-dioxane was added dropwise. The resulting mixture was refluxed for 7 days (12 g of KO-t-C_4H_9 was added after 2 days). After evaporation of the solvent, 100 mL of water and 100 mL of $CHCl_3$ were added to dissolve the solid residue. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ solution was dried ($MgSO_4$) and evaporated. The residue was passed through a short alumina column using toluene/ethanol 10/1 as the eluent and then was purified by chromatography on silica gel using CH_3OH/30% NH_4OH 70/1 as the eluent to give 0.8 g (9%) of **2** as a white solid. Monocrystals suitable for X-ray crystallography were obtained by recrystallization from $CHCl_3$: ^1H NMR δ 3.61 (s, 32 H), 4.42 (d, J = 13 Hz, 8 H), 4.67 (d, J = 13 Hz, 8 H), 7.30 (s, 4 H); ^{13}C NMR δ 136.39, 130.89, 71.21, 70.95, 69.82; MS, m/e 676 (M^+) and 677 ($M^+ + 1$, CI). An X-ray crystal structure determination proved the structure of **2**.[40]

Benzene-Bridged Macrotricyclic Polyether 2 (Scheme IV). Potassium metal (0.55 g) was dissolved in 350 mL of *tert*-butyl alcohol at 60 °C. A solution of **18** (1.1 g, 2.9 mmol) in 30 mL of anhydrous *p*-dioxane was added, and the mixture was stirred at 80–90 °C for 2 h. A solution of tetratosylate **22** (2.93 g, 2.9 mmol) in 50 mL of *p*-dioxane was added dropwise over 2 h. The resulting mixture was stirred at reflux temperature for 4 days. After 0.6 g of potassium *tert*-butoxide was added, the mixture was stirred for 2 days. The solvent was evaporated, and the residue was dissolved in water and CH_2Cl_2. After the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was dried ($MgSO_4$) and evaporated. A 2.23-g portion of the residue was purified by chromatography on alumina using toluene/ethanol 50/1 as eluent (10/1 for TLC) and then on silica gel using CH_3OH/30% NH_4OH 20/1 as the eluent (10/1 for TLC). Because of a failure of the fraction collector, only a very small amount of the product was obtained which was not enough for an NMR spectrum. However, the TLC spot was exactly the same as that of compound **2** obtained by the previous method (Scheme II).

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Supplementary Material Available: ^1H NMR spectra for **2**, **9**, **11–13**, and **15–22**; ^{13}C NMR spectra for **2**, **9**, **11**, **12**, **15**, **16**, and **19**; MS for **2** and **16**; IR spectra for **9**, **11**, **12**, **15**, **17**, and **19** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(40) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.