Synthesis of New Proton-Ionizable Dibenzocrown Ethers

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A series of structurally related dibenzo-15-crown-5, dibenzo-18-crown-6, and dibenzo-21-crown-7 compounds with oxymethylacetoxy side arms is synthesized by reaction of the corresponding crown ether alcohols with potassium hydride and bromoacetic acid. Multi-step synthetic routes to the crown ether alcohol precursors are reported.

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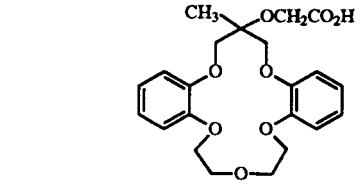

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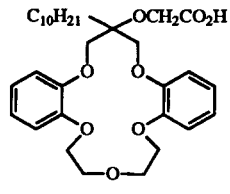

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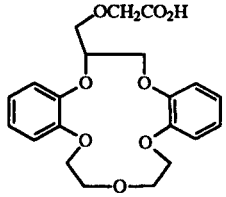

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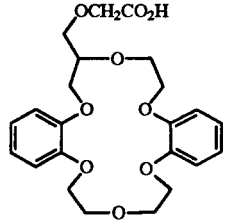

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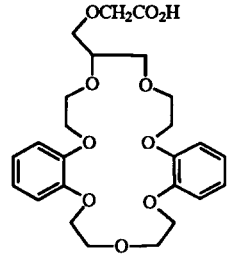

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Introduction.

The metal ion complexing behavior of synthetic macrocyclic polyether ligands has been investigated for more than three decades [1]. Several of these studies have focused on determination of the selectivity and efficiency of macrocyclic-mediated extraction of the metal ions from an aqueous source phase into an organic medium followed by transport of metal ions through the organic medium into an aqueous receiving phase [2]. The extractability of metal ions by macrocyclic polyethers may be enhanced by the introduction of proton-ionizable groups [3-5]. Metal ion extraction by such proton-ionizable crown ethers does not require concomitant transfer of the aqueous phase anion into the organic medium. This factor is of immense importance to potential applications in which hard aqueous phase anions (chloride, nitrate, and sulfate) would be involved [3].

It is also reported that the high sodium ion selectivity of *sym*-(alkyl)dibenzo-16-crown-5-oxyacetic acids **1** and **2** in solvent extraction is attributable not only to the good size-agreement between sodium ion and the cavity of dibenzo-16-crown-5, but also to preorganization of the binding site by orientation of the carboxylic acid group over the crown ether cavity [5]. This preorganization of the binding site has been probed in homogeneous solution by nmr spectroscopy [6].

We now report the synthesis of a series of dibenzo-15-crown-5, dibenzo-18-crown-6, and dibenzo-21-crown-7

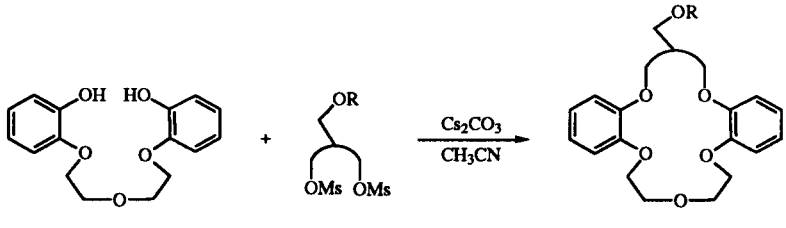


Figure 1. General Ring Closure Method.

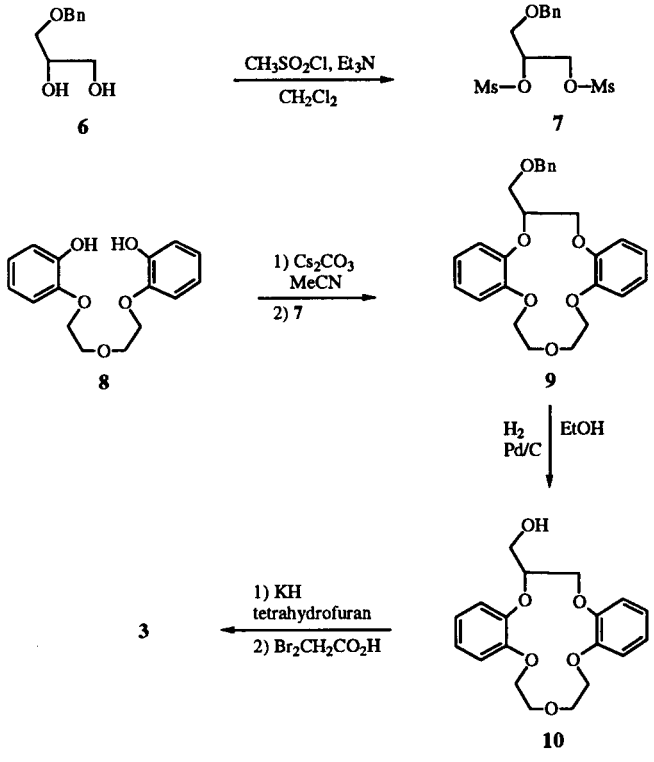
compounds with pendent methyleneoxyacetic groups, **3-5**, respectively, in which the crown ether ring size is systematically varied.

Results and Discussion.

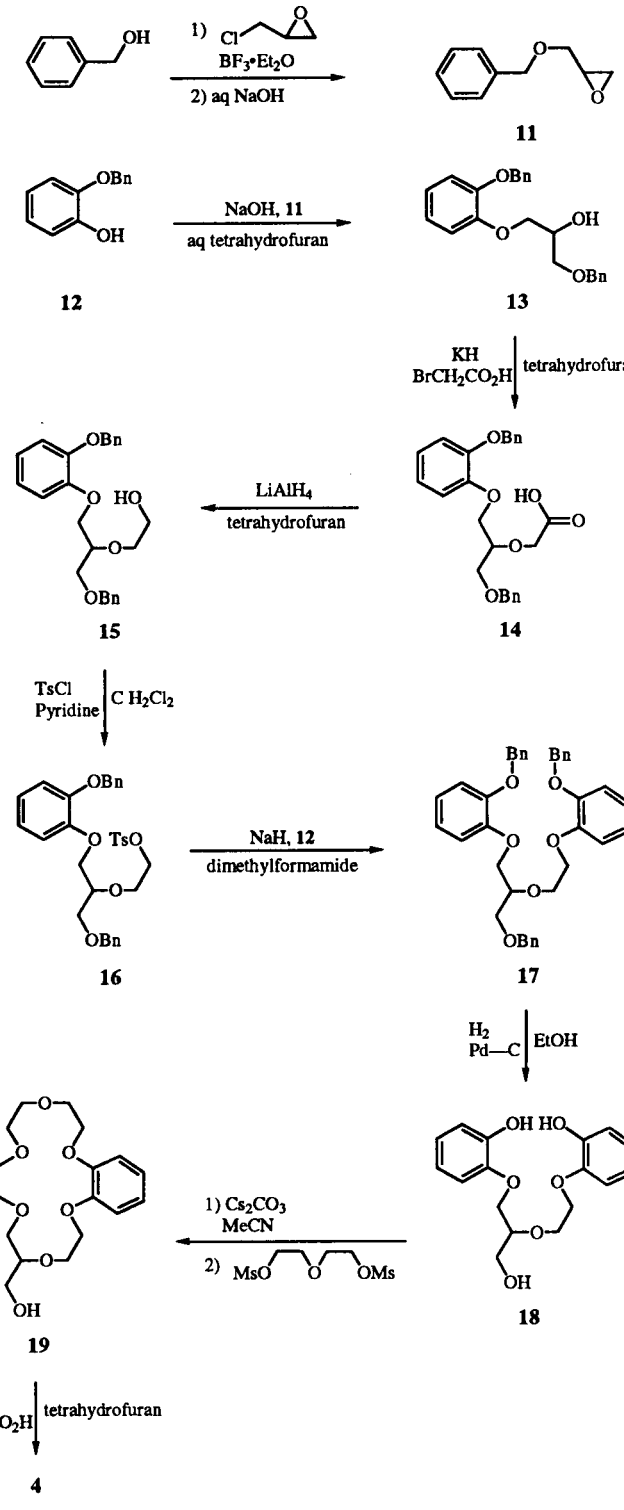
The synthetic strategy for forming the ring-closed precursors for proton-ionizable crown ethers **3** and **5** is shown in Figure 1. A bisphenol is reacted with a dimesylate containing a protected hydroxymethyl group to form a protected crown ether alcohol. Several attempts to prepare the appropriate dimesylate for construction of the dibenzo-18-crown-6 ring precursor to **4** were unsuccessful. Therefore a modified synthetic strategy was utilized in which a protected hydroxymethylated bisphenol precursor was cyclized with diethylene glycol dimesylate. For these cyclization reactions, cesium carbonate was utilized as the base. Cesium-assisted synthesis of crown ethers with aromatic subunits has been developed by Bartsch and coworkers [7,8] and found to provide superior cyclization yields to other alternative synthetic routes.

A multi-step procedure for the preparation of the dibenzo-15-crown-5 carboxylic acid **3** and the synthesis of the key intermediate **7** are summarized in Scheme 1. Using a reported procedure [9], commercially available Solketal was alkylated with benzyl chloride in the presence of potassium hydroxide, then the isopropylidene group was removed with acid to give diol **6**. Reaction of **6** with methanesulfonyl chloride in the presence of triethylamine gave dimesylate **7** in a quantitative yield. When dimesylate **7** was reacted with bisphenol **8** and cesium carbonate in acetonitrile as a solvent, the corresponding (benzyloxy)methyl-substituted dibenzo-15-crown-5 **9** was

Scheme 1
Synthetic Route for the Preparation of Dibenzo-15-crown-5 Carboxylic Acid **3**



Scheme 2
Synthetic Route for the Preparation of Dibenzo-18-crown-6 Carboxylic Acid **4**



obtained in 31% yield, which was the best yield from several attempts. It is surmised that substitution by the phenoxide ion nucleophile might be difficult because one of the mesylate groups in **7** is secondary which reduces the propensity for S_N2 reaction. Removal of the benzyl protecting group by catalytic hydrogenation of **9** gave crown ether alcohol **10** in nearly quantitative yield. Reaction of **10** with potassium hydride and bromoacetic acid in tetrahydrofuran provided crown ether carboxylic acid **3** in 97% yield.

Table 1
Variation Reaction Conditions for Alkylation of Crown Ether Alcohol **19**

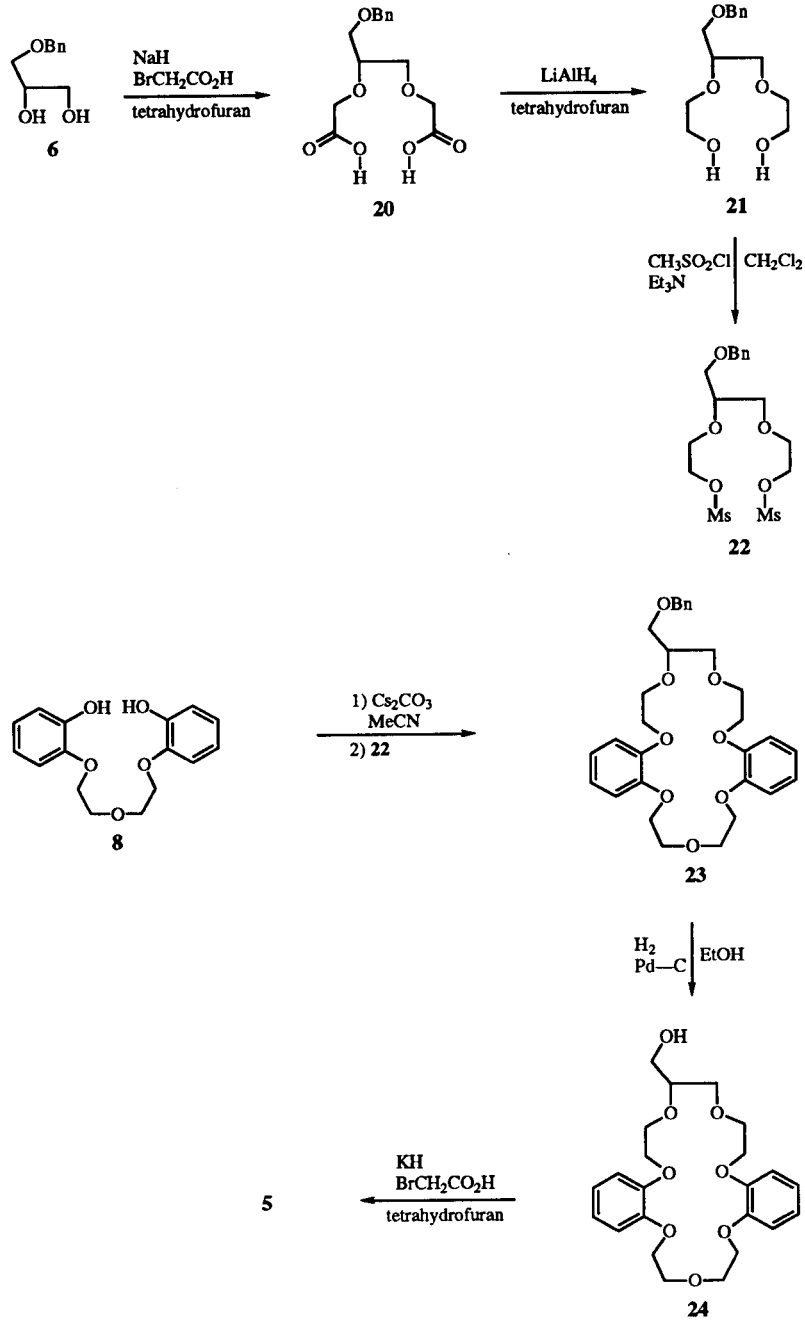
Entry	MH	Alkylating Agent	Time (hours)	Temperature	Yield of Alkylation Product (%)
1	NaH	$BrCH_2CO_2Et$	24	room	0
2	NaH	$BrCH_2CO_2Et$	10	reflux	0
3	NaH	$BrCH_2CO_2H$	24	room	0
4	NaH	$BrCH_2CO_2H$	24	reflux	5
5	KH	$BrCH_2CO_2H$	24	reflux	11

The synthesis of the dibenzo-18-crown-6 carboxylic acid **4** is outlined in Scheme 2. For preparation of intermediate **12**, catechol was reacted with benzyl chloride in the presence of sodium hydroxide in ethanol to give a monobenzyl protected catechol **12** in 57% yield [10]. To prepare epoxide **11** which would be a reactant in next step, a procedure reported by Ulbrich [12] was adapted. Reaction of benzyl alcohol with epichlorohydrin in the presence of boron trifluoride etherate gave **11** in 41% yield. To test for free epoxide, 5 drops of pyridine was added to 3 drops of reaction mixture, and the solution was shaken and heated. No color change implies that the reaction is completed. Subsequently, coupling of **12** with **11** provided **13** in an 87% yield. Alkylation of **13** with bromoacetic acid in the presence of potassium hydride in tetrahydrofuran gave a nearly quantitative yield of **14**. Reduction of **14** with lithiumaluminum hydride provided a 79% yield of **15** which was reacted with *p*-toluenesulfonyl chloride and pyridine as a base in dichloromethane to give **16** in 72% yield. For the preparation of **17**, reaction of the monoprotected catechol **12** and sodium hydride with **16** in tetrahydrofuran was attempted. No reaction occurred after stirring for 24 hours at room temperature. Stirring for 24 hours at reflux in tetrahydrofuran also gave no reaction. However, the use of dimethylformamide as a solvent and stirring for eight hours at 80° provided the desired product **17** in 58% yield. Subsequently, catalytic hydrogenolysis of **17** with Pd-C catalyst in ethanol gave bisphenol alcohol **18** in an almost quantitative yield.

The key cyclization reaction was conducted by reaction of **18** with the dimesylate of diethyleneglycol and cesium carbonate in acetonitrile to provide crown ether alcohol **19** in an 87% yield. Although both alcohol and phenolic groups are present in **18**, only the latter are deprotonated by the cesium carbonate. Alkylation of crown ether alcohol **19** with bromoacetic acid and potassium hydride in tetrahydrofuran gave the desired crown ether carboxylic acid **4** in an 11% yield. Results from a series of attempts for the coupling of crown ether alcohol **19** with bromoacetic acid under various condition are summarized in Table 1. When ethyl bromoacetate was used as the alkylating agent with sodium hydride as the base, no product was obtained at room temperature or reflux (Entries 1 and 2, respectively). No reaction was observed when bromoacetic acid was used at room temperature with sodium hydride as the base (Entry 3). A small amount of the desired product was evident by tlc when the temperature was raised to reflux. After stirring for 24 hours at reflux, workup and isolation gave the desired product **4** in only 5% yield (Entry 4). A large amount of unreacted starting material crown ether alcohol **19** was recovered. The use of potassium hydride instead of sodium hydride as the base gave **4** in a slighely enhanced yield of 11% (Entry 5). Thus the alkylation of **19** was found to be inefficient under a variety of conditions. Presumably, the alkoxide of **19** is stabilized by complexation of the metal ion within the crown ether cavity. This deactivates the crown ether alkoxide and results in an inefficient nucleophile for reaction with the alkylating agent.

The synthesis of the crown ether carboxylic acid analog with a dibenzo-21-crown-7 ring completes the series. The preparation of dimesylate **22** which is needed for the ring closure and cyclization reaction is depicted in Scheme 3. Reaction of diol **6** with sodium hydride and bromoacetic acid in tetrahydrofuran afforded dicarboxylic acid **20** in an 86% yield. Reduction of **20** with lithium aluminum hydride in tetrahydrofuran to give diol **21** in 94% yield was followed by reaction with methanesulfonyl chloride in the presence of triethylamine to provide dimesylate **22** in 92% yield. Cyclization of bisphenol **8** with dimesylate **22** in the presence of cesium carbonate gave crown ether **23** in 72% yield. Debenzylation of **23** with hydrogen and Pd-C catalyst provided crown ether alcohol **24** in 90% yield. Reaction of **24** with potassium hydride and bromoacetic acid in tetrahydrofuran afforded crown ether carboxylic acid **5** in 71% yield. In

Scheme 3
Synthetic Route for the Preparation of Dibenzo-21-crown-7 Carboxylic Acid **5**



contrast with the preparation of the dibenzo-18-crown-6 analog **4**, no difficulty was experienced with the coupling reaction. This presumably indicates that the ring size for the crown ether alkoxide formed from alcohol **24** is sufficiently large that the nucleophilicity of the alkoxide is not reduced by metal ion complexation.

Thus synthetic routes to three new dibenzocrown ethers **3-5** carboxylic acids have been established. Results of studies in alkali metal cation separations by **3-5** in solvent extraction and transport across bulk liquid membranes will be reported independently.

EXPERIMENTAL

Melting points were obtained with either a Fisher-Johns or Mel-Temp melting point apparatus. Infrared (ir) spectra were recorded with either a Nicolet MX-S FT-ir or a Perkin-Elmer

1600 Series FT-ir spectrophotometer for samples on sodium chloride plates (neat or a film deposited from solution) or as potassium bromide pellets and are reported in wave numbers (cm^{-1}). Proton nuclear magnetic resonance (^1H nmr) spectra were recorded with IBM AF-200 or AF-300 spectrometers with chemical shifts (δ) reported downfield from tetramethylsilane. Deuterated dimethyl sulfoxide was stored over activated 4 Å molecular sieves for at least 3 days before use to remove traces of water. Carbon nuclear magnetic resonance (^{13}C nmr) spectra were recorded with the same instruments with chemical shifts (δ) reported using the center line of the deuteriochloroform peak as the internal standard (77.0 ppm). Mass spectra were obtained with a Hewlett-Packard 5995 GC/MS instrument using perfluorotributylamine as the calibration standard. Elemental analyses were performed by either Galbraith Laboratories of Knoxville, Tennessee, or Desert Analytics Laboratory of Tucson, Arizona.

The 3-(*O*-benzyl)glycerol (**6**) [9], bisphenol **8** [11], and monobenzyl catechol **12** [10] were prepared by the reported methods.

General Procedure for the Preparation of Crown Ether Carboxylic Acids **3-5** from the Corresponding Alcohols.

After removal of the protecting mineral oil from potassium hydride (3.30 g, 35% dispersion in mineral oil, 0.028 mole) by washing with pentane under nitrogen, dry tetrahydrofuran (100 ml) and 5.70 mmoles of the crown ether alcohol were added with stirring at room temperature. After 30 minutes, 8.70 mmoles of bromoacetic acid in 10 ml of dry tetrahydrofuran was added dropwise at room temperature during a period of 30 minutes. The reaction mixture was stirred for an additional 3 hours at room temperature. After careful addition of water to destroy the excess of potassium hydride, the tetrahydrofuran was evaporated *in vacuo*. The resulting alkaline solution was extracted with ethyl acetate (2 x 50 ml) to remove unreacted organic starting materials. The aqueous layer was acidified *p*H 1 with 6 *N* hydrochloric acid and extracted with dichloromethane (3 x 30 ml). The combined dichloromethane layers were dried over magnesium sulfate and concentrated *in vacuo* to give a pale yellowish oil.

5-(Oxymethylacetoxy)-(2,3)(8,9)-dibenzo-15-crown-5 (**3**).

Crystallization of the oil from 50 ml of ethyl alcohol provided a 97% yield of **3** as a white solid with mp 166-167°; ir (deposit from dichloromethane solution): 3449 (O-H), 1732 (C=O), 1120 (C-O) cm^{-1}; ^1H nmr (deuterioacetone): δ 3.83-3.95 (m, 6H), 4.12-4.26 (m, 7H), 4.39-4.47 (q, 1H), 4.67 (m, 1H), 6.87-7.19 (m, 8H).

Anal. Calcd. for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.69; H, 5.96.

6-(Oxymethylacetoxy)-(2,3)(11,12)-dibenzo-18-crown-6 (**4**).

Crystallization of the oil from 50 ml of diethyl ether provided an 11% yield of **4** as a white solid with mp 128-130°; ir (deposit from dichloromethane solution): 3200-2900 (O-H), 1732 (C=O), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.50-4.35 (m, 19H), 6.89 (s, 8H).

Anal. Calcd. for $C_{23}H_{28}O_9$: C, 61.60; H, 6.29. Found: C, 61.99; H, 6.54.

8-(Oxymethylacetoxy)-(2,3)(14,15)-dibenzo-21-crown-7 (**5**).

Chromatography of the oil on silica gel with ethyl acetate as eluent gave 71% yield of **5** as a colorless oil; ir (neat): 3510 (O-H), 1735 (C=O), 1124 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.74-4.19 (m, 23H), 6.89 (s, 8H).

Anal. Calcd. for $C_{25}H_{32}O_{10}\cdot 0.6H_2O$: C, 59.66; H, 6.59. Found: C, 59.56; H, 6.43.

Preparation of the Dimesylate of 3-(*O*-Benzyl)glycerol (**7**).

To a solution of 10.0 g (54.8 mmoles) of **6**, 19.0 ml (0.137 mole) oftriethylamine, and 200 ml of dichloromethane under nitrogen was added 10.6 ml (0.137 mole) of methanesulfonyl chloride during a period of 30 minutes at 0°. After stirring for an additional 2 hours, 100 ml of water was added. The dichloromethane layer was separated and washed with 30 ml of 5% hydrochloric acid, 30 ml of 5% aqueous sodium bicarbonate, and 50 ml of brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford 18.2 g (98%) of **7** as a colorless oil; ir (neat): 1359, 1174 (S=O), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.05 (d, 6H), 3.71 (m, 2H), 3.43 (m, 2H), 4.58 (s, 2H), 4.97 (m, 1H), 4.54 (q, 4H), 7.28-7.36 (m, 5H).

Anal. Calcd. for $C_{12}H_{18}O_7S_2\cdot 0.1CH_2Cl_2$: C, 41.76; H, 5.27. Found: C, 41.70; H, 5.02.

Preparation of 5-(Benzyloxymethyl)-(2,3)(8,9)-dibenzo-15-crown-5 (**9**).

To a solution of 9.53 g (0.033 mole) of bis[2-(*o*-hydroxyphenoxy)ethyl]ether (**8**) in 150 ml of acetonitrile was added 32.06 g (0.099 mole) of cesium carbonate. The mixture was refluxed for 3 hours and cooled to room temperature. Then 11.10 g (0.033 mole) of **7** in 10 ml of acetonitrile was added dropwise at room temperature during a period of 1.5 hours followed by refluxing for 10 hours. After the unreacted cesium carbonate was filtered using Celite, the acetonitrile was removed *in vacuo* to give a yellowish oil. Chromatography of the residue on alumina with ethyl acetate-hexanes (1:7) as eluent gave 4.48 g (31%) of **9** as a colorless oil; ir (neat): 1120 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.79-3.99 (m, 6H), 4.12-4.26 (m, 5H), 4.31-4.48 (m, 1H), 4.59 (s, 2H), 4.71 (t, 1H), 6.83-7.06 (m, 6H), 7.25-7.36 (m, 7H).

Anal. Calcd. for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.37; H, 6.50.

Preparation of 5-(Hydroxymethyl)-(2,3)(8,9)-dibenzo-15-crown-5 (**10**).

A solution of 0.34 g (0.78 mmole) of **9**, 10.0 mg of 10% Pd-C, 5.0 mg of *p*-toluenesulfonic acid, and 20 ml of 95% ethyl alcohol was shaken vigorously at room temperature under 3 atmospheres of hydrogen for 24 hours. The reaction solution was decanted and filtered. After evaporation of the filtrate, chromatography of the residue on silica gel with ethyl acetate as eluent provided 0.26 g (96%) of **10** as a colorless oil; ir (neat): 3357 (O-H), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.65-4.44 (m, 12H), 4.64 (m, 1H), 6.84-7.07 (m, 8H).

Anal. Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.85; H, 6.48.

Preparation of 1-[*O*-(2-Benzyloxyphenyl)]-3-(*o*-benzyl)glycerol (**13**).

A solution of 30.00 g (0.15 mole) of **12**, 7.19 g (0.18 mole) of sodium hydroxide, 200 ml of tetrahydrofuran, and 300 ml of water was stirred for 2 hours at 50°. To the reaction mixture was added dropwise 24.7 g (0.15 mole) of **11** in 30 ml of tetrahydrofuran during a period of 2 hours followed by refluxing for 10 hours. After the tetrahydrofuran was evaporated *in vacuo*, 300

ml of diethyl ether and 200 ml of water were added. The organic layer was separated, washed with 10% hydrochloric acid (3 x 100 ml) and brine (2 x 100 ml), dried over magnesium sulfate, and concentrated *in vacuo* to give a pale yellowish oil. Chromatography of the crude product on silica gel with ethyl acetate-hexanes (1:4) provided 47.60 g (87%) of **13** as a colorless oil; ir (neat): 3455 (O-H); 1122 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.84 (d, 1H), 3.62 (d, 2H), 4.07-4.19 (m, 3H), 4.54 (s, 2H), 5.09 (s, 2H), 6.95 (s, 4H), 7.25-7.45 (m, 10H).

Anal. Calcd. for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.87; H, 6.59.

Preparation of 4-(Benzyloxymethyl)-5-[*o*-(benzyloxy)phenoxy]-3-oxapentanoic Acid (**14**).

After removal of the protecting mineral oil from potassium hydride (1.95 g, 35% dispersion in mineral oil, 17.1 mmoles) by washing with pentane under nitrogen, 2.00 g (5.7 mmoles) of **13** in dry tetrahydrofuran (100 ml) was added with stirring at room temperature. The mixture was stirred for 30 minutes and 1.23 g (8.7 mmoles) of bromoacetic acid in 10 ml of dry tetrahydrofuran was added dropwise during a period of 30 minutes. The reaction mixture was stirred for an additional 3 hours at room temperature. After careful addition of water to destroy the excess of potassium hydride, the tetrahydrofuran was evaporated *in vacuo*. The resulting alkaline solution was extracted with ethyl acetate (2 x 50 ml) to remove unreacted **13** and organic impurities. The aqueous layer was acidified *p*H 1 with 6 *N* hydrochloric acid and extracted with dichloromethane (3 x 30 ml). The combined dichloromethane layers were dried over magnesium sulfate and concentrated *in vacuo* to give 2.24 g (98%) of **14** as a pale yellowish oil; ir (neat): 3440 (O-H), 1711 (C=O), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.62 (m, 2H), 3.97-4.10 (m, 3H), 4.32 (s, 2H), 4.59 (s 2H), 5.10 (s, 2H), 6.88-6.94 (m, 4H), 7.25-7.43 (m, 10H).

Anal. Calcd. for $C_{25}H_{26}O_6$: C, 71.08; H, 6.20. Found: C, 70.84; H, 6.13.

Preparation of 4-(Benzyloxymethyl)-5-[*o*-(benzyloxy)phenoxy]-oxa-1-pentanol (**15**).

To a solution of 0.36 g (9.40 mmoles) of lithium aluminum hydride in 20 ml of dry tetrahydrofuran was added dropwise 2.00 g (4.70 mmoles) of **14** in 10 ml of dry tetrahydrofuran at room temperature under nitrogen during a period of 30 minutes. The reaction mixture was refluxed for 10 hours. After cooling to 0°, 5 ml of water was added dropwise followed by the addition of 5 ml of 10% aqueous sodium hydroxide. The white solid was filtered and the filtrate was dried over magnesium sulfate. The solution was evaporated *in vacuo* to afford a colorless oil which was chromatographed on silica gel with ethyl acetate-hexanes (1:4) as eluent to give 1.53 g (79%) of **15** as a colorless oil; ir (neat): 3454 (O-H), 1124 (C-O) cm^{-1}, ^1H nmr (deuteriochloroform): δ 2.62 (b, 1H), 3.62-3.74 (m, 6H), 3.98-4.12 (m, 3H), 4.59 (s, 2H), 5.10 (s, 2H), 6.90 (m, 4H), 7.25-7.40 (m, 10H).

Anal. Calcd. for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.72; H, 6.93.

Preparation of the Tosylate of 4-(Benzyloxymethyl)-5-[*o*-(benzyloxy)phenoxy]-oxa-1-pentanol (**16**).

A solution of 16.00 g (38.9 mmoles) of **15**, 6.15 g (77.8 mmoles) of pyridine, and 300 ml of dichloromethane was stirred for 20 minutes at -10° under nitrogen. A solution of 8.16 g (42.8 mmole) of *p*-toluenesulfonyl chloride in 10 ml of dichloromethane at -10° was added and the mixture was stirred for 3 hours at room temperature. Ethyl acetate (100 ml) and 5% hydrochloric acid (200 ml) were added. The organic layer was separated, washed with 5% hydrochloric acid (3 x 50 ml), 5% aqueous sodium bicarbonate (2 x 50 ml), and brine (2 x 100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellowish oil.

Chromatography of the residue on silica gel with ethyl acetate-hexanes (1:4) as eluent gave 15.80 g (72%) of **16** as a colorless oil; ir (neat): 1358, 1189 (S=O), 1124 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.38 (s, 3H), 3.58 (m, 2H), 3.81-4.13 (m, 7H), 4.49 (s, 2H), 5.03 (s, 2H), 6.88 (s, 4H), 7.23-7.43 (m, 12H), 7.74 (d, 2H); ^{13}C nmr (deuteriochloroform): δ 21.9, 68.4, 69.6, 69.8, 70.1, 71.0, 73.5, 78.1, 114.4, 114.7, 121.6, 127.4, 127.6, 127.8, 127.9, 128.4, 129.7, 133.1, 137.2, 138.0, 144.6, 148.9.

Anal. Calcd. for $C_{32}H_{34}O_7S$: C, 68.31; H, 6.09. Found: C, 68.33; H, 6.14.

Preparation of 1,5-bis[*o*-(Benzyloxy)phenoxy]-2-benzyloxymethyl-3-oxapentane (**17**).

After removal of the protecting mineral oil from 0.32 g (8.83 mmoles) of sodium hydride (65% dispersion in mineral oil) by washing with pentane under nitrogen, dry dimethylformamide (100 ml) and 0.35 g (1.76 mmoles) of **16** in 5 ml of dimethylformamide were added with stirring at room temperature. The mixture was stirred for 30 minutes and 0.99 g (1.76 mmoles) of **12** in 10 ml of dry tetrahydrofuran was added dropwise at room temperature during a period of 30 minutes. The reaction mixture was stirred for an additional 8 hours at 80°. After careful addition of water to destroy the excess sodium hydride, the dimethylformamide was removed by distillation. The resulting alkaline solution was extracted with ethyl acetate (2 x 50 ml) to remove unreacted **16** and organic impurities. The aqueous layer was acidified to *p*H 1 with 6 *N* hydrochloric acid and extracted with dichloromethane (3 x 30 ml). The combined dichloromethane layers were dried over magnesium sulfate, and concentrated *in vacuo* to give a pale yellowish oil. Chromatography of the residue on silica gel with ethyl acetate-hexanes (1:10) as eluent provided 0.60 g (58%) of **17** as a colorless oil; ir (neat): 3062 (O-H), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.87 (m, 2H), 4.05-4.16 (m, 7H), 4.50 (s, 2H), 5.06 (d, 4H), 6.88 (s, 8H), 7.23-7.43 (m, 15H); ^{13}C nmr (deuteriochloroform): 68.9, 69.3, 69.5, 70.1, 71.1, 71.2, 73.4, 78.0, 114.5, 114.6, 114.9, 115.3, 121.4, 121.6, 127.3, 127.5, 127.6, 127.6, 128.3, 128.4, 137.3,138.2, 148.8, 149.2.

Anal. Calcd. for $C_{38}H_{38}O_6$: C, 77.27; H, 6.48. Found: C, 77.21; H, 6.36.

Preparation of 1,5-bis[*o*-(Hydroxy)phenoxy]-2-hydroxymethyl-3-oxapentane (**18**).

A solution of 6.89 g (11.6 mmoles) of **17**, 0.1 g of 10% Pd-C, 50 mg of *p*-toluenesulfonic acid, and 50 ml of 95% of ethyl alcohol was shaken vigorously at room temperature under 3 atmospheres of hydrogen. The reaction solution was decanted and evaporated *in vacuo* to leave a residue which was chromatographed on silica gel with ethyl acetate as eluent gave 3.61 g (97%) of **18** as a colorless oil; ir (neat): 3382 (O-H) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.96 (s, 1H), 3.89-4.19 (m, 9H), 6.75-6.98 (m, 8H), 7.29 (s, 1H), 7.49 (s, 1H); ^{13}C nmr (deuteriochloroform): 61.7, 68.7, 69.5, 69.8, 79.2, 114.9, 115.2, 116.0, 120.1, 123.1, 123.3, 145.8, 145.9, 146.9, 147.0.

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.91; H, 6.21.

Preparation of 6-(Hydroxymethyl)-(2,3)(11,12)-dibenzo-18-crown-6 (**19**).

A solution of 2.59 g (8.08 mmoles) of **18** in 20 ml of acetonitrile and 7.89 g (24.2 mmoles) of cesium carbonate was refluxed for 3 hours under nitrogen. After cooling to room temperature, 2.54 g (9.7 mmoles) of ethylene glycol dimesylate in 10 ml of acetonitrile was added dropwise during a period of 1.5 hours followed by refluxing for 10 hours. The unreacted cesium carbonate was filtered using Celite and the acetonitrile was removed *in vacuo*. Chromatography of the residue on alumina with ethyl acetate-hexanes (1:7) as eluent gave 2.76 g of **19** (87%) as a white solid with mp 97-100°; ir (deposit from dichloromethane solution): 3342 (O-H), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.61-4.21 (m, 18H), 6.89 (s, 8H).

Anal. Calcd. for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.73; H, 6.74.

Preparation of 3,6-Dioxa-4-(benzyloxymethyl)-1,8-octanedicarboxylic Acid (**20**).

By the method described above for reaction of **12** with bromoacetic acid and potassium hydride, the analogous reaction of **6** with bromoacetic acid and sodium hydride was conducted to afford 22.80 g (86%) of **20** as a colorless oil; ir (neat): 1729 (C=O), 1124 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.62 (m, 2H), 3.57-3.87 (m, 5H), 4.16 (s, 2H), 4.41 (s, 2H), 4.71 (s, 2H), 7.28-7.39 (m, 5H), 9.73 (s, 2H).

Anal. Calcd. for $C_{14}H_{18}O_7$: C, 56.37; H, 6.04. Found: C, 56.42; H, 6.02.

Preparation of 3,6-Dioxa-4-(benzyloxymethyl)-1,8-octanediol (**21**).

To a solution of 4.51 g (0.12 mole) of lithium aluminum hydride in 100 ml of dry tetrahydrofuran was added dropwise 21.08 g (0.059 mole) of **20** in 30 ml of dry tetrahydrofuran during a period of 30 minutes at room temperature under nitrogen followed by refluxing for 10 hours. After cooling to 0°, 5 ml of water was added dropwise followed by adding 10 ml of 10% sodium hydroxide solution. The mixture was filtered and the filtrate was dried over magnesium sulfate and evaporated *in vacuo* to afford a colorless oil. Chromatography of the residue on silica gel with ethyl acetate as eluent gave 15.16 g (94%) of **21** as a colorless oil; ir (neat): 3405 (O-H), 1223 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): 2.61 (s, 1H), 3.42 (s, 1H), 3.52-3.80 (m, 13H), 4.55 (s, 2H), 7.33 (m, 5H).

Preparation of the Dimesylate of 3,6-dioxa-4-(benzyloxymethyl)-1,8-octanediol (**22**).

To a solution of 15.00 g (55.5 mmoles) of **21**, 19.45 ml (0.138 mole) of triethylamine, and 200 ml of dichloromethane at 0° under nitrogen was added dropwise 10.73 ml (0.138 mole) of methanesulfonyl chloride during a period of 30 minutes followed by stirring for 2 hours at room temperature. Water (50 ml) was added and the dichloromethane layer was separated, washed with 30 ml of 5% aqueous sodium bicarbonate, 30 ml of 5% hydrochloric acid, and 20 ml of brine, dried over magnesium sulfate, and concentrated *in vacuo* to give 21.77 g (92%) of **22** as a colorless oil; ir (neat): 1359, 1174 (S=O), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.01 (s, 6H), 3.53-3.75 (m, 7H), 3.89 (m, 2H), 4.35 (m, 4H), 4.53 (s, 2H), 7.26-7.36 (m, 5H).

Anal. Calcd. for $C_{16}H_{26}O_9S_2$: C, 45.06; H, 6.14. Found: C, 45.02; H, 6.09.

Preparation of 8-(Benzyloxymethyl)-(2,3)(14,15)-dibenzo-21-crown-7 (**23**).

A solution of 12.00 g (0.041 mole) of bisphenol **8** and 40.40 g (0.12 mole) of cesium carbonate in 150 ml of acetonitrile was refluxed for 3 hours under nitrogen. After cooling to room temperature, 17.65 g (0.33 mole) of **22** in 30 ml of acetonitrile was added dropwise during a period of 1.5 hours followed by refluxing for 10 hours. The unreacted cesium carbonate was filtered using Celite and the solvent was removed from the filtrate *in vacuo*. Chromatography of the residue on alumina with ethyl acetate-hexanes (1:7) as eluent gave 15.60 g (72%) of **23** as a colorless oil; ir (neat): 1120 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.53-4.17 (m, 21H), 4.52 (s, 2H), 6.85 (s, 8H), 7.28 (s, 5H).

Anal. Calcd. for $C_{30}H_{36}O_8 \cdot 0.1CH_2Cl_2$: C, 67.64; H, 6.83. C, 67.62; H, 6.71.

Preparation of 8-(Hydroxymethyl)-(2,3)(14,15)-dibenzo-21-crown-7 (**24**).

A solution of 1.30 g (2.47 mmoles) of **23**, 0.01 g of 10% Pd-C, and 0.01 g of *p*-toluenesulfonic acid in 50 ml of 95% of ethanol was shaken vigorously at room temperature under 3 atmospheres of hydrogen. The reaction solution was decanted, filtered, and evaporated *in vacuo*. Chromatography of the residue on silica gel with ethyl acetate as eluent provided a white solid which was recrystallized from 50 ml of diethyl ether to give 1.02 g (90%) of **24** as a white solid with mp 66-67°; ir (deposit from dichloromethane solution): 3448 (O-H), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.42 (s, 1H), 3.77-4.19 (m, 21H), 6.94 (s, 8H).

Anal. Calcd. for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.65; H, 6.84.

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