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A series of nine, new benzo-13-crown-4 compounds which bear one or two substituents on the three-carbon bridge has been prepared in good yields by cesium fluoride-assisted cyclization reactions of catechol with ditosylates of the appropriate glycols. The solid state structure of 9,9-dibenzyl-2,3-benzo-13-crown-4 is determined and compared with the reported structure for the unsubstituted crown ether.

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Introduction.

Small-sized, 12- to 16-membered crown ethers with four oxygen atoms in the ring are potential binders for lithium and sodium ions. In the search for selective lithium ion complexing agents, a variety of small-ring crown ethers have been studied. Most attention has been focused upon 14-crown-4 derivatives which possess good lithium ion-binding abilities [1-7]. It has been found that attachment of substituents to the crown ether ring may markedly alter the relative propensities for lithium and sodium ion complexation [3,4]. Crown ethers with 13-membered rings for which the cavities are only slightly smaller have received much less attention [2,7-9]. Of potential 13-crown-4 compounds with an incorporated benzo group, only the parent ring structure benzo-13-crown-4 (**1**) has been reported [8]. Therefore the synthesis of benzo-13-crown-4 derivatives **2-10** (Figure 1) was undertaken to provide a series of compounds with which the lithium and sodium ion-complexing behavior for this class of small ring crown ethers could be evaluated. We now report the synthetic routes to benzo-13-crown-4 compounds **2-10** and an improved preparation of benzo-13-crown-4 itself as well as the solid state structure for **6**.

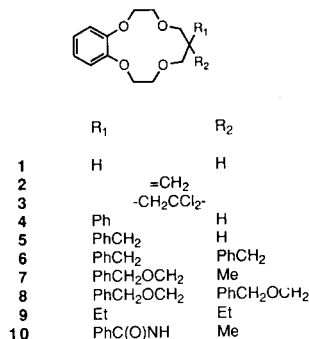


Figure 1. Benzo-13-crown-4 compounds.

Results and Discussion.

In the reported synthesis [8], benzo-13-crown-4 (**1**) was obtained in 25% yield by reaction of catechol with lithium hydroxide and 1,8-dichloro-3,7-dioxaoctane in 1-butanol. Since good yields of benzocrown ethers have been obtained from the cesium fluoride-assisted cyclization of catechol and ditosylates of oligoethylene glycols in acetonitrile [10,11], it appeared that this procedure might provide a more viable synthetic route to benzo-13-crown-4 compounds. Reaction of catechol, cesium fluoride, and 1,8-ditosyloxy-3,7-dioxaoctane (**11**) [12] in acetonitrile at 65° for two days afforded a 37% yield of benzo-13-crown-4 (**1**). In view of the appreciable yield enhancement over the reported preparative procedure, the cesium fluoride-assisted cyclization of catechol with the appropriate glycol ditosylates was selected as the synthetic route to the benzo-13-crown-4 derivatives **2, 4-10**.

The syntheses of the requisite ditosylates for cyclization with catechol to produce benzo-13-crown-4 compounds **1, 2, 4-10** are summarized in Table I. Only in the case of 1,8-ditosyloxy-3,7-dioxaoctane (**11**) was the glycol ditosylate a known compound. The 2-substituted and 2,2-disubstituted 1,3-propanediols **14** [13], **21** [4], **25** [14], **29** [15], and **37** [16] are reported compounds, but details of the preparation, yield and characterization of **21** are lacking. The 2,2-dibenzylpropane-1,3-diol (**21**) was obtained from reaction of diethyl malonate, sodium ethoxide and benzyl chloride in ethanol, followed by reduction of the intermediate diester **20** with lithium aluminum hydride in diethyl ether in an overall 61% yield. Diol **33** was a commercially available compound.

Diesters **15, 22, 30** and **34** were prepared from the corresponding 1,3-propanediols by reaction with potassium *tert*-butoxide and chloroacetic acid in *tert*-butyl alcohol followed by esterification of the intermediate diacid with

Table 1
Synthetic Routes to Ditosylates for Cyclization with Catechol to Produce Benzo-13-crown-4 Compounds 1,2,4-10

R ₁	R ₂				
H	H	—	—	—	11 [12]
	=CH ₂	—	—	12 [19]	13
Ph	H	14 [13]	15	16	17
PhCH ₂	H	—	—	18 [20]	19
PhCH ₂	PhCH ₂	21 [a]	22	23	24
PhCH ₂ OCH ₂	CH ₃	25 [14]	[b]	27	28
PhCH ₂ OCH ₂	PhCH ₂ OCH ₂	29 [15]	30	31	32
Et	Et	33 [c]	34	35	36
PhC(O)NH	CH ₃	37 [16]	[d]	39	40

[a] Prepared from diethyl dibenzylmalonate (20). [b] Diol 27 was prepared from diol 25 *via* the di-THP protected diol 26. [c] Commercially available. [d] Diol 39 was prepared from diol 37 *via* the dibenzyl-protected diol 38.

Table 2
Positional Parameters ($\times 10^4$) and Isotopic
Thermal Parameters ($\times 10^3 \text{ \AA}^2$) for Atoms of 6 with
Estimated Standard Deviations in Parentheses

Atom	x	y	z	U
O1	6301(1)	2399(1)	8407(1)	61(1) [a]
C1	6478(1)	1424(2)	8770(1)	54(1) [a]
C2	6454(1)	1885(2)	9225(1)	54(1) [a]
C3	6670(1)	940(2)	9592(1)	65(1) [a]
H3	6659	1246	9908	79
C4	6903(1)	-442(2)	9502(1)	78(1) [a]
H4	7049	-1100	9756	94
C5	6926(1)	-880(2)	9049(1)	81(1) [a]
H5	7094	-1838	8988	97
C6	6712(1)	51(2)	8685(1)	68(1) [a]
H6	6725	-262	8369	82
O2	6230(1)	3282(1)	9273(1)	62(1) [a]
C7	6140(1)	3773(2)	9731(1)	60(1) [a]
H7A	5717	3263	9843	73
H7B	6619	3614	9940	73
C8	5957(1)	5341(2)	9704(1)	62 (1) [a]
H8A	6366	5825	9569	73
H8B	5942	5699	10015	73
O3	5222(1)	5640(1)	9426(1)	60(1) [a]
C9	5290(1)	6172(2)	8968(1)	55(1) [a]
H9A	5491	7136	8992	66
H9B	5644	5570	8826	66
C10	4480(1)	6167(2)	8666(1)	47(1) [a]
C11	4276(1)	4607(2)	8539(1)	55(1) [a]
H11A	3769	4567	8350	65
H11B	4265	4056	8819	65
O4	4851(1)	4029(1)	8283(1)	60(1) [a]
C12	4872(1)	2511(2)	8275(1)	60(1) [a]
H12A	4883	2142	8587	72
H12B	4417	2147	8078	72
C13	5606(1)	2077(2)	8087(1)	66(1) [a]
H13A	5630	2584	7800	80
H13B	5589	1061	8028	80
C14	3817(1)	6711(2)	8930(1)	50(1) [a]

Table 2 (continued)

Atom	x	y	z	U
H14A	3846	6159	9213	60
H14B	3327	6514	8735	60
C15	4560(1)	7083(2)	8228(1)	53(1) [a]
H15A	5027	6773	8109	64
H15B	4619	8067	8327	64
CP1	3799(1)	8282(2)	9069(1)	47(1) [a]
CP2	4429(1)	9009(2)	9316(1)	64(1) [a]
HCP2	4917	8511	9407	77
CP3	4366(2)	10438(2)	9438(1)	76(1) [a]
HCP3	4815	10934	9599	91
CP4	3666(2)	11158(2)	9326(1)	73(1) [a]
HCP4	3623	12150	9410	88
CP5	3030(1)	10439(2)	9095	70(1) [a]
HCP5	2534	10926	9022	85
CP6	3098(1)	9028(2)	8966(1)	57(1) [a]
HCP6	2648	8547	8800	69
CH1	3890(1)	7025(2)	7828(1)	52(1) [a]
CH2	2861(2)	5990(2)	7483(1)	55(1) [a]
HCH2	4273	5286	7504	66
CH3	3262(1)	5937(2)	7110(7)	64(1) [a]
HCH3	3266	5207	6875	77
CH4	2665(1)	6922(3)	7075(1)	81(1) [a]
HCH4	2242	6883	6819	99
CH5	2680(2)	7956(3)	7410(1)	109(1) [a]
HCH5	2264	8653	7389	128
CH6	3288(2)	8019(3)	7781(1)	88(1) [a]
HCH6	3294	8770	8010	106

[a] U is the equivalent isotropic U which is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

ethanol [17] in 66, 36, 47 and 38% overall yields, respectively. Reduction of the diesters with lithium aluminum hydride [18] provided the 5-substituted and 5,5-disubstituted 3,7-dioxanonane-1,9-diols **16**, **23**, **27**, **31** and **35** in high yields (> 85%). Diols **12** [19] and **18** [20] are known compounds.

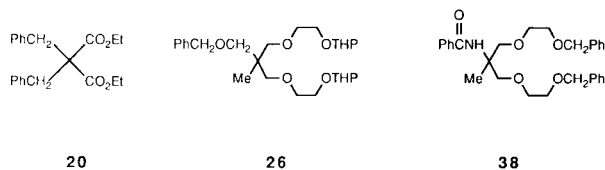
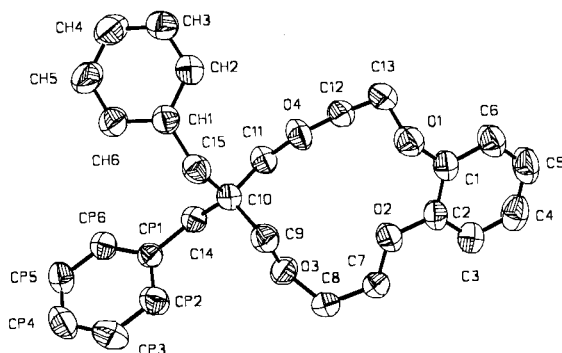


Figure 2. Precursors to Substituted Benzo-13-crown-4 Compounds.

Figure 3. Computer drawing of 9,9-dibenzyl-2,3-benzo-13-crown-4 (**6**) with the numbering system identified. Hydrogens are omitted from the drawing. Thermal ellipsoids are drawn at the 50% probability levels.

For transformation of disubstituted 1,3-propanediols **25** and **37** into elongated diols **27** and **39**, respectively, different synthetic sequences were employed. A phase transfer-catalyzed reaction [20] of **25** with THP-protected 2-chloroethanol [21] afforded the di-THP-protected compound **26** in 63% yield. Acid-catalyzed deprotection of **26** produced diol **27** in an almost quantitative yield. Treatment of diol **37** [16] with two equivalents of sodium hydride and 2-(benzyloxy)ethanol tosylate in dimethylformamide gave a 50% yield of dibenzyl compound **38** which after deprotection [cyclohexene-ethanol, palladium hydroxide] [23] produced diol **39** in 83% yield.

Ditosylates **13**, **17**, **19**, **24**, **28**, **32**, **36**, and **40** were obtained from the corresponding diols by reaction with tosyl chloride in pyridine [24] in yields ranging from 47% to 84%.

Cesium fluoride-assisted cyclizations of ditosylates **13**, **17**, **19**, **24**, **28**, **32**, **36**, and **40** with catechol in acetonitrile produced the corresponding benzo-13-crown-4 compounds in 43, 45, 55, 59, 45, 37, 57 and 44% yields, respectively. These results establish the viability of this ring closure reaction for producing a variety of substituted dibenzo-13-crown-4 compounds in good yields.

The precursor to the dichlorocyclopropyl-functionalized benzo-13-crown-4 compound **3** was 9-methylene-2,3-benzo-13-crown-4 (**2**). Phase transfer-catalyzed addition of dichlorocarbene [25] to **2** produced **3** in 98% yield.

All new compounds were fully characterized by proton

Table 3
Bond Lengths and Angles of Atoms in the Crown Ether Ring of **6**
with Estimated Standard Deviations in Parentheses

Bond			Length (Å)	Angle (deg)
1	2	3	1-2	1-2-3
C13	O1	C1	1.431(3)	115.0(2)
O1	C1	C2	1.386(2)	118.8(2)
C1	C2	O2	1.389(3)	115.8(2)
C2	O2	C7	1.368(2)	117.9(2)
O2	C7	C8	1.428(3)	108.3(2)
C7	C8	O3	1.492(3)	112.5(2)
C8	O3	C9	1.422(2)	114.0(2)
O3	C9	C10	1.433(2)	109.7(2)
C9	C10	C11	1.531(3)	107.4(2)
C10	C11	O4	1.526(3)	109.4(2)
C11	O4	C12	1.420(3)	114.1(2)
O4	C12	C13	1.412(2)	107.5(2)
C12	C13	O1	1.497(3)	112.2(2)

Table 4
Torsion Angles Involving the Atoms of the Macrocyclic Rings of
Benzo-13-crown-4 (**1**) and Its Dibenzyl Derivative **6**

Atoms	1	6	Δ
Torsion Angles (deg.)			
C6-C1-O1-C13	69	68.3(2)	1
C1-O1-C13-C12	74	79.4(2)	5
O1-C13-C12-O4	68	69.4(2)	1
C13-C12-O4-C11	-166	-168.0(1)	2
C12-O4-C11-C10	168	160.9(1)	7
O4-C11-C10-C9	-61	-60.3(2)	1
C11-C10-C9-O3	-71	-73.7(2)	3
C10-C9-O3-C8	155	168.5(1)	13
C9-O3-C8-C7	-108	-102.8(2)	5
O3-C8-C7-O2	70	64.7(2)	5
C8-C7-O2-C2	175	175.2(2)	1
C7-O2-C2-C3	3	-6.0(3)	9

magnetic resonance and infrared spectroscopy and by elemental analysis. For crown ethers **1-10** carbon magnetic resonance spectra were also obtained.

Since the attachment of substituents to the central carbon atom of the three-carbon bridge in benzo-13-crown-4 could influence the ring conformation, the solid state structure of the disubstituted derivative 9,9-dibenzyl-2,3-benzo-13-crown-4 (**6**) was determined for comparison with the reported crystal structure [26] for benzo-13-crown-4. A computer drawing showing the conformation and also the atom labels of **6** is presented in Figure 2. Because of the structural similarity and to aid in the comparison of the two structures, the atomic labels for the atoms of the crown ether ring of **6** are the same as those used in the reported structure of benzo-13-crown-4. The final atomic coordinates and isotropic thermal parameters are given in

Table 5
Crystal Data and Experimental Conditions

Formula	C ₂₇ H ₃₀ O ₄
Formula Weight	418.58
F(000)	1792
Crystal Size (nm)	0.20 x 0.40 x 0.45
μ (cm ⁻¹)	0.75
Space Group	C2/c
a (Å)	17.164(5)
b (Å)	9.303(4)
c (Å)	28.862(6)
β (deg)	98.19(2)
V(Å ³)	4562(2)
Z	8
D _x (gcm ⁻³)	1.22
sin θ/λ	0.59
Unique Observed Data	2629
Unique Unobserved data (F < 4 σ (F))	1394
R	0.046
R _w	0.043
G Term in Weights	1.4 x 10 ⁻⁴
Goodness of Fit	1.65
Largest Peaks in Difference Map (eÅ ⁻³)	0.15, -0.12

Table 2. Bond lengths and angles for atoms in the crown ring are listed in Table 3. A comparison of the torsion angles in the unsubstituted and substituted ligands (Table 4) shows that the conformation of the dibenzyl-substituted corand **6** is similar to that of the unsubstituted parent corand **1**. Thus incorporation of two bulky substituents at the 9-position does appreciably not distort the crown ether ring. The oxygen atoms of the ring are not coplanar, but none deviates more than 0.21 Å from the least-squares plane of the four oxygen atoms. Due to the rigidity of the benzene ring, O1 and O2 are directed into the cavity. In contrast, O3 and O4 are oriented above and below the plane of the ring with O3 being pointed slightly away from the cavity. The benzyl groups are directed away from the ring with a dihedral angle of 29.1° between the planes of the benzene rings.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared (ir) spectra were obtained with a Perkin-Elmer 267 spectrophotometer. Proton magnetic resonance (¹H nmr) spectra were measured with Varian EM 360A and Varian Gemini 200 MHz spectrometers. Carbon magnetic resonance (¹³C nmr) spectra were recorded on Bruker 300 MHz and Varian Gemini 200 MHz instruments. All spectra were taken in deuteriochloroform and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Elemental analysis was performed by Galbraith Laboratories in Knoxville, TN and Spang Microanalytical Laboratory of Eagle Harbor, MI.

Unless specified otherwise, reagent grade reactants and solvents were used as received from chemical suppliers. Benzene and acetonitrile were dried over molecular sieves (4-Å). Pyridine was kept over solid potassium hydroxide. Ditosylate **11** [12] and diols **12** [19], **14** [13], **18** [20], **25** [14], **29** [15], and **37** [16] were prepared according to published procedures. Diol **33** was purchased from Aldrich Chemical Company.

Preparation of Diesters **15**, **22**, **30** and **34**.

The general preparative route of Montanari and Tundo was employed [17]. Bis-alkoxides formed by treatment of the appropriate diols with potassium *tert*-butoxide in *tert*-butyl alcohol were alkylated with chloroacetic acid followed by esterification of the intermediate diacid to produce the corresponding diethyl esters which were purified by column chromatography or vacuum distillation.

Diester **15**.

This compound was obtained in 66% yield after chromatography on silica gel with petroleum ether/ethyl acetate (10/1) as eluent, colorless oil; ir (neat): 1749, 1730 (C=O), 1137 (C-O) cm⁻¹; ¹H nmr: δ 1.24 (t, 6 H), 3.23 (pentet, 1 H), 3.82 (d, 4 H), 4.04 (s, 4 H), 4.16 (q, 4 H), 7.12-7.34 (m, 5 H).

Anal. Calcd. for C₁₇H₂₄O₆: C, 62.95; H, 7.46. Found: C, 63.08; H, 7.41.

Diester **22**.

This compound was obtained in 36% yield after chromatography on silica gel with petroleum ether/ethyl acetate (5/1) as eluent, white solid with mp 34-34.5°; ir (film): 1755, 1738 (C=O), 1135 (C-O) cm⁻¹; ¹H nmr: δ 1.26 (t, 6 H), 2.84 (s, 4 H), 3.11 (s, 4 H), 4.04 (s, 4 H), 4.20 (q, 4 H), 7.10-7.30 (m, 10 H).

Anal. Calcd. for C₂₅H₃₂O₆: C, 70.07; H, 7.53. Found: C, 70.17; H, 7.58.

Diester **30**.

This compound was obtained in 47% yield after vacuum distillation, colorless oil with bp 235-238° (0.15 torr); ir (neat): 1757, 1740 (C=O), 1131 (C-O) cm⁻¹; ¹H nmr: δ 1.24 (t, 6 H), 3.58 (s, 4 H), 3.63 (s, 4 H), 4.02 (s, 4 H), 4.15 (q, 4 H), 4.46 (s, 4 H), 7.28 (s, 10 H).

Anal. Calcd. for C₂₇H₃₆O₆: C, 66.38; H, 7.43. Found: C, 66.41; H, 7.46.

Diester **34**.

This compound was obtained in 38% yield after chromatography on silica gel with petroleum ether/ethyl acetate (8/1) as eluent, colorless liquid with bp 131-133° (0.3 torr); ir (neat): 1760, 1740 (C=O), 1135 (C-O) cm⁻¹; ¹H nmr: δ 0.60-1.60 (m, 16 H), 3.36 (s, 4 H), 4.03 (s, 4 H), 4.19 (q, 4 H).

Anal. Calcd. for C₁₅H₂₈O₆: C, 59.19; H, 9.27. Found: C, 59.29; H, 9.28.

Preparation of Diols **16**, **23**, **31**, and **35**.

Reduction of the appropriate diethyl esters with lithium aluminum hydride in diethyl ether at room temperature for two hours [18] provided the corresponding diols which were purified by column chromatography on silica gel.

Diol **16**.

This compound was obtained in 87% yield after chromatography with ethyl acetate/methanol (10/1) as eluent, colorless liquid; ir (neat): 3380 (OH), 1120, 1063 (C-O) cm⁻¹; ¹H nmr: δ 2.50

(t, 2 H), 3.19 (pentet, 1 H), 3.55 (t, 4 H), 3.60-3.85 (m, 8 H), 7.15-7.35 (m, 5 H).

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.08; H, 8.30.

Diol 23.

This compound was obtained in 93% yield after chromatography with petroleum ether/ethyl acetate (1/1) as eluent, white, waxy solid with mp 100.5-101.5°; ir (deposit on a sodium chloride plate): 3380 (O-H), 1125 (C-O) cm^{-1} ; 1H nmr: δ 2.52 (br s, 2 H), 2.77 (s, 4 H), 3.06 (s, 4 H), 3.44 (t, 4 H), 3.78 (t, 4 H), 7.23 (s, 10 H).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.45; H, 8.32.

Diol 31.

This compound was obtained in 86% yield after chromatography with ethyl acetate/petroleum ether (2/1-5/1), colorless, viscous liquid; ir (neat): 3400 (O-H), 1100 (C-O) cm^{-1} ; 1H nmr: δ 2.71 (s, 2 H), 3.40-3.80 (m, 16 H), 4.48 (s, 4 H), 7.28 (s, 10 H).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 68.29; H, 7.97. Found: C, 68.07; H, 7.87.

Diol 35.

This compound was obtained in 90% yield after chromatography with ethyl acetate as eluent, colorless liquid; ir (neat): 3370 (O-H), 1120 (C-O) cm^{-1} ; 1H nmr: δ 0.55-1.55 (m, 10 H), 3.20-3.85 (m, 14 H).

Anal. Calcd. for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98. Found: C, 60.07; H, 11.07.

General Procedure for the Preparation of Ditosylates 13, 17, 19, 24, 28, 32, 36, and 40.

The ditosylates were prepared by treatment of the appropriate diols with tosyl chloride in pyridine below 0° [24] and purified by recrystallization or column chromatography on silica gel.

Ditosylate 13.

This compound was obtained in 84% yield after two recrystallizations from ethanol, white solid with mp 82-83.5°; ir (deposit on a sodium chloride plate): 1360, 1190, 1175 (S=O), 1115 (C-O) cm^{-1} ; 1H nmr: δ 2.42 (s, 6 H), 3.58 (t, 4 H), 3.90 (s, 4 H), 4.17 (t, 4 H), 5.08 (s, 2 H), 7.55 (AB q, 8 H).

Anal. Calcd. for $C_{22}H_{28}O_8S_2$: C, 54.53; H, 5.82. Found: C, 54.69; H, 5.95.

Ditosylate 17.

This compound was obtained in 52% yield after chromatography on silica gel with dichloromethane/ethanol (99/1) as eluent, colorless oil; ir (neat): 1353, 1175 (S=O), 1130, 1095 (C-O) cm^{-1} ; 1H nmr: δ 2.41 (s, 6 H), 2.95 (pentet, 1 H), 3.50-3.65 (m, 8 H), 4.08 (t, 4 H), 7.10-7.35 (m, 9 H), 7.74 (d, 4 H).

Anal. Calcd. for $C_{27}H_{32}O_8S_2$: C, 59.11; H, 5.88. Found: C, 59.04; H, 5.79.

Ditosylate 19.

This compound was obtained in 82% yield after chromatography with dichloromethane/ethanol (49/1) as eluent, colorless liquid; ir (neat): 1355, 1180 (S=O), 1130 (C-O) cm^{-1} ; 1H nmr: δ 1.80-2.20 (m, 1 H), 2.42 (s, 6 H), 2.55 (d, 2 H), 3.20-3.65 (m, 8 H), 4.15 (t, 4 H), 6.95-7.45 (m, 9 H), 7.77 (d, 4 H).

Anal. Calcd. for $C_{28}H_{34}O_8S_2$: C, 59.77; H, 6.09. Found: C, 59.60; H, 6.21.

Ditosylate 24.

This compound was obtained in 76% yield after recrystallization from ethanol, white solid with mp 98-100°; ir (deposit on a sodium chloride plate): 1357, 1175 (S=O), 1120 (C-O) cm^{-1} ; 1H nmr: δ 2.42 (s, 6 H), 2.63 (s, 4 H), 2.81 (s, 4 H), 3.50 (t, 4 H), 7.17 (s, 10 H), 7.53 (AB q, 8 H).

Anal. Calcd. for $C_{35}H_{40}O_8S_2$: C, 64.40; H, 6.18. Found: C, 64.37; H, 6.13.

Ditosylate 28.

This compound was obtained in 78% yield after chromatography on silica gel with dichloromethane/ethanol (99/1) as eluent, colorless, viscous liquid; ir (neat): 1360, 1180 (S=O), 1100 (C-O) cm^{-1} ; 1H nmr: δ 0.83 (s, 3 H), 2.42 (s, 6 H), 3.22 (s, 6 H), 3.57 (t, 4 H), 4.13 (t, 4 H), 4.48 (s, 2 H), 7.30 (s, 5 H), 7.54 (AB q, 8 H).

Anal. Calcd. for $C_{30}H_{38}O_8S_2$: C, 59.39; H, 6.31. Found: C, 59.37; H, 6.40.

Ditosylate 32.

This compound was obtained in 60% yield after chromatography on silica gel with dichloromethane/ethanol (49/1-19/1) as eluent, viscous, colorless oil; ir (neat): 1360, 1175 (S=O), 1093 (C-O) cm^{-1} ; 1H nmr: δ 2.39 (s, 6 H), 3.30-3.65 (m, 12 H), 4.08 (t, 4 H), 4.40 (s, 4 H), 7.49 (AB q, 8 H), 7.28 (s, 10 H).

Anal. Calcd. for $C_{37}H_{44}O_{10}S_2$: C, 62.34; H, 6.22. Found: C, 62.49; H, 6.28.

Ditosylate 36.

This compound was obtained in 47% yield after chromatography on silica gel with chloroform/ethanol (99/1) as eluent, colorless liquid; ir (neat): 1360, 1178 (S=O), 1128 (C-O) cm^{-1} ; 1H nmr: δ 0.50-1.40 (m, 10 H), 2.42 (s, 6 H), 3.12 (s, 4 H), 3.53 (t, 4 H), 4.11 (t, 4 H), 7.55 (AB q, 8 H).

Anal. Calcd. for $C_{25}H_{36}O_8S_2$: C, 56.80; H, 6.86. Found: C, 56.90; H, 6.85.

Ditosylate 40.

This compound was obtained in 82% yield after chromatography on silica gel with chloroform/ethanol (97/3) as eluent, viscous, pale yellow liquid; ir (neat): 3410 (N-H), 1660 (C=O), 1355, 1180, 1175 (S=O), 1130, 1095 (C-O); 1H nmr: δ 1.39 (s, 3 H), 2.39 (s, 6 H), 3.50-3.80 (m, 8 H), 4.13 (t, 4 H), 6.52 (s, 1 H), 7.20-7.50 (m, 7 H), 7.73 (d, 6 H).

Anal. Calcd. for $C_{29}H_{35}NO_8S_2$: C, 57.51; H, 5.82. Found: C, 57.45; H, 5.90.

Preparation of Diol 21.

A literature procedure [27] which describes the preparation of diethyl benzylmalonate was modified. Sodium metal (11.5 g, 0.50 gram atom) was carefully added in small pieces to absolute ethanol (250 ml). After the sodium had reacted, diethyl malonate (41.5 g, 0.26 mole) was added. Benzyl chloride (63.26 g, 0.50 mole) was then added dropwise during two hours and the mixture was refluxed overnight. The ethanol was removed *in vacuo*, water was added to the residue, and the organic layer was separated. The crude reaction product was fractionally distilled under vacuum to give diester 20 (56.2 g, 64%) as a colorless liquid with bp 151-154° (0.1 torr). The intermediate diester (1H nmr: δ 1.13 (t, 6 H), 3.25 (s, 4 H), 4.10 (q, 4 H), 7.23 (s, 10 H)] was treated with lithium aluminum hydride in diethyl ether at room temperature for two hours to give diol 21 in 95% yield, white solid with mp 76-78°; ir (deposit on a sodium chloride plate): 3380 (O-H); 1H

nmr: δ 2.85 (br s, 2 H), 3.40-3.85 (m, 8 H), 4.46 (s, 4 H), 7.29 (s, 10 H).

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.34; H, 7.98.

Preparation of Compound 26.

A literature procedure [20] was adapted. A mixture of diol **25** (15.87, 0.075 mole), THP-protected 2-chloroethanol [21] (50.0 g, 0.30 mole), and tetrabutylammonium hydrogen sulfate (2.55 g, 7.5 mmoles) was purged with argon and aqueous 50% sodium hydroxide (1.0 mole) was added dropwise. The two-phase mixture was stirred vigorously and heated at 65° for 24 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with two portions of ethyl acetate and the combined organic extracts were dried over magnesium sulfate. The solvent, unreacted THP-protected 2-chloroethanol and other volatile by-products were removed *in vacuo* (85°, 0.1 torr). The residue was dissolved in a small amount of ethyl acetate and filtered through a layer of silica gel with petroleum ether/ethyl acetate (2/1) as eluent. After the solvent was evaporated *in vacuo*, the residue was vacuum distilled to give compound **26** (22.2 g, 63%) as a colorless, viscous liquid with bp 185-187° (0.1 torr); ir (neat): 1120, 1075 and 1035 (C-O) cm^{-1} ; 1H nmr: δ 0.97 (s, 3 H), 1.30-2.10 (m, 12 H), 3.20-4.10 (m, 18 H), 4.48 (s, 2 H), 4.62 (br s, 2 H), 7.30 (s, 5 H).

Anal. Calcd. for $C_{26}H_{42}O_7$: C, 66.93; H, 9.07. Found: C, 67.14; H, 9.14.

Preparation of Diol 27.

Compound **26** (22.1 g, 0.047 mole) was dissolved in a 1:1 mixture of methanol and dichloromethane (170 ml) and concentrated hydrochloric acid (0.85 ml) was added. After stirring at room temperature for one hour, solid sodium bicarbonate (4.0 g) was added and the mixture was stirred for another two hours. The solvent was removed *in vacuo* and the crude material was chromatographed on silica gel with ethyl acetate as eluent to give diol **27** (13.9 g, 99%) as a colorless liquid with bp 171-173° (0.3 torr); ir (neat): 3400 (O-H), 1115 (C-O) cm^{-1} ; 1H nmr: δ 0.97 (s, 3 H), 2.80 (br s, 2 H), 3.25-3.90 (m, 14 H), 4.51 (s, 2 H), 7.35 (s, 5 H).

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.48; H, 9.00.

Preparation of Compound 38.

Sodium hydride (80% in mineral oil, 0.60 g, 20.0 mmoles) was added to a solution of diol **37** [16] (2.09 g, 10.0 mmoles) in dry dimethylformamide (30 ml) and the mixture was stirred under argon for one hour. A solution of 2-(benzyloxy)ethanol tosylate (6.13 g, 20.0 mmoles) was added and the mixture was stirred for three days at room temperature. The reaction was quenched by neutralizing with 6 *N* hydrochloric acid, the solvent was removed *in vacuo*, and the residue was partitioned between water and chloroform. The aqueous layer was separated and extracted with two portions of chloroform. The combined organic layers were dried over magnesium sulfate, evaporated *in vacuo*, and chromatographed on silica gel with petroleum ether/ethyl acetate (3/1-1/1) as eluent to give compound **38** (2.37 g, 50%) as colorless, viscous liquid; ir (neat): 3410 (N-H), 1660 (C=O), 1095 (C-O) cm^{-1} ; 1H nmr: δ 1.51 (s, 3 H), 3.55-3.85 (m, 12 H), 4.52 (s, 4 H), 6.74 (s, 1 H), 7.20-7.50 (m, 13 H), 7.72 (d, 2 H).

Anal. Calcd. for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.39. Found: C, 72.65; H, 7.39.

Preparation of Diol 39.

A mixture of compound **38** (2.39 g, 5.00 mmoles), 2.0 g of palladium hydroxide on carbon, ethanol (40 ml) and cyclohexene (20 ml) was refluxed for five hours. The catalyst was removed by filtration through Celite, the solvent was evaporated *in vacuo*, and the residue was chromatographed on a short silica gel column with ethyl acetate/methanol (19/1) as eluent to afford diol **39** (1.24 g, 83%) as a colorless, viscous liquid; ir (neat): 3360 (O-H + N-H), 1640 (C=O), 1120, 1070 (C-O); 1H nmr: δ 1.46 (s, 3 H), 2.69 (br s, 2 H), 3.40-3.80 (m, 12 H), 6.66 (s, 1 H), 7.30-7.50 (m, 3 H), 7.72 (d, 2 H).

Anal. Calcd. for $C_{15}H_{23}NO_5 \cdot 0.5H_2O$: C, 58.81; H, 7.90. Found: C, 58.76; H, 7.70.

General Procedure for the Synthesis of Benzo-13-crown-4 Compounds 1, 2, 4-10.

To a suspension of anhydrous cesium fluoride (1.93 g, 12.7 mmoles) in dry acetonitrile (40 ml) under argon was added catechol (1.33 g, 2.36 mmoles) and the mixture was stirred vigorously for two hours at room temperature. To this mixture a solution of the appropriate ditosylate (2.36 mmoles) in acetonitrile (17 ml) was added slowly during 20 minutes and the mixture was heated at 65° for two days. The solvent was evaporated *in vacuo* and the residue was chromatographed to produce the pure product.

Crown Ether 1.

This compound was obtained in 37% yield after chromatography on silica gel with petroleum ether/ethyl acetate (2/1) as eluent, white crystals with mp 53-55° (lit [8] mp 53°); ir (deposit on a sodium chloride plate): 1130 (C-O) cm^{-1} ; 1H nmr: δ 1.78 (q, 2 H), 3.74 (t, 8 H), 4.13 (t, 4 H), 6.95 (s, 4 H); ^{13}C nmr: δ 30.62 (CH₂); 67.36, 69.38, 71.41 (CH₂O); 117.80, 123.03, 150.73 (Ar).

Crown Ether 2.

This compound was obtained in 43% yield after chromatography on silica gel with petroleum ether/ethyl acetate (2/1) as eluent, colorless, viscous liquid; ir (neat): 1655 (C=C), 1115 (C-O) cm^{-1} ; 1H nmr: δ 3.80 (t, 4 H), 4.14 (t, 4 H), 4.24 (s, 4 H), 5.17 (s, 2 H), 6.93 (s, 4 H); ^{13}C nmr: δ 68.70, 71.54, 72.00 (CH₂O); 115.73, 117.35, 122.92, 144.24, 150.61 (C=CH₂, Ar).

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.96; H, 7.36.

Crown Ether 4.

This compound was obtained in 45% yield after chromatography on alumina with petroleum ether/ethyl acetate (3/1) as eluent, white solid with mp 85.5-87.5°; ir (deposit on a sodium chloride plate): 1120 (C-O) cm^{-1} ; 1H nmr: δ 3.05-3.25 (m, 1 H), 3.70-4.30 (m, 12 H), 6.98 (s, 4 H), 7.15-7.35 (m, 5 H); ^{13}C nmr: δ 46.38 (CH); 69.77, 71.42, 71.80 (CH₂O); 117.75, 123.06, 127.22, 128.88, 141.50, 150.76 (Ar).

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.45; H, 7.11.

Crown Ether 5.

This compound was obtained in 55% yield after chromatography on alumina with petroleum ether/ethyl acetate (4/1) as eluent, white solid with mp 51-53°; ir (neat): 1125 (C-O) cm^{-1} ; 1H nmr: δ 2.00-2.20 (m, 1 H), 2.64 (d, 2 H), 3.50-3.70 (m, 4 H), 3.72 (t, 4 H), 4.13 (t, 4 H), 6.97 (s, 4 H), 7.10-7.20 (m, 5 H); ^{13}C nmr: δ

34.95 (CH₂); 42.01 (CH); 69.53, 70.18, 71.41 (CH₂O); 118.26, 123.20, 126.37, 128.78, 129.61, 141.02, 150.89 (Ar).

Anal. Calcd. for C₂₀H₂₄O₄: C, 73.15; H, 7.37. Found: C, 72.93; H, 7.45.

Crown Ether 6.

This compound was obtained in 59% yield after chromatography on alumina with petroleum ether/ethyl acetate (1/1) as eluent, white crystals with mp 91-93°; ir (deposit on a sodium chloride plate): 1115 (C-O) cm⁻¹; ¹H nmr: δ 2.52 (s, 2 H), 2.60-3.00 (m, 4 H), 3.40 (s, 2 H), 3.50-3.85 (m, 4 H), 4.00-4.30 (m, 4 H), 6.80-7.40 (m, 14 H); ¹³C nmr: δ 36.74 (CH₂); 44.23 (C); 69.50, 71.45, 72.71 (CH₂O); 118.16, 123.11, 126.48, 128.32, 131.61, 138.49, 150.93 (Ar).

Anal. Calcd. for C₂₂H₃₀O₄·0.5H₂O: C, 75.85; H, 7.31. Found: C, 75.95; H, 7.00.

Crown Ether 7.

This compound was obtained in 45% yield after chromatography on alumina with petroleum ether/ethyl acetate (4/1) as eluent, white solid with mp 52-53°; ir (neat): 1112 (C-O) cm⁻¹; ¹H nmr: δ 0.98 (s, 3 H), 3.32 (s, 2 H), 3.47 (AB q, 4 H), 3.71 (t, 4 H), 4.12 (t, 4 H), 4.48 (s, 2 H), 6.96 (s, 4 H), 7.30 (s, 5 H); ¹³C nmr: δ 17.82 (CH₃); 41.20 (CCH₃); 69.82, 71.42, 73.01, 73.66, 74.29 (CH₂O); 118.63, 123.28, 127.80, 128.74, 139.49, 151.05 (Ar).

Anal. Calcd. for C₂₂H₂₈O₅: C, 70.95; H, 7.58. Found: C, 70.70; H, 7.66.

Crown Ether 8.

This compound was obtained in 37% yield after chromatography on alumina with petroleum ether/ethyl acetate (6/1) as eluent, white solid with mp 58.5-60°; ir (neat): 1110 (C-O) cm⁻¹; ¹H nmr: δ 3.53 (s, 4 H), 3.60 (s, 4 H), 3.70 (t, 4 H), 4.10 (t, 4 H), 4.48 (s, 4 H), 6.96 (s, 4 H), 7.27 (s, 10 H); ¹³C nmr: δ 45.90 [C(CH₂O)₄]; 69.42, 69.85, 69.93, 71.33, 73.61 (CH₂O); 118.56, 123.25, 127.79, 128.70, 139.55, 151.01 (Ar).

Anal. Calcd. for C₂₂H₃₄O₆: C, 72.78; H, 7.16. Found: C, 72.55; H, 7.23.

Crown Ether 9.

This compound was obtained in 57% yield after chromatography on alumina with petroleum ether/ethyl acetate (10/1) as eluent, white crystals with mp 37-39°; ir (deposit on a sodium chloride plate): 1135, 1110 (C-O) cm⁻¹; ¹H nmr: δ 0.80 (t, 6 H), 1.24 (q, 4 H), 3.37 (s, 4 H), 3.72 (t, 4 H), 4.13 (t, 4 H), 6.97 (s, 4 H); ¹³C nmr: δ 7.00 (CH₃); 22.02 (CH₂); 41.36 (C); 69.70, 71.53, 72.91 (CH₂O); 118.74, 123.27, 151.14 (Ar).

Anal. Calcd. for C₁₇H₂₆O₄: C, 69.36; H, 8.90. Found: C, 69.40; H, 9.09.

Crown Ether 10.

This compound was obtained in 44% yield after chromatography on silica gel with petroleum ether/ethyl acetate (1/1) as eluent, white solid with mp 75-77°; ir (film): 3410 (N-H), 1655 (C=O), 1138, 1115 (C-O) cm⁻¹; ¹H nmr: δ 1.54 (s, 3 H), 3.60-4.20 (m, 12 H), 6.85 (s, 1 H), 6.95 (s, 4 H), 7.30-7.50 (m, 3 H), 7.85-7.90 (m, 2 H); ¹³C nmr: δ 19.03 (CH₃); 57.47 (CNH); 69.64, 71.05, 72.77 (CH₂O); 117.74, 123.19, 127.39, 128.92, 131.66, 136.07, 150.43 (Ar); 167.97 (C=O).

Anal. Calcd. for C₂₁H₂₅NO₅: C, 67.91; H, 6.78. Found: C, 67.72; H, 6.71.

Preparation of Crown Ether 3.

A mixture of crown ether **2** (0.50 g, 2.00 mmoles), chloroform (0.5 ml), sodium hydroxide (0.32 g), water (0.32 g) and benzyltriethylammonium chloride (50 mg) was vigorously stirred overnight at room temperature. Additional amounts (0.5 ml) of chloroform, sodium hydroxide (0.32 g) and the ammonium salt catalyst (50 mg) were added and the reaction mixture was stirred for another eight hours. Water (10 ml) and chloroform (10 ml) were added to the reaction mixture and the organic layer was separated. After drying over magnesium sulfate, the solvent was removed *in vacuo* and the residue was chromatographed on silica gel with petroleum ether/ethyl acetate (2/1) as eluent to afford 0.65 g (98%) of **3** as a white solid with mp 71-73°; ir (deposit on a sodium chloride plate): 1138, 1117 (C-O) cm⁻¹; ¹H nmr: δ 1.45 (s, 2 H), 3.75-3.95 (m, 8 H), 4.17 (t, 4 H), 6.97 (s, 4 H); ¹³C nmr: δ 29.05 (CH₂); 34.69 (C), 64.09 (CCl₂); 69.62, 71.42, 71.59 (CH₂O); 118.05, 123.26, 150.72 (Ar).

Anal. Calcd. for C₁₅H₁₈Cl₂O₄: C, 54.07; H, 5.44. Found: C, 54.05; H, 5.40.

Crystal Growth, Crystal Data, Structure Solution, and Refinement.

Single crystals of **6** suitable for X-ray structure study were prepared by seeding a diethyl ether solution of the compound and allowing the solvent to evaporate slowly. The compound formed clear, colorless, plate-like crystals. A suitable crystal was mounted on a Nicolet R3 automated refractometer which utilized MoK α radiation ($\lambda = 0.71069^\circ$). The lattice parameters and orientation matrix were obtained using a least-square procedure involving 24 carefully centered reflections ($10.9^\circ < 2\theta < 24.6^\circ$). Crystal data and experimental procedures are summarized in Table 5. Intensity data were collected to a $\sin\theta/\lambda$ limit of 0.59 using a variable speed $\theta - 2\theta$ scanning technique.

The trial structure was obtained using direct methods. All non-hydrogen atoms were refined anisotropically. Positions for all hydrogen atoms were calculated based on known chemical geometry. These atoms were allowed to ride on their neighboring carbon atoms during the refinement. Each hydrogen was assigned an isotropic thermal parameter which was 1.2 times the value of the initial equivalent isotropic thermal parameter of its neighboring carbon and these values were not refined. The final R and R_w values were 0.046 and 0.043, respectively. Weights were based on counting statistics and were of the form $w = 1/\sigma^2(F) + GF^2$. An empirical isotropic extinction correction was applied to the data. Atomic scattering factors were obtained from Volume 4 of The International Tables for X-ray Crystallography [28]. All programs used in the solving and display of the structure are contained in the program package SHELXTL [29].

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