Synthesis of Substituted 14-Crown-4 Compounds

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Seventeen new substituted 14-crown-4 derivatives **3-10**, **35-40**, **42**, **45** and **46** are described. A series of nine compounds **2-10** with two, three or four substituents in the 6- and/or 13-positions was synthesized in good yields from the appropriate diols and ditosylates using improved cyclization conditions. The solid state structures of 6,6,13,13-tetra(benzyloxymethyl)-14-crown-4 (**8**) and lithium thiocyanate complexes of *trans*- and *cis*-6,13-bis(spiro-2,2-dichlorocyclopropyl)-14-crown-4 (**45**) and (**46**), respectively, have been determined.

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Introduction.

Lithium has applications in medicine and many branches of technology [1] and its simple and reliable determination is an important objective in analytical chemistry. Several potential lithium ion-selective ionophores for utilization in polymeric membrane electrodes have been synthesized and evaluated [2-11]. High selectivity for Li^+ over ubiquitous Na^+ is the most desired feature of the potential lithium ionophore. Several ionophores based upon the small-ring crown ether 14-crown-4 (**1**) have been found to exhibit significant preference for Li^+ over Na^+ [5,6,9,10]. In general, it has been observed that the attachment of bulky groups and/or substituents with additional metal ion coordination sites enhances lithium selectivity. In this paper, we report the synthesis of 17 new 14-crown-4 derivatives **3-10**, **35-40**, **42**, **45** and **46** which bear various substituents attached to the central carbon atom of one or both of the three-carbon linkages. New cyclization conditions are utilized which provide efficient preparation of the substituted 14-crown-4 compounds. Solid state structures of 6,6,13,13-tetra(benzyloxymethyl)-14-crown-4 (**8**) and lithium thiocyanate complexes of *trans*- and *cis*-6,13-bis(spiro-2,2-dichlorocyclopropyl)-14-crown-4 (**45**) and (**46**), respectively, have been determined.

Results and Discussion.

Substituted 14-crown-4 compounds have been synthesized by reactions of appropriate diols and ditosylates or dichlorides in the presence of lithium cations as templates for the cyclization. Different template-base-solvent systems have been employed which include lithium perchlorate-sodium hydride-dioxane [4,6], lithium bromide-lithium-*tert*-butoxide-*tert*-butyl alcohol [3,9,10] and lithium perchlorate-sodium hydroxide-dimethyl sulfoxide [5,7]. In this work, we have found that a lithium perchlorate-sodium hydride-dimethyl sulfoxide system produces substituted 14-crown-4 compounds in enhanced yields.

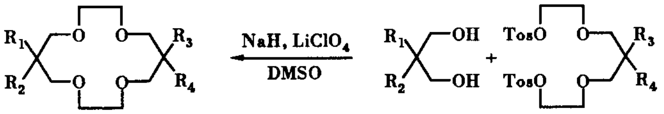
Crown ethers **1-10** were prepared by cyclization of the appropriate 1,3-propanediols and ditosylates of 3,7-dioxanonane-1,9-diols with sodium hydride and lithium perchlorate in dimethyl sulfoxide (Table 1). Except for the parent compound 14-crown-4 (**1**) [5], isolated yields were good and ranged from 31% to 67%. For this method, the yield of 6,6-dibenzyl-14-crown-4 (**2**) was increased to 55% from a reported yield of 17% [6].

Good cyclization yields were not obtained in cases where the diol component was 1,3-propanediol (**13**) itself. When this diol was used to prepare the parent 14-crown-4 (**1**), only a low, reproducible yield (5.4%) of **1** could be isolated. A comparison of yields for two different cyclization pathways to 6-(benzyloxy)-6-methyl-14-crown-4 (**6**) further emphasizes this limitation. Cyclization of 2-(benzyloxymethyl)-2-methylpropane-1,3-diol (**16**) [12] and ditosylate **22** [13] produced a 65% yield of **6**. In sharp contrast, from the attempted cyclization of 1,3-propanediol (**13**) with ditosylate **25** [14] no **6** was isolated.

The 61-67% cyclization yields of crown ethers **6-8** which

Table 1

Formation of 14-Crown-4 Compounds by Cyclization of 1,3-Propanediols with Ditosylates of 3,7-Dioxanonane-1,9-diols



Compound	Yield, %	R_1	R_2	R_3	R_4	Compound	Compound
1 [a]	5.4	H	H	H	H	**13** [c]	**22** [e]
2 [b]	55	Bzl	Bzl	H	H	**14** [d]	**22** [e]
3	31	Bzl	H	Bzl	H	**15** [g]	**23** [f]
4	51	Bzl	H	Bzl	Bzl	**15** [g]	**24** [f]
5	50	Bzl	Bzl	Bzl	Bzl	**14** [d]	**24** [f]
6	65	BzlOCH$_2$	Me	H	H	**16** [d]	**22** [e]
6	0	H	H	BzlOCH$_2$	Me	**13** [c]	**25** [f]
7	67	BzlOCH$_2$	Me	BzlOCH$_2$	Me	**16** [d]	**25** [f]
8	61	BzlOCH$_2$	BzlOCH$_2$	BzlOCH$_2$	BzlOCH$_2$	**17** [i]	**26** [f]
9	49	3-MeOBzl	H	3-MeOBzl	H	**18**	**27**
10	55	Et	Et	Et	Et	**19** [c]	**28** [f]
11	0	Ph	H	Ph	H	**20** [g]	**29** [f]
12	0	PhC(O)NH	Me	PhC(O)NH	Me	**21** [h]	**30** [f]

[a] Reference 5. [b] Reference 6. [c] Commercially available. [d] Reference 12. [e] Reference 13. [f] Reference 14. [g] Reference 15. [h] Reference 16. [i] Reference 17.

have benzyloxymethyl substituents were the highest achieved. Apparently additional binding sites provided by the benzyloxymethyl group(s) make the templating of these ring closures more efficient.

Mixtures of *cis* and *trans* isomers are anticipated for the 6,13-disubstituted 14-crown-4 compounds **3** and **9** and the 6,6,13,13-tetra-substituted compound **7**. In the case of **3**, the presence of a 7:3 mixture of the two isomers was discerned from integration of the two doublets centered at $\delta = 2.62$ and 2.65 for methylene protons of the benzyl group in the nmr spectrum.

In the course of this study, two cases were encountered in which the cyclization was unsuccessful even though substituted 1,3-propanediols were reactants. Thus the attempted preparation of 6,13-diphenyl-14-crown-4 (**11**) from diol **20** [15] and ditosylate **29** [14] gave none of the desired macrocyclic product. Similarly the attempted synthesis of 6,13-dibenzamido-6,13-dimethyl-14-crown-4 (**12**) by cyclization of diol **21** [16] and ditosylate **30** [14] was unsuccessful. Insight into this latter failure was provided by an attempted cyclization of diol **21** with the ditosylate of ethylene glycol in *N,N*-dimethylacetamide which gave heterocyclic compound **34**, the product of intramolecular cyclization of the diol reactant.

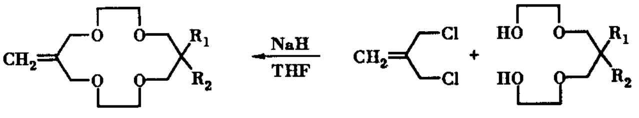
The requisite diols **14** [6,14], **15** [15], **16** [12], **17** [17], **20** [13], **21** [16] and ditosylates **22** [13], **23-26**, **28-30** [14] are known compounds. Diols **13** and **19** are commercially available. Diol **18** was obtained in 26% yield by reaction of diethyl malonate, sodium ethoxide and 3-methoxybenzyl bromide in ethanol, followed by reduction of the intermediate diester **31** with lithium aluminum hydride in diethyl ether in 79% yield. Reaction of diol **18** with potassium *tert*-butoxide and chloroacetic acid in *tert*-butyl alcohol, followed by esterification of the intermediate diacid with ethanol provided the corresponding diester **32** in 39% yield. Reduction of the diester with lithium aluminum hydride gave an 86% yield of diol **33**. Ditosylate **27** was obtained from diol **33** in 79% yield by reaction with tosyl chloride in pyridine.

The crown ether amide **40** was synthesized in six steps from 6-(benzyloxymethyl)-6-methyl-14-crown-4 (**6**). Thus, **6** was hydrogenated (10% palladium on carbon, ethanol) to afford crown ether alcohol **35** in 93% yield. Tosylation of compound **35** in pyridine gave tosylate **36** in 86% yield. This tosylate was reacted with the sodium salt of ethyl thiosalicylate in tetrahydrofuran to produce crown ether ester **37** (64%) which was hydrolyzed quantitatively to crown ether acid **38**. The acid was quantitatively converted into acid chloride **39** with thionyl chloride and the acid chloride was subsequently reacted with dimethylamine to afford crown ether amide **40** in 68% yield.

It was found that the improved cyclization conditions which were used for the preparation of crown ethers **1-10** could not be applied to the synthesis of methylenyl-substituted 14-crown-4 compounds due to vulnerability of the double bond to oxidation. Methylenyl-substituted crown ethers **41** and **42** were prepared by high dilution cyclization [18] of 3-chloro-2-(chloromethyl)-1-propene with the

Table 2

Formation of Methylenyl-Substituted 14-Crown-4 Compounds by Cyclization of 3,7-Dioxanonane-1,9-diols with 3-Chloro-2-(chloromethyl)-1-propene



Compound	Yield, %	R_1	R_2	Compound
41 [a]	37	$=CH_2$		**43** [b]
42	27	Bzl	Bzl	**44** [c]

[a] References 19 and 20. [b] Reference 19. [c] Reference 14.

appropriate diols and sodium hydride in tetrahydrofuran (Table 2). Thus, 6,13-bismethylenyl-14-crown-4 (**41**) was obtained in 37% yield. Previously **41** has been obtained from ω,ω′,ω″-tribromopivalophenone and the disodium salt of ethylene glycol in tetrahydrofuran in 9% yield [19] and more recently by cyclization of 5-methylenyl-3,7-dioxa-1,9-nonanediol with 3-chloro-2-(chloromethyl)-1-propene in the presence of sodium *tert*-butoxide and lithium perchlorate in dioxane in 30% yield [20]. The 13,13-dibenzyl-6-methylenyl-14-crown-4 (**42**) was obtained in 27% yield. Diols **43** [19] and **44** [14] which were utilized in these cyclization are known compounds.

Table 3

Positional Parameters (x10^4) and Isotropic Thermal Parameters (Å^2 x 10^3) for Atoms of the Lithium Thiocyanate Complex of **45**

Atom	x	y	z	U(eq)
Cl(1)	1203(1)	6318(1)	6609(1)	71(1) [a]
C1	425(5)	7500	6988(3)	45(2) [a]
C2	-1036(6)	7500	7095(3)	52(2) [a]
H2	-1482	6762	6941	82(14)
C3	-119(5)	7500	7800(3)	38(2) [a]
C4	-75(4)	6448(3)	8264(2)	45(1) [a]
H4A	-195	5840	7616	46(10)
H4B	-779	6452	8647	71(13)
O5	1186(2)	6351(2)	8652(1)	38(1) [a]
C6	1312(4)	5328(3)	9049(2)	49(1) [a]
H6A	582	5230	9407	46(10)
H6B	1320	4739	8678	60(12)
C7	2622(4)	5364(3)	9490(2)	48(1) [a]
H7A	3358	5380	9129	47(11)
H7B	2702	4737	9824	85(15)
O8	2604(3)	6341(2)	9949(2)	46(1) [a]
C9	3744(4)	6461(3)	10447(2)	46(1) [a]
H9A	3797	5850	10799	49(11)
H9B	4543	6494	10136	65(12)
C10	3591(5)	7500	10907(3)	42(2) [a]
C11	4108(6)	7500	11755(3)	54(2) [a]
H11	4541	8186	11921	54(11)
C12	2670(6)	7500	11612(3)	47(2) [a]
Cl(2)	1738(1)	6313(1)	11827(1)	70(1) [a]
Li	1383(9)	7500	9540(5)	45(3) [a]
N	-398(5)	7500	10061(3)	59(2) [a]
C	-1346(6)	7500	10437(3)	45(2) [a]
S	-2693(2)	7500	10984(1)	71(1) [a]

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

Phase transfer-catalyzed addition of dichlorocarbene [21] to 6,13-bismethylenyl-14-crown-4 (**41**) produced a mixture of the 6,13-bis(spiro-2,2-dichlorocyclopropyl)-14-crown-4 compounds **45** and **46** in 25% yield. The two isomers were separated by column chromatography. The ^{1}H nmr spectrum of the faster eluting isomer exhibited a well-defined AB quartet for the eight isolated CH_2O protons at δ 3.78 and a sharp singlet for the eight centrally located CH_2O protons at δ 3.67. The slower moving isomer showed only an ill-defined AB quartet for the isolated CH_2O protons incorporated into a wider multiplet (δ 3.56-3.85) for the remaining CH_2O protons. The ^{13}C nmr spectra of the two isomers were almost identical. To establish the stereostructure of the faster and slower eluting isomers, complexes of each compound with lithium thiocyanate were formed and their solid state structures determined.

The conformations and atomic labels for the lithium thiocyanate complexes of the faster and slower eluted isomers are shown in Figures 2 and 3, respectively. In both structures the asymmetric unit consists of one-half of the molecule. For both complexes the oxygen atoms are directed into the cavity and the lithium ion has a square pyramidal coordination geometry and is complexed by the four oxygen atoms of the ligand and by the thiocyanate anion. The complex shown in Figure 3 contains a twofold rotational axis which clearly establishes that the slower eluting compound is the *cis* isomer **46**. Therefore the faster eluting compound is the corresponding *trans* isomer **45**. The final atomic coordinates and isotropic thermal parameters for the lithium thiocyanate complexes of the *trans* isomer **45** and the *cis* isomer **46** are given in Tables 3

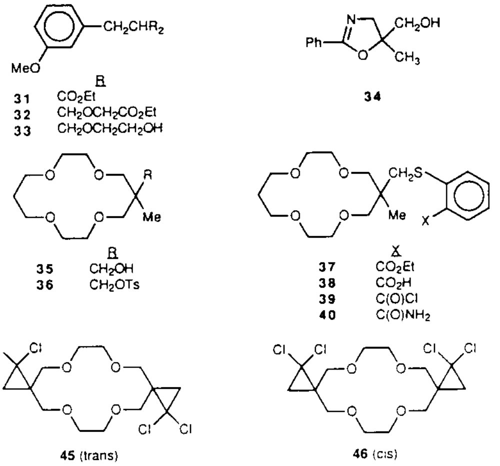


Figure 1. Synthetic intermediates and substituted 14-crown-4 products.

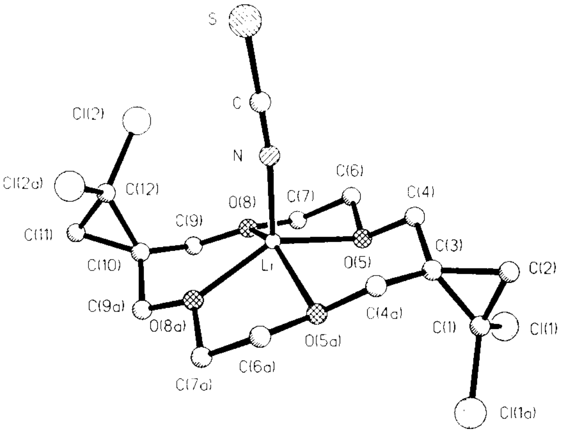


Figure 2. Computer drawing of the structure for the lithium thiocyanate complex of *trans*-6,13-bis(spiro-2,2-dichlorocyclopropyl)-14-crown-4 (**45**).

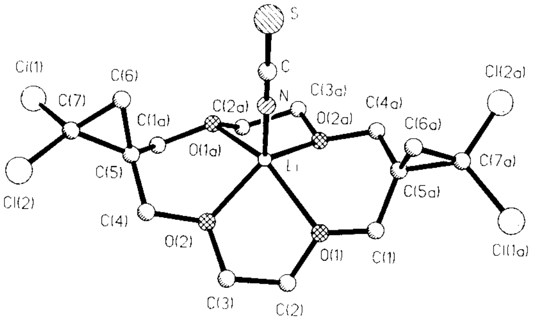


Figure 3. Computer drawing of the structure for the lithium thiocyanate complex of *cis*-6,13-bis(spiro-2,2-dichlorocyclopropyl)-14-crown-4 (**46**).

and 4, respectively. Distances from the lithium ion to the crown ether oxygens and from the lithium ion to the nitrogen of the thiocyanate anion are recorded in Table 5.

Table 4

Atomic Parameters (x10^4) and Isotropic Thermal Parameters (Å^{2}x10^3) for Atoms of the Lithium Thiocyanate Complex of **46**

Atom	x	y	z	U(eq)
Cl(1)	3153(1)	730(1)	8182(1)	64(1) [a]
Cl(2)	2781(1)	-152(1)	10285(1)	77(1) [a]
C1	-1535(2)	1933(4)	7506(3)	53(1) [a]
H1A	-1453	2905	7211	52(10)
H1B	-1947	1822	7981	79(13)
O1	-867(1)	1497(3)	8268(2)	49(1) [a]
C2	-568(2)	2585(4)	9081(3)	53(1) [a]
H2A	-816	2688	9697	78(13)
H2B	-510	3517	8590	67(11)
C3	158(2)	2060(4)	9748(3)	56(2) [a]
H3A	405	2841	10213	65(11)
H3B	74	1202	10220	72(12)
O2	570(1)	1649(3)	8923(2)	54(1) [a]
C4	1296(2)	1235(4)	9423(3)	55(1) [a]
H4A	1563	2118	9892	56(10)
H4B	1335	388	9949	82(14)
C5	1685(2)	901(4)	8479(3)	48(1) [a]
C6	1817(2)	-647(4)	8189(3)	60(2) [a]
H6A	1822	-841	7322	77(12)
H6B	1608	-1379	8659	60(11)
C7	2431(2)	229(4)	8824(3)	56(1) [a]
Li	0	774(9)	7500	53(3) [a]
N	0	-1306(6)	7500	73(2) [a]
C	0	-2513(7)	7500	59(2) [a]
S	0	-4218(2)	7500	155(2) [a]

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

The 14-crown-4 ring conformation in the crystal structure of the lithium thiocyanate complex of *trans* isomer **45** resembles those for lithium thiocyanate complexes of 6,13-dimethylenyl-14-crown-4 [20] and *cis-syn-cis*-dicyclohexano-14-crown-4 [8]. The central carbon of one three-carbon bridge is oriented above the plane of the four ethereal oxygens while that for the other three-carbon bridge is located below the plane. For all three complexes the distances

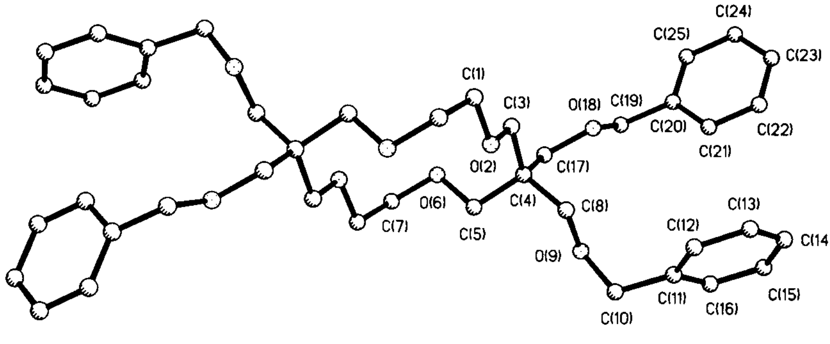


Figure 4. Computer drawing of the structure for 6,6,13,13-tetra(benzylmethyl)-14-crown-4 (**8**).

Table 5

Lithium-oxygen and Lithium-nitrogen Distances for the Lithium Thiocyanate Complexes of Crown Ethers **45** and **46**

1	2	1-2 Distance (Å)
	Complex with trans Isomer **45**	
Li	O5	2.079(7)
Li	O8	1.996(7)
Li	N	1.990(10)
	Complex with cis Isomer **46**	
Li	O1	2.148(4)
Li	O2	1.986(4)
Li	N	1.960(10)

from the lithium ion to the crown ether oxygens and to the thiocyanate nitrogen are optimal for square pyrimidal complexation of lithium [22]. On the other hand, the twofold rotational axis in **46** requires that both three-carbon bridges are on the same side of the plane of the four ethereal oxygens. This difference does not change the geometry of the lithium ion coordination as indicated by the Li-O distances in Table 5 and as shown in Figures 2 and 3.

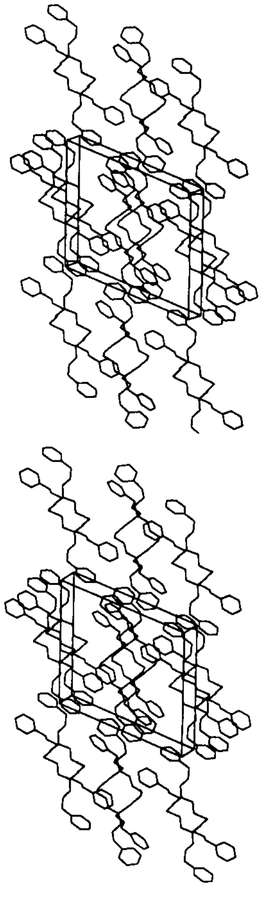


Figure 5. Computer drawing of the unit cell packing of **8**.

Table 6

Atomic Parameters ($x10^4$) and Thermal Parameters for Atoms of **8**

Atom	x	y	z	B(eq)
C1	4591(2)	5275(3)	-1700(1)	3.3(1)
O2	5458(1)	4800(2)	-1038(1)	3.21(7)
C3	5567(2)	3023(3)	-976(2)	3.0(1)
C4	6469(2)	2568(3)	-227(1)	2.61(9)
C5	6437(2)	3204(3)	643(2)	3.0(1)
O6	5665(1)	2433(2)	799(1)	3.13(7)
C7	5595(2)	2890(3)	1613(1)	3.3(1)
C8	7301(2)	3381(3)	-392(2)	3.5(1)
O9	8163(1)	2861(2)	260(1)	4.36(8)
C10	8961(2)	3773(4)	222(2)	4.9(1)
C11	9271(2)	3252(3)	-513(2)	3.9(1)
C12	8884(2)	3935(4)	-1347(2)	4.9(1)
C13	9152(2)	3393(5)	-2027(2)	5.7(1)
C14	9823(2)	2176(5)	-1885(3)	6.1(1)
C15	10237(2)	1498(4)	-1060(3)	5.8(2)
C16	9954(2)	2031(4)	-386(3)	4.8(1)
C17	6579(2)	660(3)	-186(2)	3.2(1)
O18	6685(1)	73(2)	-967(1)	3.65(7)
C19	7089(2)	-1544(3)	-875(2)	3.7(1)
C20	7267(2)	-1965(3)	-1965(1)	3.0(1)
C21	7880(2)	-983(3)	-1945(2)	3.9(1)
C22	8030(2)	-1338(4)	-2715(2)	4.7(1)
C23	7574(2)	-2666(4)	-3232(2)	4.5(1)
C24	6964(2)	-3641(3)	-2989(2)	3.9(1)
C25	6816(2)	-3291(3)	-2220(2)	3.4(1)
H1	4625	5071	-2260	3.7
H2	4091	4628	-1638	3.0
H3	5042	2541	-873	4.2
H4	5594	2595	-1508	3.2
H5	7011	2924	1105	3.3
H6	6360	4385	620	3.2
H7	5096	2269	1685	3.8
H8	6173	2607	2065	4.1
H9	7294	3061	-954	3.6
H10	7247	4568	-372	4.3
H11	8799	4933	149	3.4
H12	9473	3621	757	6.8
H13	8424	4794	-1453	5.7
H14	8870	3866	-2593	6.1
H15	10010	1801	-2349	6.0
H16	10714	668	-956	6.4
H17	10238	1544	177	5.4
H18	7130	367	305	3.9
H19	6045	158	-119	3.0
H20	7665	-1568	-387	5.3
H21	6665	-2345	-784	4.8
H22	8196	-65	-1592	5.4
H23	8448	-662	-2889	5.5
H24	7684	-2908	-3758	5.2
H25	6649	-4556	-3346	4.6
H26	6395	-3971	-2051	4.5

For the parent 14-crown-4 molecule, the X-ray crystal structure, determined at $-150°$, has been published [23]. More recently the solid state structures for the *cis-anti-cis* and *cis-syn-cis* isomers of dicyclohexano-14-crown-4 [8] and for *syn*-6,13-bis(hydroxymethyl)-14-crown-4 [20] have been reported. Since well-formed crystals of 6,6,13,13-

Table 7

U Values for Non-hydrogen atoms **8**

Atom	U11	U22	U33	U12	U13	U23
C1	0.048(2)	0.048(2)	0.030(1)	0.007(1)	0.016(1)	-0.001(1)
O2	0.044(1)	0.032(1)	0.045(1)	0.0029(8)	0.0140(8)	0.0003(8)
C3	0.047(1)	0.033(1)	0.036(1)	0.001(1)	0.019(1)	-0.003(1)
C4	0.041(1)	0.030(1)	0.033(1)	0.001(1)	0.019(1)	-0.001(1)
C5	0.044(1)	0.034(1)	0.041(1)	-0.002(1)	0.020(1)	-0.004(1)
O6	0.048(1)	0.038(1)	0.042(1)	-0.0035(8)	0.0268(8)	-0.0058(8)
C7	0.052(2)	0.047(2)	0.035(1)	0.011(1)	0.023(1)	0.004(1)
C8	0.049(2)	0.040(2)	0.049(2)	0.005(1)	0.025(1)	0.008(1)
O9	0.038(1)	0.069(1)	0.060(1)	-0.002(1)	0.0190(9)	0.011(1)
C10	0.042(2)	0.072(2)	0.073(2)	-0.011(2)	0.021(1)	-0.003(2)
C11	0.034(1)	0.047(2)	0.070(2)	-0.006(1)	0.021(1)	0.003(1)
C12	0.048(2)	0.062(2)	0.084(2)	0.003(2)	0.031(2)	0.017(2)
C13	0.060(2)	0.087(3)	0.072(2)	-0.008(2)	0.030(2)	0.018(2)
C14	0.066(2)	0.086(3)	0.094(3)	-0.019(2)	0.048(2)	-0.015(2)
C15	0.054(2)	0.058(2)	0.116(3)	0.002(2)	0.041(2)	-0.004(2)
C16	0.045(2)	0.054(2)	0.079(2)	-0.003(2)	0.017(2)	0.011(2)
C17	0.057(2)	0.035(1)	0.038(1)	0.005(1)	0.027(1)	0.000(1)
O18	0.072(1)	0.036(1)	0.036(1)	0.018(1)	0.0262(9)	0.0021(8)
C19	0.057(2)	0.040(2)	0.044(2)	0.015(1)	0.019(1)	0.002(1)
C20	0.042(1)	0.036(1)	0.036(1)	0.014(1)	0.013(1)	0.001(1)
C21	0.045(2)	0.050(2)	0.052(2)	-0.004(1)	0.015(1)	-0.013(1)
C22	0.056(2)	0.064(2)	0.073(2)	-0.007(2)	0.040(2)	-0.006(2)
C23	0.071(2)	0.059(2)	0.052(2)	0.004(2)	0.036(2)	-0.012(2)
C24	0.058(2)	0.043(2)	0.048(2)	0.01(1)	0.019(1)	-0.013(1)
C25	0.047(2)	0.033(1)	0.052(2)	0.007(1)	0.020(1)	0.002(1)

tetra(benzyloxymethyl)-14-crown-4 (**8**) could be obtained, the X-ray crystal structure was determined to provide additional information about the conformation of substituted 14-crown-4 compounds.

The conformation and atomic labels for **8** and crystal packing within the unit cell are shown in Figures 4 and 5. Once again the crystallographic asymmetric unit consists of only one-half of the molecule. Therefore only this unique part of the molecule is numbered (Figure 4) and listed in the molecular structure parameters (Tables 6, 7 and 8). Molecule **8** contains a crystallographic inversion center which is located at the center of the crown ether ring (equidistant from the crown ether ring oxygens). In the following discussion and in Table 8, the symmetry-related atoms of this asymmetric unit are designated by the corresponding primed numbers. The final atomic coordinates and isotropic thermal parameters for **8** are listed in Tables 6 and 7. Selected intramolecular distances, bond angles and torsion angles are presented in Table 8.

Table 8

Selected Intramolecular Distances, Bond Angles and Torsion Angles for **8**

Interatomic Distances

Bond	Length (Å) [a]	Bond	Length (Å) [a]
C1-O2	1.424(3)	C4-C5	1.528(3)
C1-C7'	1.509(3)	C4-C17	1.531(3)
O2-C3	1.428(3)	C5-O6	1.425(3)
C3-C4	1.520(3)	O6-C7	1.421(3)
C4-C8	1.528(3)		

Bond Angles

Bond	Angle (deg) [a]	Bond	Angle (deg) [a]
O2-C1-C7'	109.9(2)	C8-C4-C17	110.3(2)
C1-O2-C3	111.8(2)	C5-C4-C17	109.2(2)
O2-C3-C4	110.1(2)	O6-C5-C4	108.9(2)
C3-C4-C8	108.6(2)	C7-O6-C5	113.4(2)
C3-C4-C5	110.6(2)	O6-C7-C1	114.7(2)
C3-C4-C17	109.0(2)	O9-C8-C4	109.9(2)
C8-C4-C5	109.1(2)	O18-C17-C4	109.5(2)

Torsion Angles

Atoms	Angle (deg) [a,b]	Atoms	Angle (deg) [a,b]
C1-O2-C3-C4	-176.5(2)	C4-C5-O6-C7	177.6(2)
C1-C7-O6-C5	89.2(2)	C4-C17-O18-C19	160.7(2)
O2-C1-C7-O6	-42.7(1)	C5-C4-C8-O9	64.3(2)
O2-C3-C4-C8	-58.7(2)	C5-C4-C17-O18	-175.4(2)
O2-C3-C4-C5	61.0(2)	O6-C5-C4-C8	-179.5(3)
O2-C3-C4-C17	-178.9(2)	O6-C5-C4-C17	-59.0(2)
C3-O2-C1-C7'	167.6(2)	C8-C4-C17-O18	-55.6(3)
C3-C4-C8-O9	-175.1(2)	O9-C8-C4-C17	-55.6(3)
C3-C4-C5-O6	61.0(2)	C17-O18-C19-C20	-173.8(2)
C3-C4-C17-O18	63.6(2)	O18-C19-C20-C25	-117.0(2)
C4-C8-O9-C10	-171.1(2)	O18-C19-C20-C21	61.5(3)

[a] Estimated standard deviation in the least significant figure are given in parentheses. [b] The sign is positive if when looking from the second atom listed to the third atom a clockwise motion of the first atom listed would superimpose it on the fourth atom.

The macrocyclic ring of **8** has a "chair-like" shape in which the phenyl rings are directed away from the center of the crown ether cavity. The four oxygen atoms of the crown ether ring form a perfect plane such that the two halves of the molecule (which are related by a center of symmetry) are extended above and below this general molecular plane. Atom C4, the quarternary carbon of the first half of **8**, is positioned 0.50 Å above this plane, while the symmetry-related atom (C4') is position 0.50 Å below this plane which creates a "chair" conformation for the crown ether ring (Figure 4). In contrast to this structure for the 6,6,13,13-tetrasubstituted 14-crown-4 derivative **8**, the four crown ether oxygens in 14-crown-4 [23], *cis-anti-cis*-dicyclohexano-14-crown-4 [8], *cis-syn-cis*-dicyclohexano-14-crown-4 [8] and *syn*-6,13-bis(hydroxymethyl)-14-crown-4 [20] do not lie in a perfect plane.

The crown ether ring in **8** is elongated along the C4-C4' molecular axis such that the C4-C4' distance of 6.2 Å is significantly longer than the C1-C7 distance of 5.4 Å. Although the crown ether oxygens are close together (O2-O6, 3.5 Å; O2-O6', 2.9 Å), the four oxygens do not point in the same direction. The two oxygens on one side of the C4-C4'

Table 9

Crystal Data and Experimental Parameters

Compound	**45**•LiNCS	**46**•LiNCS	**8**
Formula	$C_{14}H_{20}O_4Cl_4$•LiNCS	$C_{14}H_{20}O_4Cl_4$•LiNCS	$C_{42}H_{52}O_8$
Formula Weight	459.18	459.18	648.87
F(000)	944	944	736
Crystal Size, mm	0.32 x 0.35 x 0.42	0.25 x 0.30 x 0.35	0.8 x 0.7 x 0.2
μ	0.68 mm^{-1}	0.69 mm^{-1}	0.78 cm^{-1}
Space Group	Pnma	C2/c	$P2_1/c$
a(Å)	9.980(5)	18.735(11)	15.183(4)
b(Å)	12.244(7)	9.424(5)	7.984(2)
c(Å)	17.116(7)	12.020(4)	16.358(4)
β(deg)	90	102.66(3)	110.94(2)
V, (Å^3)	2091(2)	2070(1)	1852(1)
Z	4	4	2
ρ(g/cm^3)	1.46	1.47	1.23
2σ Range (deg)	4-50	4-50	4-55
Scan Speed Range, (deg/min)	3.91-29.30	4.0-58.60	
Unique Observed Data	1291	1251	2172
Unobserved Data	643 $F<4\sigma(F)$	573 $F<4\sigma(F)$	2389 $I<3\sigma(I)$
R	0.0486	0.0453	0.043
Rw	0.0618	0.0519	0.053
Goodness of Fit	1.357	1.863	1.53
Largest Peaks in Difference Maps (eÅ^{-3})	0.41, -0.26	0.060, -0.47	0.20, -0.165

axis are pointing "down", while the other two are pointing "up" relative to the plane of the crown ether oxygens. Such an arrangement minimizes the electrostatic repulsion between the partial negative charges on the oxygens. The same arrangement of etheral oxygens has been found in the crystal structures of dibenzo-12-crown-4 [24], *cis-anti-cis*-dicyclohexano-12-crown-4 [25] and *cis-anti-cis*-dicyclohexano-24-crown-4 [8].

The size of the macrocyclic cavity can be estimated from the diagonal distance of oxygen atoms positioned across the crown ether ring. The 02-02′ and 06-06′ diagonal distances are 4.2 and 4.9 Å, respectively. Subtracting the radii for the two oxygen atoms (1.4 Å) gives an adjusted cavity diameter [26] of 1.4-2.1 Å. In principle a cavity of this size should readily accommodate a lithium cation (calculated effective diameters for four-coordinate and six-coordinate lithium cations are 1.18 and 1.52 Å, respectively [27]). However, the conformational arrangement with two oxygens pointing "up" and two "down" would not favor direct coordination of a lithium cation without a pronounced conformational change.

The side chains attached to carbons C4 and C4′ of the 14-crown-4 framework extend away from the macrocyclic ring approximately along the C4-C4′ axis. The phenyl rings are nealy planar with an average least squares deviation of 0.004 Å and form an interplanar dihedral angle of 84° between their least squares planes (Figures 4 and 5). The Van de Waals surfaces for the phenyl rings of the (benzyloxy)methyl groups attached to a common crown ether ring carbon atom are in close contact (C21 and C22 of one phenyl ring are positioned only 3.8 Å above the least squares plane of the adjacent phenyl ring). Such a close and nearly perpendicular arrangement of the phenyl rings has been recognized recently as an "edge-to-face" interaction which may be a significant stabilizing factor for both intramolecular and intermolecular aromatic groups in molecular systems [28,29]. The "edge-to-face" interaction appears to extend throughout the unit cell of **8** (Figure 5) and contributes to its packing forces. Pairs of adjacent molecules of **8** in the crystal are close enough to form an extend alternating chain of "edge-to-face-to-edge-to-face" type of interactions. Furthermore, it appears that each set of such pairs is connected to the neighboring pair *via* parallel "face-to-face' interactions, so that a chain of alternating "edge-to-face" and "face-to-face" interactions extends throughout the crystal.

All new compounds were fully characterized by nmr and ir spectroscopy and by elemental analysis.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were obtained with Perkin-Elmer 267 and Nicolet MX-S spectrophotometers and are recorded in reciprocal centimeters. Proton magnetic resonance (^{1}H nmr) spectra were recorded with a Varian Gemini 200 MHz spectrometer. Carbon magnetic resonance (^{13}C nmr) spectra were obtained with Bruker 300 MHz and Varian 200 MHz nmr spectrometers. All spectra were taken in deuteriochloroform and chemical shifts are reported in parts million (δ) downfield from tetramethylsilane. Mass spectra were taken on a 5995B Hewlett Packard spectrometer. Elemental analysis was performed by Galbraith Laboratories of 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. Tetrahydrofuran was distilled before use from sodium benzophenone ketyl. Benzene and dimethyl sulfoxide were dried over molecular sieves (4A). Pyridine was stored over solid potassium hydroxide. Diols **14** [6,14], **15** [15], **16** [12], **17** [17], **20** [15], **21** [16], **43** [19], **44** [14] and ditosylates **22** [11], **23-26**, **28-30** [14] were prepared according to literature procedures. Diols **13** and **19** are commercially available.

General Procedure for Preparation of 14-Crown-4 Compounds **1-10**.

Sodium hydride (80% in mineral oil, 4.10 g, 139 mmoles), followed by anhydrous lithium perchlorate (1.82 g, 17.1 mmoles) (**CAUTION! Although no problems were encountered, lithium perchlorate is a strong oxidizing agent and its combination with dimethyl sulfoxide is potentially dangerous.**) were added to a solution of an appropriate 1,3-propanediol (13.0 mmoles) in dry dimethyl sulfoxide (855 ml). The mixture was stirred under argon for one hour at room temperature, then a solution of an appropriate ditosylate (13.0 mmoles) in dimethyl sulfoxide (170 ml) was added over a 30-minute period and the resulting mixture was heated to 55°. After stirring for three days at this temperature, the mixture was filtered and the solvent was removed from the filtrate *in vacuo* to give a residue which was partitioned between water (200 ml) and dichloromethane (50 ml). The aqueous layer was separated and extracted two more times with dichloromethane and the combined organic layers were dried over magnesium sulfate and evaporated *in vacuo* to give a crude product which was purified by column chromatography or recrystallization.

14-Crown-4 (**1**) [5].

This compound was obtained in 5.4% yield after chromatography on silica gel with ethyl acetate as eluent; ^{13}C nmr: δ 30.57 (CH_2), 67.06, 70.95 (CH_2O).

6,6-Dibenzyl-14-crown-4 (**2**).

This compound was obtained in 55% yield after chromatography on silica gel with petroleum ether/ethyl acetate (2/1) as eluent, followed by chromatography on alumina with petroleum ether/ethyl acetate (20/1) as eluent, white crystals with mp 100-102° (lit 102-103° [6]); ir (deposit on a sodium chloride plate): 1128, 1111 (C-O) cm^{-1}; ^{13}C nmr: δ 30.49, 37.38, 43.91, (CH_2,C), 66.63, 70.35, 70.82, 72.53 (CH_2O), 126.47, 128.33, 131.54, 138.62 (Ar).

6,13-Dibenzyl-14-crown-4 (**3**).

This compound was obtained as a mixture of two isomers in 31% yield after chromatography on silica gel with petroleum ether then petroleum ether/ethyl acetate (2/1) as eluents; white crystals with mp 106-111°; ir (deposit on a sodium chloride plate): 1132, 1106 (C-O) cm^{-1}; ^{1}H nmr: δ 1.97-2.16 (m, 2H), 2.62, 2.64 (dd, 4H), 3.41-3.65 (m, 16H), 7.14-7.33 (m, 10H); ^{13}C nmr: δ 34.69 (CH_2), 41.82 (CH), 69.42, 69.49, 70.24, 70.35 (CH_2O), 125.35, 128.22, 129.08, 140.49.

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.47.

6,6,13-Tribenzyl-14-crown-4 (**4**).

This compound was obtained in 51% yield after chromatography on alumina with petroleum ether/ethyl acetate (20/1) as eluent as a heavy, colorless oil; ir (neat): 1145-1100 (C-O) cm^{-1}; ^{1}H nmr: δ 2.04 (m, 1H), 2.50-2.68 (m, 6H), 3.23-3.69 (m, 16H), 7.10-7.35 (m, 15H); ^{13}C nmr: δ 35.01, 37.25, 37.36, 41.81, 43.87 (CH_2,CH), 69.47, 70.06, 70.75, 72.38 (CH_2O), 126.38, 126.46, 128.33, 128.79, 129.62, 131.54, 138.57, 138.63, 141.01 (Ar).

Anal. Calcd. for $C_{31}H_{38}O_4$: C, 78.45; H, 8.07. Found: C, 78.55; H, 8.04.

6,6,13,13-Tetrabenzyl-14-crown-4 (**5**).

This compound was obtained in 50% yield after washing with ethyl acetate and recrystallization from dichloromethane; white crystals with mp 195-197°; ir (nujol): 1120 (C-O) cm^{-1}; ^{1}H nmr (deuteriodichloromethane): δ 2.51 (s, 8H), 3.24 (s, 8H), 3.56 (s, 8H), 7.20-7.32 (m, 20); ^{13}C nmr (deuteriodichloromethane): δ 37.69 (CH_2), 43.92 (C), 70.26, 72.23 (CH_2O), 126.27, 128.13, 131.36, 138.50 (Ar).

Anal. Calcd. for $C_{38}H_{44}O_4$: C, 80.82; H, 7.85. Found: C, 80.76; H, 7.92.

6-(Benzyloxymethyl)-6-methyl-14-crown-4 (**6**).

This compound was obtained in 65% yield after chromatography on silica gel with petroleum ether/ethyl acetate (10/1) as eluent; a viscous, pale-yellow liquid; ir (neat): 1130-1090 (C-O) cm^{-1}; ^{1}H nmr: δ 0.95 (s, 3H), 1.74 (pentet, 1H), 3.30 (s, 2H), 3.39 (q, 4H), 3.53-3.67 (m, 12H), 4.47 (s, 2H), 7.29 (s, 5H); ^{13}C nmr: δ 17.86 (CH_3), 30.51 (CH_2), 40.93 (C), 66.80, 70.69, 71.10, 73.05, 73.64, 74.27 (CH_2O), 127.77, 128.73, 139.53 (Ar).

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.35; H, 8.85.

6,13-Bis(benzyloxymethyl)-6,13-dimethyl-14-crown-4 (**7**).

This compound was obtained as a mixture of two isomers in 67% yield after chromatography on silica gel with ethyl acetate/petroleum ether (6/1) as eluent; a viscous, colorless oil which solidified during storage (mp 55-62°); ir (neat): 1130-1090 (C-O) cm^{-1}; ^{1}H nmr: δ 0.95 (s, 6H), 3.30-3.45 (m, 12H), 3.57 (s, 8H), 4.50 (s, 4H), 7.29 (s, 10H); ^{13}C nmr: δ 17.73 (CH_3), 40.58 (C), 70.27, 72.36, 73.25, 73.95 (CH_2O), 127.24, 127.28, 128.22, 138.94 (Ar).

Anal. Calcd. for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 70.95; H, 8.60.

6,6,13,13-Tetra(benzyloxymethyl)-14-crown-4 (**8**).

This compound was obtained in 61% yield after chromatography on alumina with petroleum ether/ethyl acetate (10/1) as eluent, a white solid with mp 114-116°; ir (nujol): 1140, 1095, 1073 (C-O) cm^{-1}; ^{1}H nmr: δ 3.50 (s, 8H), 3.52 (s, 8H), 3.54 (s, 8H), 4.50 (s, 8H), 7.29 (s, 20H); ^{13}C nmr: δ 45.57 (CH), 69.56, 69.60, 70.56, 73.62 (CH_2O), 127.80, 128.67, 128.74, 139.59 (Ar).

Anal. Calcd. for $C_{42}H_{52}O_8$: C, 73.66; H, 7.65. Found: C, 73.49; H, 7.73.

6,13-Bis(3-methoxybenzyl)-14-crown-4 (**9**).

This compound was obtained as a mixtue of two isomers in 49% yield after chromatography on silica gel with petroleum ether/ethyl acetate (2/1) as eluent as a pale-yellow oil; ir (neat): 1143 (C-O) cm^{-1}; ^{1}H nmr: δ 2.06 (m, 2H), 2.56-2.62 (m, 4H), 3.40-3.70 (m, 16H), 3.77 (s, 6H), 6.70-6.80 (m, 6H), 7.10-7.22 (m, 2H); ^{13}C nmr: δ 35.04, 41.75, 41.81, 55.40, 69.82, 69.89, 70.63, 70.74, 111.66, 115.27, 122.02, 129.69, 142.69, 160.17.

Anal. Calcd. for $C_{26}H_{36}O_6$: C, 70.25; H, 8.17. Found: C, 70.18; C, 8.18.

6,6,13,13-Tetraethyl-14-crown-4 (**10**).

This compound was obtained in 55% yield after chromatography on alumina with petroleum ether then petroleum ether/ethyl acetate (50/1) as eluent, a white solid with mp 53-55°; ir (deposit on a sodium chloride plate): 1130 (C-O) cm^{-1}; ^{1}H nmr: δ 0.75 (t, 12H), 1.19 (q, 8H), 3.26 (s, 8H), 3.54 (s, 8H); ^{13}C nmr: δ 7.05 (CH_3), 22.16 (CH_2), 40.95 (CH), 70.80, 72.66 (CH_2O).

Anal. Calcd. for $C_{18}H_{36}O_4$: C, 68.31; H, 11.46. Found: C, 68.40; H, 11.55.

Diethyl (3-Methoxybenzyl)malonate (**31**).

Sodium metal (2.29 g, 0.10 gram atom) was added to absolute ethanol (50 ml) and after the metal had reacted, diethyl malonate (16.6 g, 104 mmoles) was added dropwise. A white slurry formed and benzyl bromide (16.0 g, 100 mmoles) was added slowly. The mixture was stirred overnight at room temperature and then refluxed for eight hours. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane and water. The aqueous layer was separated and extracted two more times with dichloromethane. The organic layers were combined and the solvent was evaporated *in vacuo* to give an orange liquid. The crude reaction product was filtered through a layer of silica gel with dichloromethane and dichloromethane/methanol (100/1) as eluents. The solvent was evaporated *in vacuo* and the residue was vacuum distilled. A fraction with bp 130-140° (0.15 torr) was additionally purified on a silica gel column using an eluent gradient of petroleum ether/ethyl acetate (4/1) to ethyl acetate to afford diester **31** (7.50 g, 26%) as a viscous, colorless oil; ir (neat): 1730 (C=O) cm^{-1}; ^{1}H nmr: δ 1.18 (t, 6H), 3.16 (d, 2H), 3.61 (t, 1H), 3.75 (2, 3H), 4.13 (1, 4H), 6.74 (t, 3H), 7.16 (t, 1H).

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.14.

2-(3-Methoxybenzyl)-1,3-propanediol (**18**).

A solution of diester **31** (6.80 g, 24.2 mmoles) in diethyl ether (17 ml) was added dropwise to a suspension of lithium aluminum hydride (1.29 g, 33.9 mmoles) in diethyl ether (95 ml). The mixture was stirred at room temperature for two hours then treated with diethyl ether saturated with water (27.3 ml), water (1.45 ml), aqueous 15% sodium hydroxide (1.45 ml) and water (5.8 ml) again. The inorganic salts were filtered, washed with diethyl ether and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with dichloromethane/methanol (97/3→90/10) as eluent to produce diol **18** (3.76 g, 79%) as a white solid with mp 81-83°; ir (deposit on a sodium chloride plate): 3320 (O-H), 1038 (C-O) cm^{-1}; ^{1}H nmr: δ 2.05 (m, 1H), 2.27 (br s, 2H), 2.58 (d, 2H), 3.58-3.84 (m+s, 7H), 6.70-6.80 (m, 3H), 7.14-7.23 (m, 1H).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.33; H, 8.22. Found; C, 67.12; H, 8.30.

Diethyl 3,7-Dioxa-5-(3-methoxybenzyl)-1,9-nonanedicarboxylate (**32**).

Potassium *tert*-butoxide (7.26 g, 64.5 mmoles) was added to a solution of diol **18** (2.54 g, 12.9 mmoles) in *tert*-butyl alcohol (52 ml). The mixture was stirred under argon for one hour at room temperature, brought to reflux and a solution of chloroacetic acid (3.05 g, 32.25 mmoles) in *tert*-butyl alcohol (10 ml) was added dropwise. After refluxing for 15 hours, the solvent was removed *in vacuo*, the residue was acidified with 6*N* hydrochloric acid and extracted with ethyl acetate. The extract was dried over magnesium sulfate, the solvent was removed *in vacuo* and the crude diacid was dissolved in a mixture of benzene and ethanol containing a catalytic among of *p*-toluenesulfonic acid. The mixture was refluxed for six hours with the vapors circulating through a thimble containing anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was dissolved in diethyl ether and washed with aqueous 5% sodium bicarbonate. The ether layer was dried over sodium sulfate and the solvent was evaporated *in vacuo*. The crude product was purified on a silica gel column with petroleum ether/ethyl acetate (5/1→3/1) as eluent to afford diester **32** (1.87 g, 39%) as a pale-yellow liquid; ir (neat): 1750, 1730 (C=O), 1140 (C-O) cm^{-1}: ^{1}H nmr: δ 1.24 (t, 6H), 2.18 (m, 1H), 2.70 (d, 2H), 3.51 (d, 4H), 3.76 (s, 3H), 4.03 (s, 4H), 4.17 (q, 4H), 6.74 (t, 3H), 7.16 (t, 1H).

Anal. Calcd. for $C_{19}H_{28}O_7$: C, 61.94; H, 7.68. Found: C, 62.12; H, 7.71.

3,7-Dioxa-5-(3-methoxybenzyl)-1,9-nonanediol (**33**).

Diester **32** was reduced with lithium aluminum hydride in diethyl ether in a manner similar to that utilized for the reduction of diester **31**. The crude product was purified by column chromatography on silica gel with dichloromethane/methanol (95/5) as eluent to give diol **33** in 86% yield as a colorless liquid; ir (neat): 3410 (O-H), 1125, 1060 (C-O) cm^{-1}; ^{1}H nmr: δ 2.18 (m, 1H), 2.48 (br s, 2H), 2.62 (d, 2H), 3.44-3.54 (m, 8H), 3.69 (br s, 4H), 3.78 (s, 3H), 6.68-6.77 (m, 3H), 7.18 (t, 1H).

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.30; H, 8.61.

Ditosylate **27**.

Diol **33** (1.14 g, 4.01 mmoles) in pyridine was treated with tosyl chloride (1.91 g, 10.0 mmoles) in the manner described for the preparation of tosylate **36** (*vide infra*). Purification by column chromatography on silica gel with dichloromethane/ethanol (100/1) as eluent afforded ditosylate **27** (1.88 g, 79%) as a colorless, viscous oil; ir (neat): 1355, 1188, 1176 (S=O) cm^{-1}; ^{1}H nmr: δ 1.96 (m, 1H), 2.40 (s, 6H), 2.49 (d, 2H), 3.26 (d, 4H), 3.53 (t, 4H), 3.77 (s, 3H), 4.11 (t, 4H), 6.65-6.75 (m, 3H), 7.10-7.21 (m, 1H), 7.55 (AB q, 8H).

Anal. Calcd. for $C_{29}H_{36}O_9S_2$: C, 58.77; H, 6.12. Found: C, 58.99; H, 6.32.

Attempted Cyclization of Diol **21** with the Ditosylate of Ethylene Glycol.

Under argon, sodium hydride (80% in mineral oil, 0.24 g, 8.12 mmoles) was added to a solution of diol **21** (0.85 g, 4.06 mmoles) in *N,N*-dimethylacetamide (82 ml). After stirring at room temperature for one hour, ethylene glycol ditosylate (1.80 g, 4.06 mmole) was added and the mixture was stirred at room temperature for 5 days. Methanol was added to quench the reaction, the solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and water acidified with 6*N* hydrochloric acid. The organic layer was dried over magnesium sulfate, the solvent was removed *in vacuo* and the residue was chromatographed on alumina with chloroform/methanol (19/1) as eluent to afford 0.18 g of compound **34** as a white solid with mp 100.5-102.5°; ir (nujol): 3160 (O-H), 1640 (C=N), 1085 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform + deuterium oxide): δ 1.27 (s, 3H), 3.58 (AB q, 2H), 7.23-7.47 (m, 3H), 7.79 (d, 2H); ^{13}C nmr 23.91 (CH_3), 68.32 (CH_2O), 72.29 (C), 75.00 (CH_2O), 127.83, 128.70, 128.79, 131.87 (Ar), 164.84 (C=N); MS 191.20 (M$^+$).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 68.88; H, 6.97.

6-(Hydroxymethyl)-6-methyl-14-crown-4 (**35**).

Crown ether **6** (1.95 g, 5.76 mmoles) in ethanol (20 ml) containing 200 mg of a 10% palladium on carbon was hydrogenated under 50 psi of hydrogen for 48 hours. The catalyst was filtered, the solvent was removed *in vacuo* and the crude product was chromatographed on alumina with petroleum ether/ethyl acetate (3/1) to afford crown ether **35** (1.33 g, 93%) as a colorless oil; ir (neat): 3410 (O-H), 1120 (C-O) cm^{-1}; ^1H nmr: δ 0.75 (s, 3H), 1.75 (pentet, 2H), 2.95 (br s, 1H), 3.42-3.67 (m, 18H); ^{13}C nmr: δ 17.81 (CH_3), 30.33 (C), 40.52 (CH_2), 66.92, 70.51, 71.12, 75.11 (CH_2O).

Anal. Calcd. for $C_{12}H_{24}O_5$: C, 58.04; H, 9.74. Found: C, 57.93; H, 9.79.

6-(Tosyloxymethyl)-6-methyl-14-crown-4 (**36**).

A solution of tosyl chloride (1.03 g, 5.39 mmoles) in pyridine (8 ml) was added dropwise to a solution of crown ether alcohol **35** (1.07 g, 4.31 mmoles) in pyridine (10 ml) at −10°. After the addition was completed, the mixture was kept at 4° overnight then acidified with cold 6*N* hydrochloric acid and partitioned between cold water and dichloromethane. The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give the crude product. Column chromatography on silica gel with dichloromethane/ethanol (97/3) as eluent gave tosylate **36** (1.49 g, 86%) as white crystals with mp 67-69°; ir (deposit on a sodium chloride plate): 1354, 1188, 1173 (S=O), 1129 (C-O) cm^{-1}; ^1H nmr: δ 0.88 (s, 3H), 1.70 (pentet, 2H), 2.42 (s, 3H), 3.29 (s, 4H), 3.42-3.62 (m, 12H), 3.84 (s, 2H), 7.53 (AB q, 4H); ^{13}C nmr: δ 17.10, 21.81 (CH_3), 30.40 (CH_2), 40.39 (C), 66.79, 70.57, 71.03, 71.80, 73.83 (CH_2O), 128.48, 130.24, 133.49, 145.13 (Ar).

Anal. Calcd. for $C_{19}H_{30}O_7S$: C, 56.70; H, 7.51. Found: C, 56.65; H, 7.55.

Crown Ether **37**.

A solution of ethyl thiosalicylate (0.62 g, 3.42 mmoles) in tetrahydrofuran (15 ml) was added dropwise to a suspension of sodium hydride (80% in mineral oil, 0.13 g, 4.33 mmoles) in tetrahydrofuran (10 ml). The mixture was stirred under argon for a half hour, a solution of tosylate **36** (1.52 g, 3.78 mmoles) in tetrahydrofuran (10 ml) was added, and the mixture was refluxed for three days. Methanol (5 ml) was added to quench the reaction, the solvent was evaporated *in vacuo*, and the residue was chromatographed on alumina with petroleum ether/ethyl acetate (1/1) to afford ester **37** (0.91 g, 64%) as a colorless liquid; ir (neat): 1715 (C=O), 1137, 1120 (C-O); ^1H nmr: δ 1.03 (s, 3H), 1.36 (t, 3H), 1.73 (pentet, 2H), 2.90 (s, 2H), 3.37-3.66 (m, 16H), 4.35 (1, 2H), 7.03-7.15 (m, 1H), 7.32-7.43 (m, 2H), 7.88 (d, 1H); ^{13}C nmr: δ 14.49, 19.37 (CH_3), 30.44, 38.48, 40.19 (C, CH_2, CH_2S), 61.34, 66.75, 70.55, 70.98, 74.08 (CH_2O), 124.20, 126.85, 129.07, 131.37, 132.50, 142.61 (Ar), 167.29 (C=O).

Anal. Calcd. for $C_{21}H_{32}O_6S$: C, 61.14; H, 7.82. Found: C, 61.06; H, 7.76.

Crown Ether **38**.

A solution of ester **37** (0.90 g, 2.18 mmoles) in a mixture of ethanol (20 ml) and aqueous 20% sodium hydroxide (20 ml) was refluxed overnight. The solvent was removed *in vacuo* and the residue was acidified with 6*N* hydrochloric acid. The aqueous mixture was extracted with chloroform (3 x 10 ml). The combined extracts were dried over magnesium sulfate, and evaporated *in vacuo* to give **38** (0.84 g, 100%) as a white, wax-like solid with mp 128-130°; ir (deposit on a sodium chloride plate); 3600-2400 (COOH), 1712, 1688 (C=O), 1134 (C-O) cm^{-1}; ^1H nmr: δ 1.05 (s, 3H), 1.76 (pentet, 2H), 2.93 (s, 2H), 3.38-3.75 (n, 18H), 7.08-7.22 (m, 1H), 7.43 (d, 2H), 8.05 (d, 1H); ^{13}C nmr: δ 19.49 (CH_3), 30.36, 38.85, 40.23 (CH_2, C, CH_2S), 66.84, 70.58, 70.99, 74.13 (CH_2O), 124.53, 127.31, 127.82, 132.68, 133.34, 143.27 (Ar), 171.35 (C=O).

Anal. Calcd. for $C_{19}H_{28}O_6S$: C, 59.36; H, 7.34. Found: C, 59.25; H, 7.41.

Crown Ether **39**.

A solution of **38** (0.87 g, 2.26 mmoles) in benzene (1 ml) containing thionyl chloride (0.40 g, 3.39 mmoles) was refluxed for 5 hours. The solvent was evaporated and a small amount of fresh benzene was added to the residue and removed *in vacuo* to afford acid chloride **39** (0.90 g, 100%) as a pale yellow solid with mp 100-102°: ir (deposit on a sodium chloride plate): 1755, 1715 (C=O), 1130 (C-O) cm^{-1}; ^1H nmr: δ 1.03 (s, 3H), 1.75 (pentet, 2H), 2.93 (s, 2H), 3.39-3.67 (m, 16H), 7.18 (d, 1H), 7.45 (t, 2H), 8.22 (d, 1H); ^{13}C nmr: δ 19.43 (CH_3), 30.41, 38.55, 40.19 (C, CH_2, CH_2S), 66.79, 70.58, 71.02 (CH_2O), 124.50, 126.80, 131.03, 134.52, 135.43, 145.25 (Ar), 166.79 (C=O).

Anal. Calcd. for $C_{19}H_{27}ClO_5S$: C, 56.64; H, 6.75. Found: C, 56.39; H, 6.90.

Crown Ether **40**.

A solution of acid chloride **39** (0.80 g, 1.99 mmole) in benzene (10 ml) was added dropwise at 0-5° to 25 ml of benzene saturated with dimethylamine and the mixture was kept stoppered overnight. The solvent was dissolved *in vacuo* and the residue was chromatographed on silica gel with ethyl acetate as eluent to give amide **40** (0.56 g, 68%) as a colorless, viscous oil: ir (neat): 1642 (C=O); 1135 (C-O) cm^{-1}; ^1H nmr: δ 0.94 (s, 3H), 1.73 (pentet, 2H), 2.80 (s, 3H), 2.94 (s, 2H), 3.10 (s, 3H), 3.38 (q, 4H), 3.47-3.66 (m, 12H), 7.10-7.32 (m, 2H), 7.43 (d, 1H); ^{13}C nmr: δ 19.17 (CH_3), 30.46, 34.86, 38.56, 40.53, 40.70 (CH_3, C, CH_2, CH_2S), 66.79, 70.59, 71.00, 73.83 (CH_2O), 126.74, 127.00, 129.55, 130.76, 134.91, 139.19 (Ar), 170.77 (C=O).

Anal. Calcd. for $C_{21}H_{33}NO_5S$: C, 61.29; H, 8.08. Found: C, 61.28; H, 7.82.

General Procedure for Preparation of Crown Ethers **41** and **42**.

A solution (55 ml) of an appropriate diol (27.0 mmoles) in dry tetrahydrofuran and a solution (55 ml) of 3-chloro-2-(chloromethyl)-1-propene (3.38 g, 27.0 mmoles) in tetrahydrofuran were added simultaneously to a refluxing suspension of sodium hydride (80% in mineral oil, 2.42 g, 80.7 mmoles) in tetrahydrofuran (215 ml). After the addition was complete, the mixture was refluxed for two days then it was cooled and methanol (25 ml) was added carefully. The solvent was evaporated *in vacuo* and the residue was partitioned between dichloromethane (25 ml) and water (25 ml). The aqueous layer was separated and extracted two more times with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered through a layer of Celite and evaporated to give the crude product which was purified by column chromatography.

6,13-Bismethylenyl-14-crown-4 (**41**).

This compound was obtained in 37% yield after chromatography on alumina with petroleum ether/ethyl acetate (5/1) as pale-yellow crystals with mp 25.5-27.5° (lit 26.8° [19]); ir (neat): 1650 (C=C), 1100 (C-O) cm^{-1}; ^{1}H nmr: δ 3.65 (s, 8H), 4.10 (s, 8H), 5.14 (s, 4H); ^{13}C nmr: δ 69.97, 71.93 (CH_2O), 116.05, 144.03 ($C=C$).

13,13-Dibenzyl-6-methylenyl-14-crown-4 (**42**).

This compound was obtained in 27% yield after chromatography on silica gel with petroleum ether/ethyl acetate (9/1) as a colorless, viscous liquid; ir (neat): 1655 (C=C), 1120 (C-O) cm^{-1}; ^{1}H nmr: δ 2.51 (s, 4H), 3.27 (s, 4H), 3.61 (s, 8H), 4.10 (s, 4H), 5.12 (s, 2H), 7.10-7.30 (m, 10H); ^{13}C nmr: δ 37.41 (CH_2), 43.84 (C), 69.88, 70.83, 71.86, 72.64 (CH_2O), 115.05, 126.49, 128.32, 131.49, 138.50, 144.50 (Ar, $C=C$).

Anal. Calcd. for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.51; H, 8.19.

trans- and *cis*-6,13-Bis(dichlorocyclopropyl)-14-crown-4 (**45** and **46**).

Aqueous 50% sodium hydroxide (8.0 mmoles) was added dropwise to a vigorously stirred solution of 6,13-dimethylene-14-crown-4 (**41**) (0.46 g, 2.00 mmoles) and triethylbenzylammonium chloride (50 mg) in chloroform (0.72 g, 6.0 mmoles). The mixture was stirred at room temperature for 20 hours. The reaction mixture was partitioned between chloroform (10 ml) and water (10 ml). The aqueous layer was separated and extracted with chloroform two more times and the combined organic extracts were dried over magnesium sulfate and the solvent was evaporated *in vacuo* to give the crude product which was purified by column chromatography on alumina with petroleum ether/ethyl acetate (5/1) as eluent to produce a mixture of isomers **45** and **46** in 25% yield. Small amounts of individual isomers were separated by column chromatography on silica gel with petroleum ether/ethyl acetate (5/1 → 1/1) as eluent.

trans **45**.

This compound was eluted first and gave white, wax-like crystals which sintered at 130-132° and had a mp 144-146°; ir (deposit on a sodium chloride plate): 1105 (C-O), 755 (C-Cl) cm^{-1}; ^{1}H nmr: δ 1.43 (s, 4H), 3.67 (s, 8H), 3.78 (AB 1, J = 9 Hz, 8H); ^{13}C nmr: δ 29.19 (CH_2), 34.43 (C), 64.14 (CCl_2), 71.01, 71.24 (CH_2O).

Anal. Calcd. for $C_{14}H_{20}Cl_4O_4$: C, 42.67; H, 5.11. Found: C, 42.47; H, 5.17.

cis **46**.

This compound was eluted second and gave white, wax-like crystals which sintered at 105-107° and had a mp 124-125.5°; ir (deposit on a sodium chloride plate): 1113 (C-O), 752 (C-Cl) cm^{-1}; ^{1}H nmr: δ 1.42 (s, 4H), 3.56-3.85 (m, 16H); ^{13}C nmr: δ 29.16 (CH_2), 34.46 (C), 64.15 (CCl_2), 71.00, 71.24 (CH_2O).

Anal. Calcd. for $C_{14}H_{20}Cl_4O_4$: C, 42.67; H, 5.11. Found: C, 42.42; H, 5.30.

Crystal Growth, Crystal Data, Structure Solution and Refinement of Lithium Thiocyanate Complexes of **45** and **46**.

Single crystals of the lithium thiocyanate complexes of **45** and **46** were grown from acetonitrile solutions by slow evaporation. While the same diffractometer (originally a Nicolet P3) was utilized for the data collection for both complexes at Brigham Young University, data for the **45**•LiSCN complex were collected using the R3 system and that for the **46**•LiSCN complex were collected utilizing an updated R3m/V system. The lattice parameters and orientation matrix for each crystal were obtained using a least-squares procedure involving suitable numbers of carefully centered reflectors. Crystal data, some experimental parameters and refinement details are contained in Table 9. Single crystal data for both crystals were obtained using a variable speed θ-2θ scanning procedure. An empirical extinction correction was applied to both data sets, but absorption corrections were not made.

Both structures were solved by a combination of direct and heavy atom methods. In both structures the asymmetric unit consisted of one-half the molecule. The **45**•LiSCN complex contains a mirror plane which passes through the two cyclopropane rings, while the **46**•LiSCN complex contains a twofold rotational axis passing through the center of the cavity. All non-hydrogen atoms were refined anisotropically. In the **45**•LiSCN complex, positions for all hydrogen atoms were calculated except for those bonded to C2 and C11, which lie in the mirror plane. These hydrogen atoms were located in a difference map. Positions for all hydrogen atoms of the **46**•LiSCN complex were obtained from difference maps. During the refinement process the hydrogen atoms for both structures were allowed to ride on the carbons to which they are bonded. The isotropic thermal parameters of the hydrogen atoms were refined. Atomic scattering factors for all atoms were obtained from the International Tables for X-ray Crystallography [30]. Programs used for the solution and refinement of the structure for the **45**•LiSCN complex are contained in the SHELXTL program package [31] while the programs used for the solution and refinement of the structure for the **46**•LiSCN complex are contained in the SHELXTL PLUS computer package [32]. The computer drawings for both structures were prepared using the graphic programs of the SHELXTL PLUS system.

Crystal Growth, Crystal Data, Structure Solution and Refinement of **8**.

Single crystals of **8** were prepared by crystallization from a solution of the compound in 1:1 (v/v) dichloromethane and methanol. The reulting crystals were well-formed, transparent plates of about 0.2 mm thickness, which were stable and showed distinct birefringence. All crystallographic data were collected at The Hebrew University of Jerusalem on one such single crystal. The diffraction data was measured on a Philips PW1100/20 automatic four circle diffractometer with a graphite monochromated molybdenum radiation (λ[MoKα] = 0.71069 Å). The lattice parameters and orientation matrix of the crystal were obtained using a least-squares procedure involving 25 carefully centered reflections in the range of $12° < 2\theta < 24°$. The systematic absences in the diffraction pattern indicated clearly a monoclinic $P2_1/c$ space group. The crystallographic data, including the main experimental parameters and refinement details are listed in Table 9. Single crystal intensity data for **8** were obtained using a constant speed scanning procedure. The integrated intensities of 4561 independent reflections were measured in the range of $4° < 2\theta < 55°$. The intensity data were reduced and corrected for Lorentz and polarization effects. An empirical extinction correction was applied, but due to the small absorption coefficient and insignigicant radiation damage it was not necessary to make correction for radiation decay or absorption. Only those 2172 reflections for which $I_o > 3.0\sigma(I_o)$ were used for further calculations.

The structure of **8** was solved by direct methods with the MITHRIL program [33]. The best phase set yielded a preliminary model containing most of the non-hydrogen atoms of the molecule. The remainder of the non-hydrogen atoms were located by successive cycles of least-squares refinement and difference electon density maps using standard Fourier synthesis and full matrix least squares techniques. All non-hydrogen atoms were refined with anisotropic temperature factors (total of 9 parameters per atom). All hydrogen atoms of **8** could be located from the difference maps, but for convenience were obtained by calculation at optimized positions from the corresponding carbon atoms. During the first few cycles of refinement the hydrogen atoms positions were recalculated after each cycle. The positions of the hydrogen atoms were then refined with isotropic temperature factors (total of 4 parameters per atom). The resulting positions and thermal parameters of the hydrogens were then fixed in the last cycle of refinement. The coordinates of the atoms of the final model are listed in Table 6. The relatively small thermal parameters of the atoms (Table 7) and the small difference in electron densities in the final map (Table 9) are evidence for the high quality of the final model of the molecular structure of **8**.

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