Synthesis of Lariat Ether Carboxylic Acids Based on Dibenzo-16-crown-5

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Received September 25, 2000

Synthetic routes to forty-seven dibenzo-16-crown-5 compounds with pendant carboxylic acid groups are reported. When taken together with previously described lariat ether carboxylic acids, these new compounds provide several series with systematic structural variations including changes in the identity and attachment site(s) of one or more lipophilic groups and the length of the spacer that connects the carboxylic acid group to the polyether framework.

Journal of Heterocyclic Chem., **38**, 311 (2001).

Introduction.

Synthetic macrocyclic polyether ligands (crown ethers) have been used widely for the complexation and selective extraction of a variety of metal ion species [1]. In such systems, the counteranion plays an important role in determining the extraction efficiency and selectivity [2]. The potential of crown ethers as the next generation of specific extracting agents for metal ions was markedly enhanced by the introduction of crown ethers which bear pendant acidic functions [3]. An important advantage of such proton-ionizable lariat ethers is that the ionized group on the side arm provides the counteranion necessary for transport of a metal ion into an organic layer during separation by solvent extraction or transport across liquid membranes. This factor is of immense importance to potential practical applications in which hard aqueous phase anions of chloride, nitrate, and sulfate would be involved [4].

For several years, we have been involved in the design and preparation of lariat ether carboxylic acids and the study of their behavior in metal ion separation processes [4-20]. These ligands have been found to be effective chelating agents for alkali and alkaline earth metal cations and trivalent lanthanide ions [4-25]. In addition to their use as metal ion complexing agents, lariat ether carboxylic acids are important starting materials for the synthesis of lariat ethers with pendant alcohol [26,27], amide [26,28], ester [29], hydroxamate [19,21], and *N*-(X)sulfonyl carboxamide [30,31] groups, as well as bis(crown ether)s and macrotricyclic polyether compounds [26].

Previously we have described the preparation of several dibenzo-16-crown-5 carboxylic acids [7,9,11,13, 14,19,26,32-34]. However, these compounds provide only limited structural variation. We now report synthetic strategies for the preparation of 47 new dibenzo-16-crown-5 carboxylic acids. In combination with the reported compounds, these proton-ionizable lariat ethers provide systematic variations of several structural features.

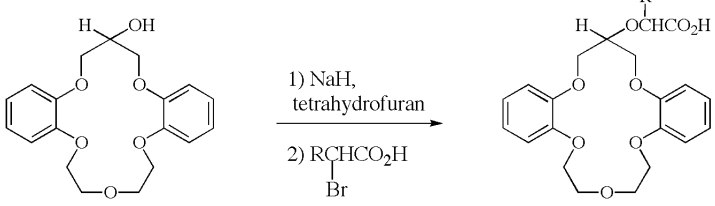
Results and Discussion.

Structures, physical properties, nmr and ir spectral data and elemental analyses data for the new compounds are given in Tables 1-8. In several instances, previously reported compounds are included for comparison. For the preparation of the new lariat ether carboxylic acids, several different synthetic strategies were utilized which will be discussed for each family of compounds.

Synthesis of *sym*-(R)dibenzo-16-crown-5-oxyacetic Acids.

As shown in Scheme 1, *sym*-hydroxydibenzo-16-crown-5 (**82**) [35] was reacted with sodium hydride and the appropriate 2-bromocarboxylic acid in tetrahydrofuran to rovide dibenzo-16-crown-5 lariat ether carboxylic acids **1-8** in which a linear alkyl group is incorporated in the side arm alpha to the carboxylic acid group (Table 1). Attachment of a lipophilic alkyl group was found to reduce loss of ionized *sym*-dibenzo-16-crown-5-oxyacetic acid from a chloroform solution into a contacting aqueous solution during competitive solvent extraction of alkali metal cations [5].

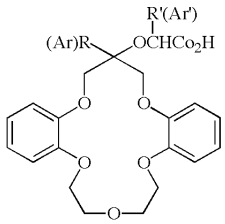
Scheme 1



82 **1-8**

Table 1

Data for Lariat Ether Carboxylic Acids **1-11**



Compound	R (Ar)	R'(Ar')	Method [a]	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[b]	Molecular Formula	Analysis % Calcd./Found C	H
1	H	C_2H_5	A	40[c]						
2	H	C_4H_9	A	40[c]						
3	H	C_6H_{13}	A	23[c]						
4	H	C_8H_{17}	A	27[c]						
			B	85[d]						
5	H	$C_{10}H_{21}$	B	80[e]						
6	H	$C_{12}H_{25}$	B	66[e]						
7	H	$C_{14}H_{29}$	B	70[e]						
			B	90[d]						
8	H	$C_{16}H_{33}$	B	64[e]						
9	CH_3	C_8H_{17}	A	48	95-96	0.70-1.90 (m, 20H), 3.50-4.30 (m, 13H) 6.90 (s, 8H), 8.20 (br s, 1H)	3390-3200 (COOH) 1706 (C=O)	$C_{30}H_{42}O_8$• $0.75CH_2Cl_2$	62.14 62.39	7.38 7.41
10	C_6H_5	C_6H_5	B	97[d]						
11	$C_{10}H_{21}$	C_6H_5	B	86[d]						

[a] See Scheme 2; [b] Deposit from dichloromethane solution on a sodium chloride plate; [c] Reference 7; [d] Later preparation; [e] Reference 19.

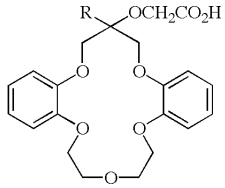
Lariat ether carboxylic acids **12**-**58** (Tables 2-4) with an alkyl, branched alkyl, cycloalkyl, fluoroalkyl, aryl, aralkyl, alkenyl and alkynyl group attached to the polyether ring carbon geminal to an oxyacetic acid side arm were prepared by reaction of the corresponding lariat ether alcohol with sodium or potassium hydride in tetrahydrofuran followed by addition of bromoacetic acid. Lariat ether carboxylic acids **9**-**11** (Table 1) with lipophilic groups at both the geminal position and on the side arm were prepared by reaction of the appropriate lariat ether alcohol and sodium or potassium hydride in tetrahydrofuran and the appropriate 2-bromocarboxylic acid as shown in Scheme 2. The *sym*-(R)(hydroxy)dibenzo-16-crown-5 precursors were prepared by reaction of [9] and the appropriate Grignard reagent [9,19,21,27]. In addition to reducing ligand loss from the organic phase during extraction of metal ions from aqueous solutions, the geminal substituent preorganizes the metal ion binding site by orienting the carboxylic acid group over the crown ether cavity [36].

Dibenzo-16-crown-5 lariat ether carboxylic acids with substituents on both benzene rings (Table 5) were prepared by two methods. In the first method (Scheme 3), the appropriate lariat ether alcohol containing the ring substituents [27,32] was reacted with sodium hydride in tetrahydrofuran and then bromoacetic acid to give the lariat ether carboxylic acids **59**, **63** and **67**. In the second method (Scheme 4), nitro and sulfonic acid groups were introduced into the benzene rings of the pre-formed lariat ether carboxylic acids by nitration [33] and sulfonation [11], respectively. Nitration of *sym*-dibenzo-16-crown-5-oxyacetic acid (**12**) and *sym*-(propyl)dibenzo-16-crown-5-oxyacetic acid (**15**) was conducted with nitric acid in acetic acid-chloroform at room temperature to give dinitrated lariat ether carboxylic acids **60** and **64**, respectively, in very high yields. Under these mild conditions [37], clean dinitration occurred. With only acetic as the solvent, over-nitration might take place [38]. In **60** and **64**, structural isomers of the dinitrated products are possible due to the four potential nitration positions in each aromatic ring of the dibenzocrown ether carboxylic acids. Multiple spots were observed for both dinitrated products **60** and **64** when analyzed by thin layer chromatography. Broad melting point ranges indicate the presence of isomeric mixtures in dinitrated lariat ether carboxylic acids **60** and **64**.

Reduction of di(nitrobenzo)-18-crown-6 to the corresponding diamine was reported by catalytic hydrogenation in *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide [33,37]. However, catalytic hydrogenation (Pd/C catalyst, 50 psi of hydrogen) of the dinitrated lariat ether carboxylic acid **60** in *N*,*N*-dimethylformamide, 2-methoxyethanol, or ethanol produced

Table 2

Data for Lariat Ether Carboxylic Acids **12-37**



Compound	R	Method [a]	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[b]	Molecular Formula	Analysis Calcd./Found C	H
12	H	A	82[c]						
13	CH_3	A	84[d]						
		C	92[e]						
14	C_2H_5	C	69[d]						
		C	91[e]						
15	C_3H_7	A	62						
		C	93[f]						
16	$CH(CH_3)_2$	C	88	124-125	1.17 (s, 6H), 2.63-2.68 (m, 1H), 3.81-4.18 (m, 10H), 4.81-4.86 (d, 2H, J = 10Hz), 4.88 (s, 2H), 6.80-6.90 (m, 8H)	3350 (COOH) 1743 (C=O)	$C_{24}H_{30}O_8$	64.56 64.35	6.77 6.77
17	C_3F_7	A	71	116-118	3.63-4.40 (m, 10H), 4.63-4.68 (d, 2H, J = 10Hz), 5.07 (s, 2H), 6.69-7.02 (m, 8H), 8.50 (br s, 1H)	3358 (COOH) 1748 (C=O)	$C_{24}H_{23}F_7O_8$	50.36 50.62	4.05 4.19
18	C_4H_9	A	55[g]						
19	C_5H_{11}	A	79	155-157	0.80-2.20 (m, 11H), 3.75-4.35 (m, 10H), 4.63-4.68 (d, 2H, J = 10Hz), 4.85 (s, 2H), 6.69-7.00 (m, 8H)	3361 (COOH) 1752 (C=O)	$C_{26}H_{34}O_8$	65.81 65.96	7.22 7.32
20	$CH_2C(CH_3)_3$	C	76	138-139	1.15 (s, 9H), 2.05 (s, 2H), 3.86-4.13 (m, 10H, 4.63-4.68 (d, 2H, J = 10Hz), 4.87 (s, 2H), 6.80-6.97 (m, 8H)	3384 (COOH) 1734 (C=O)	$C_{26}H_{34}O_8$	65.81 66.17	7.22 7.06
21	c-C_6H_{11}	B	26[h]						
22	C_6H_{13}	A	88[d]						
		C	85						
		C	93[e]						
23	C_6F_{13}	A	90	115-117	3.65-4.42 (m, 10H), 4.61-4.66 (d, 2H, J = 10Hz), 5.09 (s, 2H), 6.89-7.04 (m, 8H)	3356 (COOH) 1750 (C=O)	$C_{27}H_{23}F_{13}O_8$	44.89 44.42	3.21 3.41
24	C_7H_{15}	A	79	102-103	0.89-0.94 (t, 3H, J = 6Hz), 1.33 (s, 10H),1.93-1.98 (q, 2H, J = 6Hz), 3.82-3.99 (m, 4H), 4.02-4.17 (m, 6H), 4.58-4.61 (d, 2H, J = 9Hz), 4.85 (s, 2H), 6.81-6.99 (m, 8H)	3358 (COOH) 1771 (C=O)	$C_{28}H_{38}O_8$	66.91 66.85	7.62 7.66
		B	76						
		C	77						
25	C_8H_{17}	A	90[g]						
		C	95[e]						
26	C_8F_{17}	A	87	58-60	3.68-4.45 (m, 10H), 4.68-4.73 (d, 2H, J = 10Hz), 5.10 (s, 2H), 6.85-7.03 (m, 8H)	3360 (COOH) 1751 (C=O)	$C_{29}H_{23}F_{17}O_8 \bullet H_2O$	41.48 41.48	2.91 3.06
27	$CH_2CH(C_2H_5)$-$(CH_2)_3CH_3$	C	58	oil	0.89-1.02 (m, 6H), 1.27-1.68 (m, 9H),1.88-2.01 (m, 2H), 3.83-4.18 (m, 10H), 4.53-4.58 (dd, 2H, J = 10, 2 Hz), 4.88 (s, 2H), 6.82-7.00 (m, 8H)	3366 (COOH) 1772, 1774 (C=O)	$C_{29}H_{40}O_8 \bullet 0.25C_6H_{14}$	68.00 67.99	8.11 8.03

Table 2 (continued)

Data for Lariat Ether Carboxylic Acids **12-37**

Compound	R	Method [a]	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[b]	Molecular Formula	Analysis Calcd./Found C	H
28	C_9H_{19}	B C	98 82	98-99	0.87-0.92 (t, 3H, J = 6Hz), 1.30-1.43 (m, 14H), 1.93-1.96 (m, 2H), 3.82-3.91 (m, 4H), 4.02-4.18 (m, 6H), 4.58-4.61 (d, 2H, J = 9Hz), 4.85 (s, 2H), 6.81-7.00 (m, 8H)	3364 (COOH) 1748 (C=O)	$C_{30}H_{42}O_8$	67.90 68.06	7.98 8.01
29	$C_{10}H_{21}$	A B C	57[i] 78[h] 93[e]						
30	$C_{11}H_{23}$	C	78	109-111	0.85-0.91 (t, 3H, J = 6Hz), 1.15-1.30 (m, 18H), 1.89-1.95 (m, 2H), 3.80-4.10 (m, 10H, 4.50-4.55 (d, 2H, J = 10Hz), 4.80 (s, 2H), 6.85-7.00 (m, 8H)	3368 (COOH) 1771 (C=O))	$C_{32}H_{46}O_8$	68.79 68.83	8.30 8.45
31	$C_{12}H_{25}$	A C	92 76	104-105	0.85-0.91 (t, 3H, J = 6Hz), 1.20-1.30 (m, 20H), 3.70-4.30 (m, 10H), 4.50-4.55 (d, 2H, J = 10Hz), 4.85 (s, 2H), 6.89-7.05 (m, 8H)	3363 (COOH) 1770 (C=O)	$C_{33}H_{48}O_8$	69.20 68.63	8.45 8.54
32	$C_{13}H_{27}$	C	55	99-101	0.85-0.91 (t, 3H, J = 6Hz), 1.25 (s, 22H), 1.92-2.04 (m, 2H), 3.80-4.21 (m, 10H), 4.56-4.61 (d, 2H, J = 10Hz), 4.84 (s, 2H), 6.79-7.00 (m, 8H)	3356 (COOH)	$C_{34}H_{50}O_8$ 1769 (C=O)	69.60 69.38	8.53 8.57
33	$C_{14}H_{29}$	A	72[g]						
34	$C_{15}H_{31}$	A	81	98-100	0.84-0.90 (t, 3H, J = 6Hz), 1.21 (s, 26H), 1.92-2.01 (m, 2H), 3.70-4.20 (m, 10H), 4.52-4.57 (d, 2H, J = 10Hz), 4.77 (s, 2H), 6.72-7.04 (m, 8H)	3367 (COOH) 1772 (C=O)	$C_{36}H_{54}O_8$	70.33 70.26	8.85 9.17
35	$C_{16}H_{33}$	A C	85 54	101-103	0.85-0.91 (t, 3H, J = 6Hz), 1.22-1.38 (m, 28H), 1.92-2.01 (m, 2H), 3.70-4.27 (m, 10H), 4.52-4.57 (d, 2H, J = 10Hz), 4.80 (s, 2H), 6.85-7.09 (m, 8H)	3369 (COOH) 1771 (C=O)	$C_{37}H_{56}O_8$	70.67 70.25	8.98 9.03
36	$C_{18}H_{37}$	A B	84 89[h]						
37	$C_{20}H_{41}$	A	92	102-104	0.83-0.88 (t, 3H, J = 6Hz), 1.20 (s, 36H), 1.95-2.13 (m, 2H), 3.60-4.20 (m, 10H), 4.53-4.58 (d, 2H, J = 10Hz), 4.82 (s, 2H), 6.87-7.11 (m, 8H)	3370 (COOH) 1771 (C=O)	$C_{41}H_{64}O_8$	71.89 72.01	9.42 9.43

[a] See Scheme 2; [b] Deposit from dichloromethane solution on a sodium chloride plate; [c] Reference 7; [d] Reference 16; [e] Reference 34; [f] Reference 14; [g] Reference 9; [h] Reference 19; [i] Reference 13.

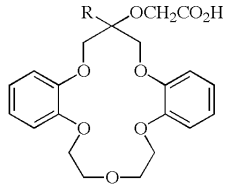
dark-colored products which could not be purified by recrystallization, sublimation or column chromatography. Acetylation of the crude product also failed to provide material that could be purified. Subsequently, it was found that 85% hydrazine hydrate in ethanol reduced **60** to the corresponding diamine **61** in good yield.

Synthesis of Lariat Ether 3-Oxypropanoic, 4-Oxybutanoic and 5-Oxypentanoic Acids.

The length of the spacer that connects the acidic function to the polyether ring is an important structural parameter for proton-ionizable lariat ethers [39]. Compared with *sym*-(R)dibenzo-16-crown-5-oxyacetic acids, lariat ether carboxylic acids **68**-**73** (Table 6) have one to three additional methylene groups in the spacer. For the preparation of lariat ether carboxylic acids **68**-**72**, two methods were employed. In the first synthetic route (Scheme 5), potassium *tert*-butoxide-catalyzed cyanoethylation of the corresponding lariat ether secondary alcohols **82** and **83** in neat acrylonitrile (for **82**) or acrylonitrile in tetrahydrofuran (for **83**) gave the corresponding lariat ether nitriles **84** and **85** in 63 and 48% yields, respectively. Attempted cyanoethylation of lariat ether alcohol **83** in neat acrylonitrile gave a complex

Table 3

Data for Lariat Ether Carboxylic Acids **38-50**



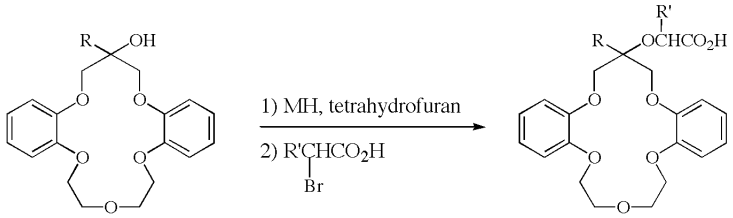
Compound	R	Method [a]	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[b]	Molecular Formula	Analysis % Calcd./Found C	H
38	$CH_2CH_2C_6H_5$	C	75	154-155	2.03-2.34 (m, 2H), 2.81-2.90 (m, 2H), 3.80-4.38 (m, 10H), 4.59-4.64 (d, 2H, J = 10Hz), 4.94 (s, 2H), 6.47-7.07 (m, 8H), 7.27-7.37 (m, 5H), 9.76 (br s, 1H)	3356 (COOH) 1768 (C=O)	$C_{29}H_{32}O_8$	68.50 68.23	6.34 6.40
39	$(CH_2)_3C_6H_5$	C	68	135-136	1.78-1.89 (m, 2H), 1.94-2.05 (m, 2H), 2.70-2.77 (t, 2H, J = 7Hz), 3.76-4.28 (m, 10H), 4.47-4.52 (d, 2H, J = 10Hz), 4.83 (s, 2H), 6.78-7.00 (m, 8H), 7.19-7.36 (m, 5H), 9.91 (br s, 1H)	3357 (COOH) 1768 (C=O)	$C_{30}H_{34}O_8$	68.96 68.57	6.56 6.63
40	$(CH_2)_4C_6H_5$	C	53	85-86	1.52-1.59 (m, 2H), 1.69-1.84 (m, 2H), 1.94-2.02 (m, 2H), 2.67-2.74 (t, 2H, J = 8Hz), 3.79-4.23 (m, 10H), 4.54-4.59 (d, 2H, J = 10Hz), 4.84 (s, 2H), 6.79-7.00 (m, 8H), 7.16-7.34 (m, 5H), 9.95 (br s, 1H)	3354 (COOH) 1769 (C=O)	$C_{31}H_{36}O_8$	69.39 69.57	6.76 6.70
41	$(CH_2)_5C_6H_5$	C	63	104-105	1.45-1.49 (m, 4H), 1.67-1.74 (m, 2H), 1.91-2.03 (m, 2H), 2.62-2.69 (t, 2H, J = 6Hz), 3.78-4.19 (m, 10H), 4.53-4.58 (d, 2H, J = 10Hz), 4.88 (s, 2H), 6.78-6.99 (m, 8H), 7.14-7.32 (m, 5H), 9.89 (br s, 1H)	3355 (COOH) 1770 (C=O)	$C_{32}H_{38}O_8$	69.81 69.97	6.96 6.81
42	C_6H_5	B	76[c]						
43	2-$(CH_3)C_6H_4$	B	67	122-124	2.59 (s, 3H), 3.85-3.90 (m, 2H), 4.03-4.19 (m, 6H), 4.51-4.55 (d, 2H, J = 8Hz), 4.80-4.83 (d, 2H, J = 6Hz), 4.84 (s, 2H), 6.78-6.98 (m, 8H), 7.27-7.32 (m, 3H), 7.67-7.70 (m, 1H)	3656-2900 (COOH), 1734 (C=O)	$C_{28}H_{30}O_8$	68.00 67.61	6.11 6.28
44	3-$(CH_3)C_6H_4$	B	87	161-163	2.44 (s, 3H), 3.85-3.90 (m, 2H), 4.05-4.19 (m, 6H), 4.26-4.30 (d, 2H, J = 8Hz), 4.79-4.82 (d, 2H, J = 6Hz), 4.92 (s, 2H), 6.71-6.98 (m, 8H), 7.20-7.34 (m, 1H), 7.37-7.45 (m, 3H)	3628-2900 (COOH), 1731 (C=O)	$C_{28}H_{30}O_8$	68.00 68.40	6.11 6.33
45	4-$(CH_3)C_6H_4$	B	82	179-180	2.40 (s, 3H), 3.85-3.90 (m, 2H), 4.02-4.15 (m, 6H), 4.28-4.31 (d, 2H, J = 6Hz), 4.74-4.77 (d, 2H, J = 6Hz), 4.88 (s, 2H), 6.72-6.98 (m, 8H), 7.24-7.29 (m, 2H), 7.52-7.55 (d, 2H, J = 6Hz)	3645-2900 (COOH), 1734 (C=O)	$C_{28}H_{30}O_8$	68.00 67.84	6.11 6.32
46	3-$(CF_3)C_6H_4$	B	89[d]						
47	4-$(CH_2{=}CH)C_6H_4$	C	90	178-179	3.91-4.20 (m, 8H), 4.27-4.32 (d, 2H, J = 10Hz), 4.77-4.83 (d, 2H, J = 10.6Hz), 4.91 (s, 2H), 5.35 (s, 1H) 5.78 (s, 1H), 5.87 (s, 1H),6.70-6.96 (m, 8H), 7.50-7.63 (m, 4H)	3430 (COOH) 1735 (C=O)	$C_{29}H_{30}O_8$	68.76 68.52	5.97 5.98

Table 3 (continued)
Data for Lariat Ether Carboxylic Acids **38**-**50**

Compound	R	Method [a]	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[b]	Molecular Formula	Analysis % Calcd./Found C	H
48	4-[CH_2=C(CH_3)]-C_6H_4	A	80	195-196	2.17 (s, 3H), 3.99-4.18 (m, 8H), 4.46-4.51 (d, 2H), J = 10Hz), 4.57-4.62 (d, 2H, J = 10Hz), 4.66 (s, 2H), 5.09 (s, 1H), 5.40 (s, 1H), 6.78-6.91 (m, 8H), 7.45-7.54 (t, 2H, J = 8Hz), 7.78-7.82 (d, 2H, J = 8Hz)	3425 (COOH) 1734 (C=O)	$C_{30}H_{32}O_8$• O.2H_2O	68.74 68.73	6.23 6.23
49	3,5-$(CH_3)_2C_6H_3$	B	72	115-117	2.40 (s, 6H), 3.96-4.12 (m, 2H), 4.13-4.21 (m, 6H), 4.23-4.28 (d, 2H, J = 10Hz), 4.78-4.83 (d, 2H, J = 10Hz), 4.92 (s, 2H), 6.70-6.96 (m, 9H), 7.26 (s, 2H)	3650-2900 (COOH), 1734 (C=O)	$C_{29}H_{32}O_8$	71.98 72.08	6.71 6.70
50	3,5-$(CF_3)_2C_6H_3$	B	96[d]						

[a] See Scheme 2; [b] Deposit from dichloromethane solution on a sodium chloride plate; [c] Reference 19; [d] Reference 21.

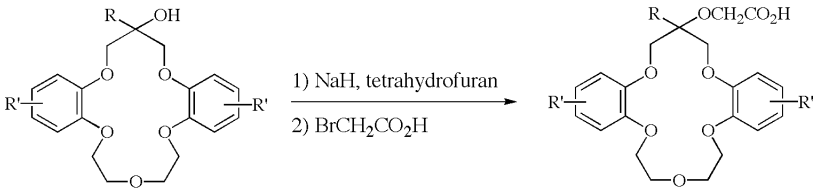
Scheme 2



9-**58**

Method	MH
A	NaH, 60% dispersion in mineral oil
B	NaH, dry
C	KH, 35% dispersion in mineral oil

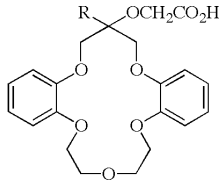
Scheme 3



	R	R'
59	H	*t*-Bu
63	CH_3	*t*-Bu
67	H	F

Table 4

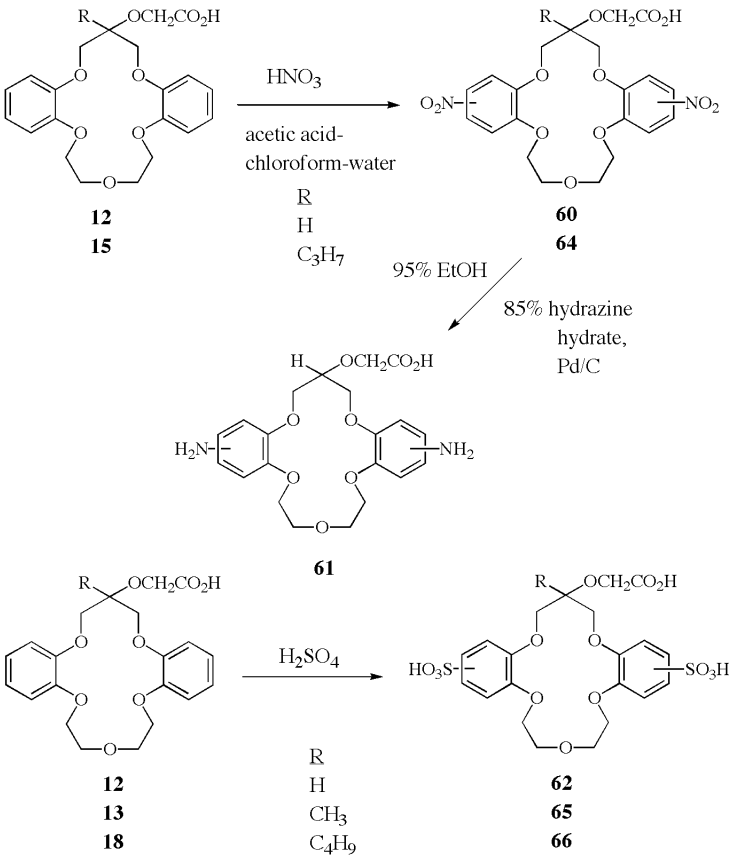
Data for Lariat Ether Carboxylic Acids **51-58**



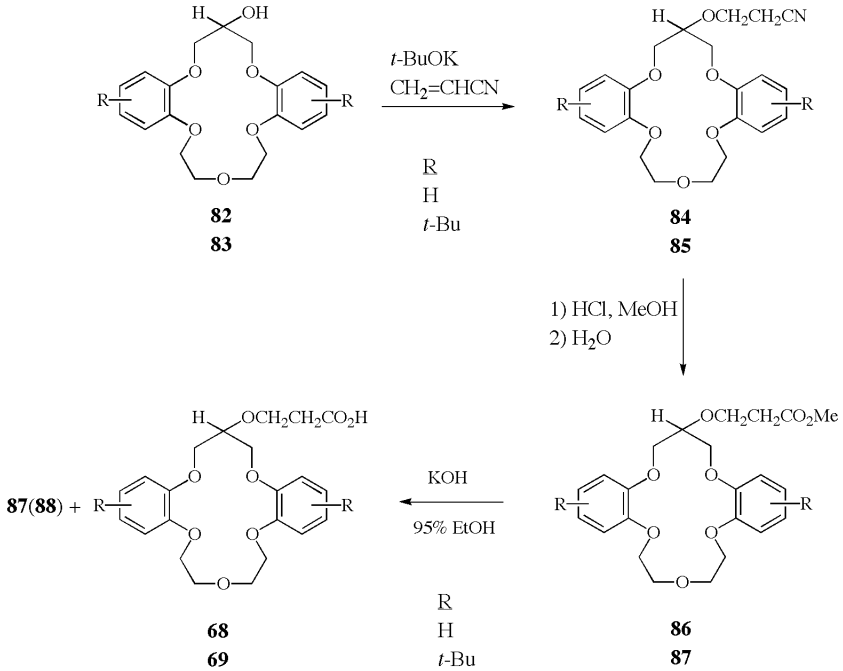
Compound	R	Method [a]	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[b]	Molecular Formula	Analysis % Calcd./Found C	H
51	$CH=C(CH_3)_2$	C	92	65-67	1.94-1.97 (d, 6H, J = 6Hz), 3.84-4.17 (m, 10H), 4.50-4.55 (d, 2H, J = 10Hz), 4.66 (s, 2H), 5.43-5.65 (m, 1H), 6.81-6.96 (m, 8H)	3384 (COOH) 1770 (C=O)	$C_{25}H_{30}O_8$• $0.4H_2O$	64.47 64.55	6.67 6.84
52	$(CH_2)_6CH=CH_2$	A	92	87-89	1.30-2.02 (m, 12H), 3.90-4.26 (m, 10H), 4.56-4.62 (d, 2H, J = 12Hz), 4.87 (s, 2H),4.91-5.03 (m, 2H), 5.72-5.91 (m, 1H), 6.87-7.01 (m, 8H)	3357 (COOH) 1744 (C=O)	$C_{29}H_{38}O_8$	67.68 67.80	7.44 7.49
53	$(CH_2)_8CH=CH_2$	A	97	oil	1.32-2.05 (m, 16H), 3.90-4.26 (m, 10H), 4.56-4.62 (d, 2H, J = 12Hz), 4.85 (s, 2H), 4.90-5.04 (m, 2H), 5.70-5.90 (m, 1H), 6.89-7.00 (m, 8H)	3357 (COOH) 1746 (C=O)	$C_{31}H_{42}O_8$	68.61 68.51	7.80 7.51
54	$C\equiv C(CH_2)_3CH_3$	C	94	66-67	0.90-0.96 (t, 3H, J = 7.1Hz), 1.32-1.64 (m, 4H), 2.26-2.32 (t, 2H, J = 6.9Hz), 3.81-4.05 (m, 4H), 4.09-4.26 (m, 6H), 4.48 (s, 2H), 4.52-4.57 (d, 2H, J = 10Hz), 6.78-7.08 (m, 8H)	3700-2300 (COOH), 2241 (C≡C), 1741 (C=O)	$C_{27}H_{32}O_8$	66.93 66.91	6.66 6.72
55	$C\equiv C(CH_2)_5CH_3$	C	85	103-105	0.85-0.91 (t, 3H, J = 6Hz), 1.18-1.66 (m, 8H), 2.25-2.31 (t, 2H, J = 7Hz), 3.82-4.05 (m, 4H), 4.08-4.27 (m, 6H), 4.48 (s, 2H), 4.52-4.57 (d, 2H, J = 10Hz), 6.79-7.08 (m, 8H)	3700-2300 (COOH), 2241 (C≡C), 1745 (C=O)	$C_{29}H_{36}O_8$	67.95 67.71	7.08 6.92
56	$C\equiv C(CH_2)_7CH_3$	C	84	105-106	0.87-0.93 (t, 3H, J = 6Hz), 1.14-1.67 (m, 12H), 2.25-2.31 (t, 2H, J = 7Hz), 3.80-4.05 (m, 4H), 4.08-4.28 (m, 6H), 4.48 (s, 2H), 4.52-4.57 (d, 2H, J = 10Hz), 6.78-7.10 (m, 8H)	3700-2300 (COOH) 2241 (C≡C) 1741 (C=O)	$C_{31}H_{40}O_8$	68.87 68.94	7.46 7.23
57	$C\equiv C(CH_2)_9CH_3$	C	88	90-91	0.87-0.93 (t, 3H, J = 6Hz), 1.17-1.66 (m, 16H), 2.25-2.31 (t, 2H, J = 7Hz), 3.81-4.05 (m, 4H), 4.08-4.27 (m, 6H), 4.48 (s, 2H), 4.52-4.57 (d, 2H, J = 10Hz), 6.79-7.08 (m, 8H)	3700-2300 (COOH) 2243 (C≡C) 1742 (C=O)	$C_{33}H_{44}O_8$	69.69 69.75	7.80 7.81
58	$C\equiv C(CH_2)_{11}CH_3$	C	86	88-90	0.88-0.94 (t, 3H, J = 6Hz), 1.16-1.66 (m, 20H), 2.25-2.31 (t, 2H, J = 7Hz), 3.80-4.05 (m, 4H), 4.08-4.29 (m, 6H), 4.48 (s, 2H), 4.51-4.56 (d, 2H, J = 10Hz), 6.78-7.09 (m, 8H)	3700-2300 (COOH) 2241 (C≡C) 1741 (C=O)	$C_{35}H_{48}O_8$	70.45 70.52	8.11 8.27

[a] See Scheme 2; [b] Deposit from dichloromethane solution on a sodium chloride plate.

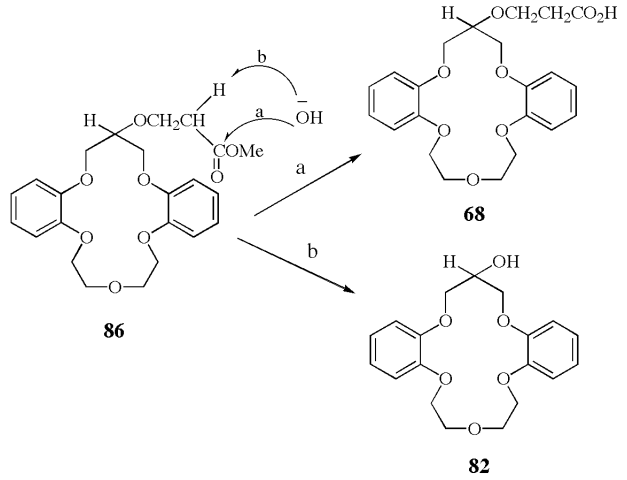
Scheme 4



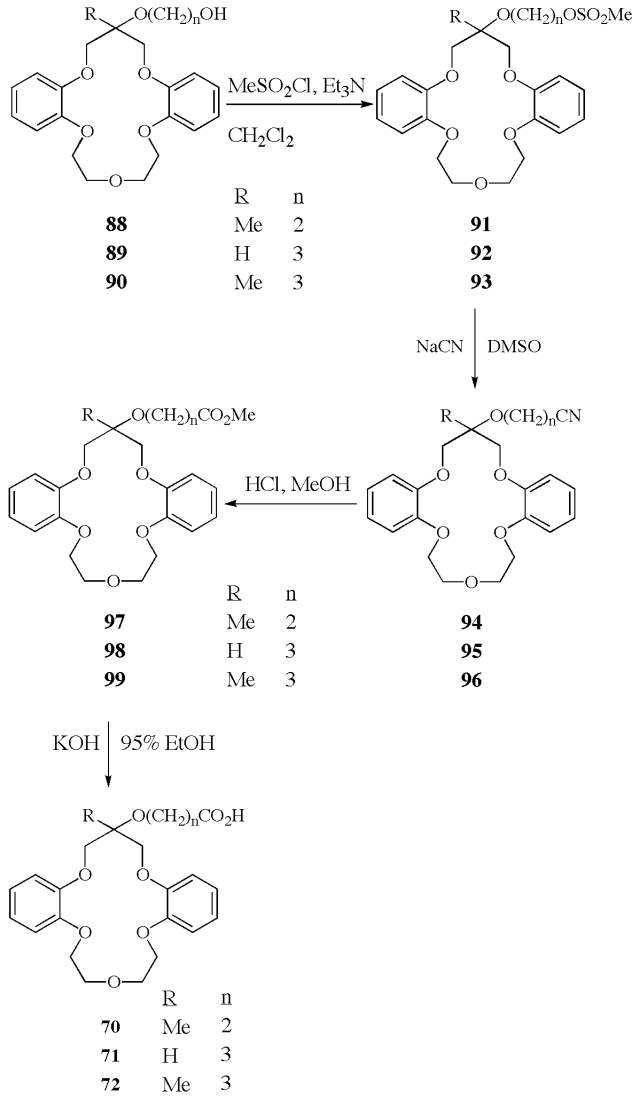
Scheme 5



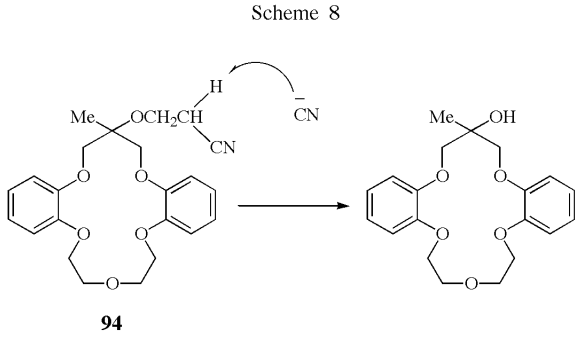
Scheme 6



Scheme 7



Scheme 8



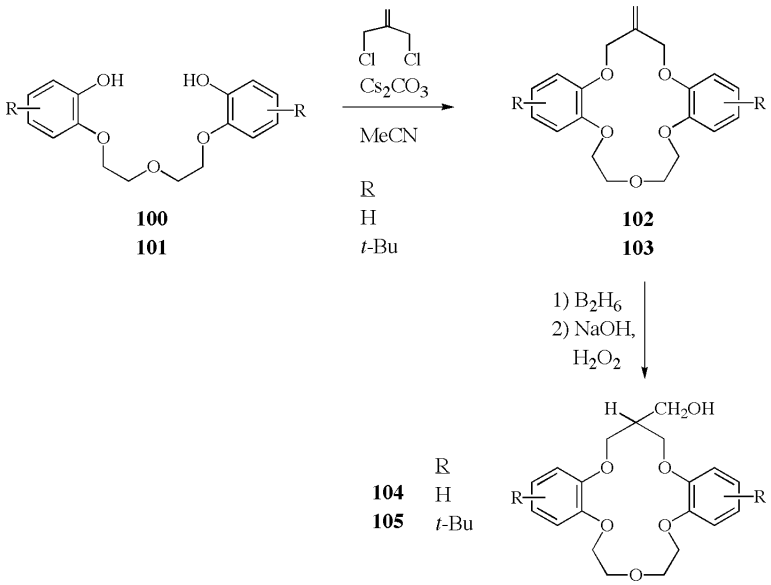
mixture of oligomers. Hydrolysis of **84** and **85** was performed by bubbling hydrochloric acid gas through a refluxing methanol solution of the lariat ether nitrile to give lariat ether methyl esters **86** and **87** in 94 and 74% yields, respectively. Saponification with potassium hydroxide in 95% ethanol gave the lariat ether oxypropanoic acids **68** and **69** in 65 and 90% yields, respectively.

Lariat ether esters **86** and **87** showed a pronounced tendency to undergo a retro Michael addition (Scheme 6, path b) during hydrolysis, if the ester group was not cleaved quickly (Scheme 6, path a). Therefore, methyl esters were favored over ethyl esters in this synthetic route. The preparation of lariat ether carboxylic acid **68** was reported previously [7] by another method, but in low overall yield.

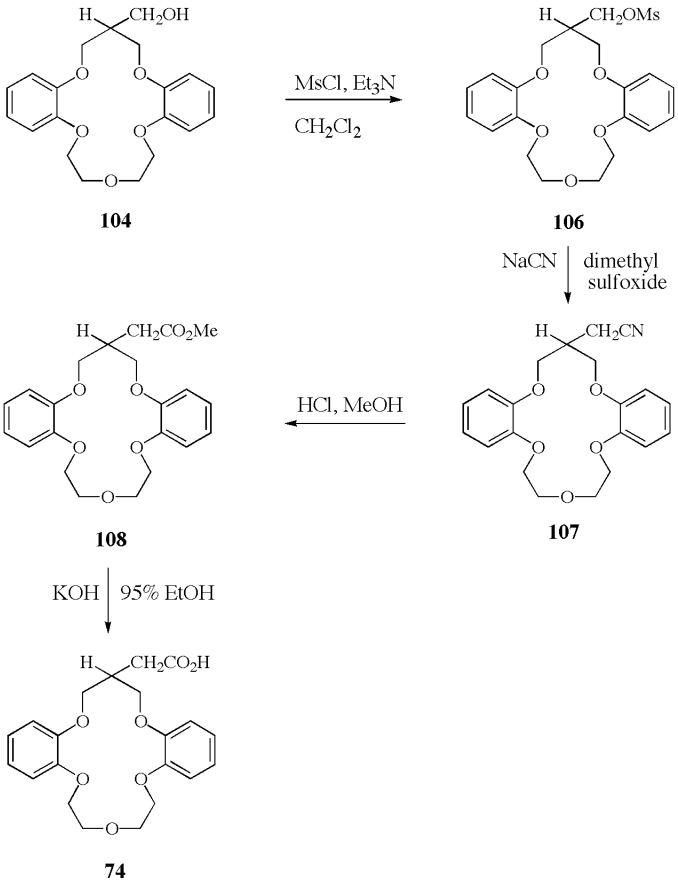
The hydrolysis of methyl ester **87** and the corresponding ethyl ester was investigated using several reaction conditions (Table 9). The hydrolyses were conducted at room temperature using varying amounts of potassium hydroxide as the base in 95% ethanol and in dioxane. In addition to the desired lariat ether carboxylic acid **69**, the retro Michael adduct **83** (15%) and some recovered reactant were obtained when four equivalents of potassium hydroxide were used to hydrolyze the ethyl ester in 95% ethanol (Entry 1). With eight equivalents of potassium hydroxide in 95% ethanol, a 91% yield of lariat ether carboxylic acid **69** was obtained (Entry 2). With 10 equivalents of potassium hydroxide in dioxane, the amount of retro Michael decomposition increased relative to the desired hydrolysis product (Entries 3 and 4). When the more labile methyl ester **87** (Entry 5) was reacted with eight equivalents of potassium hydroxide in 95% ethanol, lariat ether carboxylic acid **69** was obtained in 90% yield.

For lariat ether carboxylic acids **70-72** (Table 6), a somewhat different approach was utilized (Scheme 7). Reaction of lariat ether alcohols **88-90** with methanesulfonyl chloride in dichloromethane in the presence of triethylamine provided lariat ether mesylates **91-93**, respectively, in 90-94% yields. The lariat ether mesylates **91** and **92** were reacted with sodium cyanide in dimethyl sulfoxide at 45° (at 90° for **98**) to give the lariat ether nitriles **94-96**, respectively, in 60-84% yields. The progress of these reactions were

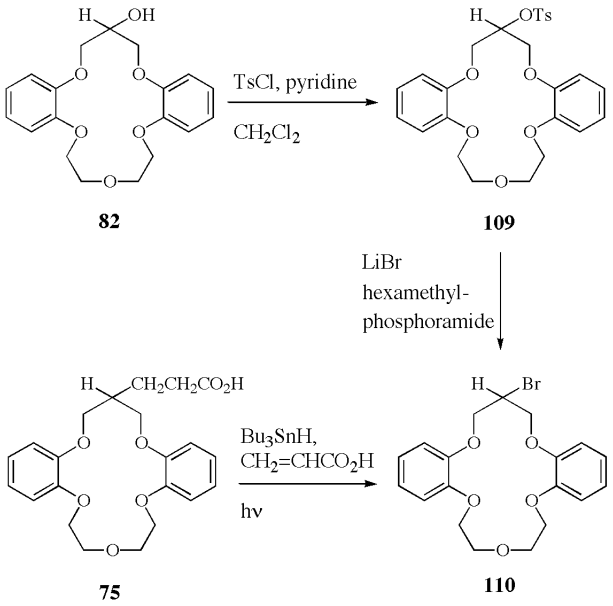
Scheme 9



Scheme 10



Scheme 11



conveniently monitored by thin layer chromatography. When the preparation of **94** was attempted in dimethyl sulfoxide at 90°, the primary product was a 57% yield of *sym*-(hydroxy)(methyl)dibenzo-16-crown-5. This decomposition product is proposed to result from the retro Michael-type elimination shown in Scheme 8. For hydrolysis, lariat ether nitriles **94**-**96** were refluxed in anhydrous methanol and anhydrous hydrochloric acid gas was bubbled through the solution for 50 hours. After quenching with water, lariat ether methyl esters **97**-**99** were obtained in 42-79% yields, respectively. Hydrolysis with potassium hydroxide in 95% ethanol at room temperature gave the lariat ether carboxylic acids **70**-**72**, respectively, in high yields (88-97%).

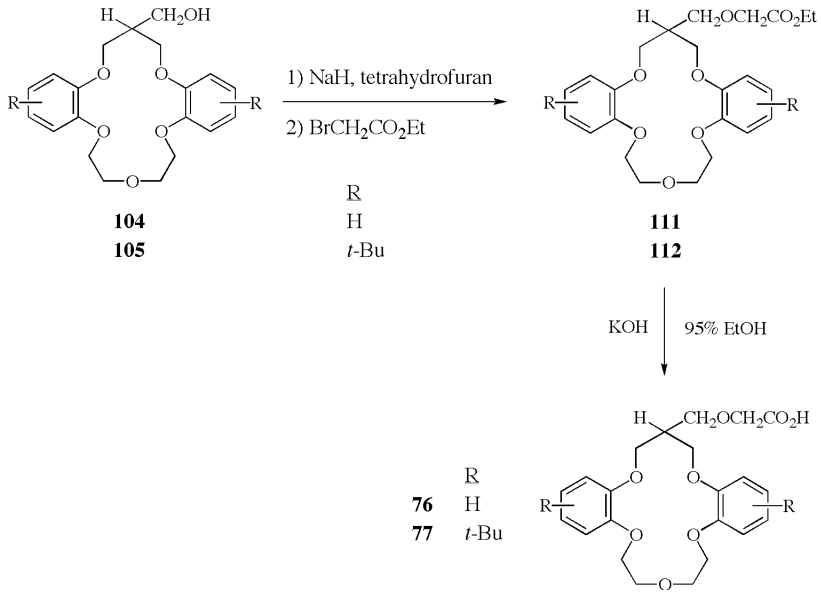
Synthesis of Lariat Ether Acetic, 3-Propanoic and 4-(2-Oxabutanoic Acid)s.

For the dibenzo-16-crown-5 carboxylic acids described above, an oxygen atom connects the side arm to the polyether ring. In contrast, for lariat ether carboxylic acids **74**-**77** (Table 7) a carbon atom connects the side arm to the dibenzo-16-crown-5 unit.

The synthesis of hydroxymethyl lariat ethers **104** and **105** which are precursors to lariat ether carboxylic acids **79**, **81** and **82** is shown in Scheme 9. Vinylidine dibenzo-crown ethers **102** and **103** were prepared by cyclization of bisphenols **100** and **101** with methallyl dichloride and cesium carbonate in acetonitrile to give the desired products in 72-74% yields. Hydroboration-oxidation of **102** and **103** with borane-tetrahydrofuran complex, followed by oxidation with hydrogen peroxide and basic hydrolysis gave lariat ether alcohols **104** and **105** in 60 and 45% yields, respectively.

(*sym*-Dibenzo-16-crown-5)acetic acid (**74**) was synthesized as shown in Scheme 10. Reaction of lariat ether alcohol **104** with methanesulfonyl chloride in dichloromethane in the presence of triethylamine gave lariat ether mesylate **106**, which was treated with sodium cyanide in dimethyl sulfoxide at 60° to provide a 98% yield of lariat ether nitrile **107**. Passing hydrogen chloride gas through a refluxing methanolic solution of **107** for 16 hours gave a quantitive yield of lariat ether methyl ester

Scheme 12



Scheme 13

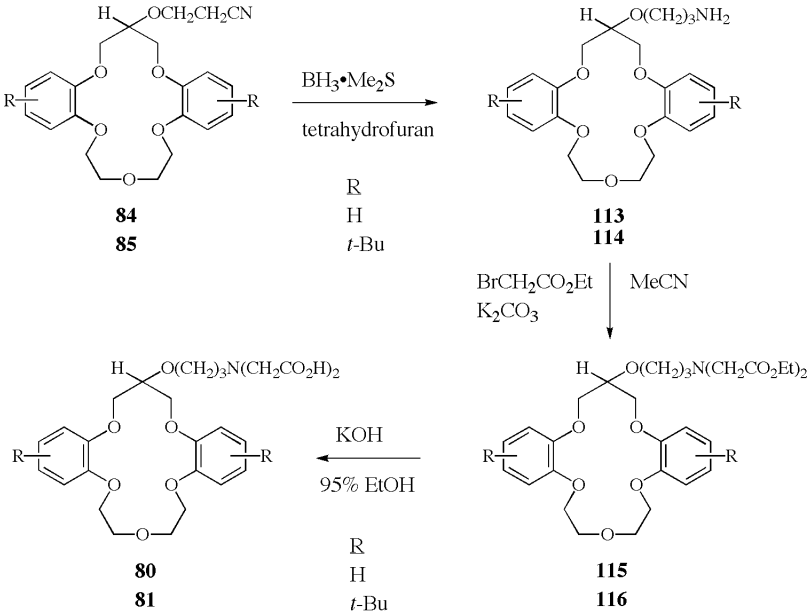


Table 5

Data for Lariat Ether Carboxylic Acids **59-67**

Compound	R	R'	Method [a]	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[b]	Molecular Formula	Analysis % Calcd./Found C	H
59	H	$C(CH_3)_3$	A	86[c]						
60	H	NO_2		99[d]						
61	H	NH_2		89	179-180	3.20-4.50 (m, 15H), 4.50-4.52 (br s, 4H), 5.80-7.00 (m, 6H), 8.80-9.20 (br s, 1H) [e]	3370, 3290, 3180 (COOH, NH_2), 1680 (C=O) [f]	$C_{21}H_{26}N_2O_8$• $0.3H_20$	57.34 57.42	6.10 6.21
62	H	SO_3H		93[e]						
63	CH_3	$C(CH_3)_3$	A	74	97-99	0.80-1.30 (m, 21H), 3.40-4.30 (m, 12H) 4.75 (s, 2H), 6.80-7.00 (m, 6H), 8.90 (br s, 1H)	3550 (COOH) 1715 (C=O)	$C_{30}H_{42}O_8$• $2.0H_2O$	63.59 63.41	8.13 7.72
64	C_3H_7	NO_2		99	83-89	1.00-1.20 (m, 3H), 1.40-1.70 (m, 2H), 1.85-2.10 (m, 2H), 3.80-4.90 (m, 14H), 6.80-7.05 (m, 2H), 7.65-8.10 (m, 4H)	3412 (COOH) 1735 (C=O)	$C_{24}H_{28}N_2O_{12}$	53.73 53.54	5.26 5.27
65	CH_3	SO_3H		86[e]						
66	C_4H_9	SO_3H		82(e)						
67	H	F	B	49[h]						

[a] See Scheme 2.; [b] Deposit from dichloromethane solution onto a sodium chloride plate.; [c] Reference 32; [d] Reference 33; [e]Reference 11; [f] Dimethyl sulfoxide d-6; [g] Potassium bromide pellet; [h] Reference 21.

108. Hydrolysis with potassium hydroxide in 95% ethanol at room temperature gave a quantitative yield of lariat ether carboxylic acid **74**.

The synthetic route to 3-(*sym*-dibenzo-16-crown-5)-propanoic acid (**75**) is shown in Scheme 11. Lariat ether alcohol **82** was converted into tosylate **109** in 97% yield. This tosylate was reacted with 10 equivalents of lithium bromide in hexamethylphosphoramide to give an 85% yield of lariat ether bromide **110** which was photolyzed in the presence of acrylic acid and tributyltin hydride [40] to produce a 30% yield of the desired lariat ether carboxylic acid **75**.

Table 6

Data for Lariat Ether Carboxylic Acids **68-73**

Compound	R	R'	n	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[b]	Molecular Formula	Analysis % Calcd./Found C	H
68	H	H	2	65, 6[b]						
69	H	$C(CH_3)_3$	2	90	oil	1.27 (s, 18H), 2.71-2.82 (m, 2H), 3.80-4.51 (m, 15H), 6.67-7.12 (m, 6H)	3700-2500 (COOH), 1728 (C=O)	$C_{30}H_{42}O_8$• $0.5CH_2Cl_2$	63.92 64.01	7.56 7.73
70	CH_3	H	2	88	161-162	1.52 (s, 3H), 2.65-2.71 (t, 2H, J = 6Hz), 3.91-4.36 (m, 14H), 6.60-6.99 (m, 8H)	3212 (COOH) 1719 (C=O)	$C_{23}H_{28}O_8$	63.88 63.55	6.47 6.20
71	H	H	3	97	oil	1.90-1.98 (q, 2H, J = 6Hz), 2.54-3.00 (t, 2H, J = 6Hz), 3.65-4.50 (m, 15H), 6.80-7.00 (m, 8H), 9.15 (br s, 1H)	3600-2400 (COOH) 1709 (C=O)	$C_{23}H_{28}O_8$	63.88 63.59	6.53 6.95
72	CH_3	H	3	92	128-129	1.49 (s, 3H), 1.87-1.92 (m, 2H), 2.47-2.53 (t, 2H, J = 6Hz), 3.80-3.94 (m, 6H), 4.10-4.27 (m, 8H) 6.60-6.99 (m, 8H)	3440 (COOH) 1707 (C=O)	$C_{24}H_{30}O_8$	64.56 64.34	6.77 6.60
73	H	H	4	72[b]						

[a] Deposited from dichloromethane solution on a sodium chloride plate; [b] Reference 7.

The preparation of dibenzo-16-crown-5 compounds **76** and **77** with 4-(2-oxabutanoic acid) side arms is summarized in Scheme 12. Reaction of hydroxymethyl lariat ethers **104** and **105** with ethyl bromoacetate and sodium hydride in tetrahydrofuran at room temperature gave lariat ether esters **111** and **112** in 63 and 40% yields, respectively. Hydrolysis with potassium hydroxide in 95% ethanol provided lariat ether carboxylic acids **76** and **77** in 94% yields.

Synthesis of Lariat Ether Dicarboxylic Acids.

Dibenzo-16-crown-5 compounds **80** and **81** with two carboxylic acid groups per molecule were prepared as depicted in Scheme 13. Reduction of lariat ether nitriles **84** and **85** with borane-dimethylsulfide in tetrahydrofuran gave lariat ether amines **113** and **114** in 54 and 40% yields, respectively. Condensations of **113** and **114** with ethyl bromoacetate and potassium carbonate in acetonitrile at room temperature gave lariat ether diesters **115** and **116** in

Table 7

Data for Lariat Ether Carboxylic Acids **74-77**

Compound	R	R'	X	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[a]	Molecular Formula	Analysis % Calcd./Found C	H
74	H	H	CO_2H	99	oil	2.87 (s, 3H), 3.70-4.00 (m, 4H), 4.05-4.35 (m, 8H), 6.69-7.09 (m, 8H)	3400-2700 (COOH), 1709 (C=O)	$C_{21}H_{24}O_7$• $0.25CH_2Cl_2$	62.31 62.53	6.03 6.06
75	H	H	CH_2CO_2H	30	157-158	1.41-2.04 (q, 2H, J = 6Hz), 2.35-2.44 (m, 1H), 2.66-2.72 (t, 2H, J = 6Hz), 3.91-3.96 (m, 4H), 4.13-4.19 (m, 8H), 6.81-6.99 (m, 8H)	3600-2400 (COOH), 1707 (C=O)	$C_{22}H_{26}O_7$• $0.1CDCl_3$	64.05 64.00	6.35 6.22
76	H	H	OCH_2CO_2H	62	106-107	2.43-2.75 (m, 1H), 3.70-4.41 (m, 16H), 6.68-7.05 (m, 8H), 7.95 (br s, 1H)	3700-2600 (COOH), 1738 (C=O)	$C_{22}H_{26}O_8$	63.15 63.28	6.26 6.41
77	H	$C(CH_3)_3$	OCH_2CO_2H	38	oil	1.27 (s, 18H), 2.51-2.81 (m, 1H), 3.69-4.44 (m, 16H), 6.68-7.07 (m, 6H)	3700-2400 (COOH), 1740 (C=O)	$C_{30}H_{42}O_8$• $0.8CH_2Cl_2$	61.80 61.74	7.34 7.43

[a] Deposit from dichloromethane solution on a sodium chloride plate.

Table 8

Data for Lariat Ether Carboxylic Acids **78**-**81**

Compound	R	X	Yield (%)	Mp (°C)	^{1}H NMR (deuteriochloroform) δ (ppm)	IR (cm^{-1})[a]	Molecular Formula	Analysis % Calcd./Found C	H
78	H	OCH_2CO_2H	60[b]						
79	H	$OCH(C_6H_5)CO_2H$	65[b]						
80	H	$CH_2N(CH_2CO_2H)_2$	96	oil	1.75-2.20 (m, 2H), 3.05-4.51 (m, 21H), 6.65-7.08 (m, 8H), 11.5 (br s, 2H)	3600-2400 (COOH), 1731,1633 (C=O)	$C_{26}H_{33}NO_{10}$• 0.6HCl	57.67 57.73	6.25 5.86
81	$C(CH_3)_3$	$CH_2N(CH_2CO_2H)_2$	97	oil	1.17 (s, 18H), 1.68-2.10 (m, 2H), 3.10-4.61 (m, 21H), 6.50-6.95 (m, 6H), 11.5 (br s, 2H)	3700-2400 (COOH, 1739, 1606 (C=O)	$C_{34}H_{49}NO_{10}$• 0.3$CDCl_3$	61.62 61.72	7.58 7.44

[a] Deposited from dichloromethane solution onto a sodium chloride plate; [b] Reference 26.

100 and 62% yields, respectively. Hydrolysis with potassium hydroxide in 95% ethanol produced the lariat ether dicarboxylic acids **80** and **81** in 97% yields.

EXPERIMENTAL

Reagents and solvents were purchased from commercial sources and used without further purification unless otherwise noted. Tetrahydrofuran was dried and purified by distillation from sodium under nitrogen with benzophenone ketyl as indicator. Pentane, hexane and hexanes were dried by distillation from lithium aluminum hydride. Acetonitrile was dried over and distilled from calcium hydride. Lariat ether alcohol **82** [35] and bisphenols **100** [41] and **101** [32] were prepared by reported methods.

Melting points were determined with a Mel-Temp melting point apparatus. Infrared (ir) spectra were recorded with a Perkin-Elmer Model 1600 FT-IR spectrophotometer. Proton nuclear magnetic resonance (nmr) spectra were obtained with a Bruker AF-200 (200 MHz) spectrometer. Elemental analyses were performed by Desert Analytics Laboratory of Tucson, AZ.

Preparation of 2-[*sym*-(Methyl)dibenzo-16-crown-5-oxy]-decanoic Acid (**9**).

Under nitrogen, 4.70 g (97 mmoles) of sodium hydride (50% dispersion in mineral oil) was washed three times with pentane to remove the mineral oil and was suspended in tetrahydrofuran (50 ml). To the stirred mixture, 34 mmoles of *sym*-(methyl)-hydroxydibenzo-16-crown-5 [27] in tetrahydrofuran (50 ml) was added over a 1-hour period and the mixture was stirred for 2 hours. A solution of 7.16 g (28.5 mmoles) of 2-bromodecanoic acid in tetrahydrofuran (50 ml) was added over a 10-hour period and the mixture was stirred at room temperature for 48 hours. The mixture was evaporated *in vacuo* and water (250 ml) was added. The resultant basic aqueous solution was extracted with hexane (3 x 100 ml) to remove the unreacted lariat ether alcohol. The aqueous solution was acidified to pH 3 with 6 *N* hydrochloric acid and extracted with dichloromethane (3 x 100 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo* to give a crude product which was chromatographed twice on silica gel with dichloromethane and ethanol-dichloromethane (1:1) as the eluents to afford a white crystalline solid. The yield and physical, spectral and analysis data for **9** are given in Table 1.

Table 9

Basic Hydrolysis of Lariat Ether Methyl Ester **87** and the Corresponding Ethyl Ester

Entry	Ester	Equivalents of Potassium Hydroxide	Solvent	Time (hours)	Yield of **69** (%)
1	ethyl	4	95% ethanol	2.50	57[a,b]
2	ethyl	8	95% ethanol	1.75	91
3	ethyl	10	dioxane	0.50	16[a]
4	ethyl	10	dioxane	0.25	32[b]
5	methyl	8	95% ethanol	0.25	90

[a] Decomposition product **82** was also observed; [b] Some unhydrolyzed ester was present in the product mixture.

General Procedure for the Preparation of *sym*-(Alkyl)-, (Fluoroalkyl)- or (Alkenyl)dibenzo-16-crown-5-oxyacetic Acids **16**, **17**, **19**, **20**, **22**-**24**, **26**-**28**, **30**-**32** and **34**-**37**.

Under nitrogen, sodium hydride (60 mmoles) or potassium hydride (20 mmoles) was washed with hexanes to remove the protecting mineral oil (when dry sodium hydride was used, this step was omitted). The metal hydride was suspended in tetrahydrofuran (40 ml). To the stirred mixture, a solution of the lariat ether alcohol (13 mmoles) [27] in tetrahydrofuran (100 ml) was added dropwise over a 30-minute period and stirring was continued for 1 hour. To the mixture, 4.16 g (30 mmoles) of bromoacetic acid in tetrahydrofuran (10 ml) was added dropwise during a 1-hour period. The mixture was stirred at room temperature overnight and cooled to 0°. Water (20 ml) was added dropwise to destroy the unreacted metal hydride and the tetrahydrofuran was evaporated *in vacuo*. The alkaline aqueous solution was washed with ethyl acetate or diethyl ether (2 x 100 ml) and acidified to pH 1 with 6 *N* hydrochloric acid. Dichloromethane

(30 ml) was added and the organic layer was separated, dried over magnesium sulfate and evaporated *in vacuo*.

Compounds **16** and **20** were crystallized from ethanol. Compounds **17**, **19**, **23**, **26**, **30**-**32**, **34**, **35**, and **37** were crystallized from ethyl acetate-hexanes. Compounds **24**, **28** and **30** were crystallized from diethyl ether.

The yields and physical, spectral and analysis data are given in Table 2.

General Procedure for the Preparation of *sym*-(Aryl)- or (Aralkyl)dibenzo-16-crown-5-oxyacetic Acids **38**-**50**.

Tetrahydrofuran (30 ml) was added to 1.44 g (60 mmoles) of dry sodium hydride or 2.46 g (60 mmoles) of potassium hydride (which had been washed with pentane to remove the mineral oil) under nitrogen and the metal hydride was suspended in tetrahydrofuran (20 ml). The lariat ether alcohol (6.0 mmoles) [27] in tetrahydrofuran (50 ml) was added dropwise over a 1-hour period. The mixture was stirred at room temperature for an additional hour and a solution of bromoacetic acid (1.66 g, 12 mmoles) in tetrahydrofuran (25 ml) was added dropwise over a 2-hour period. The mixture was stirred at room temperature for 12-24 hours. The excess of metal hydride was destroyed by careful addition of water and the tetrahydrofuran was evaporated *in vacuo*. The alkaline aqueous solution was extracted with diethyl ether (2 x 100 ml) to remove the unreacted lariat ether alcohol, acidified to pH 1 with 6 *N* hydrochloric acid and extracted with dichloromethane (2 x 60 ml). The combined organic layers were washed with water, dried over magnesium sulfate and evaporated *in vacuo* to give a white to pale yellow solid that was purified by recrystallization from ethyl acetate-hexanes to give a white solid. The yields and physical, spectral and analysis data are given in Table 3.

General Procedure for the Preparation of *sym*-(Alkenyl)dibenzo-16-crown-5-oxyacetic Acids **51**-**53**.

The protecting mineral oil from sodium hydride (1.26 g, 32 mmoles, 60% dispersion in mineral oil) was removed by washing with pentane (2 x 20 ml) and tetrahydrofuran (25 ml) was added. The lariat ether alcohol (5.24 mmoles) [27] in tetrahydrofuran (20 ml) was added dropwise and the mixture was stirred for 1 hour. After a solution of bromoacetic acid (1.46 g, 10.5 mmoles) in tetrahydrofuran (20 ml) was added dropwise, the reaction mixture was stirred overnight at room temperature and then refluxed for 6 hours. After cooling to room temperature, water (40 ml) was added carefully to destroy the excess of sodium hydride. The tetrahydrofuran was evaporated *in vacuo* and the alkaline aqeuous mixture was acidified to pH 1 with 6 *N* hydrochloric acid. The aqueous solution was extracted with dichloromethane (2 x 60 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo*. Compounds **51** and **52** were recrystallized from ethanol and diethyl ether, respectively. The yields and physical, spectral and analysis data are given in Table 4.

General Procedure for the Synthesis of *sym*-(1-Alkynyl)dibenzo-16-crown-5-oxyacetic Acids **54**-**58**.

Under nitrogen, potassium hydride (2.37 g, 35 wt. % dispersion in mineral oil, 21 mmoles) was washed with pentane to remove the protecting mineral oil and tetrahydrofuran (40 ml) was added. A solution of the *sym*-(1-alkynyl)(hydroxy)dibenzo-16-crown-5 compound (4.14 mmoles) [27] in tetrahydrofuran (40 ml) was added over a 10-minute period and the mixture was stirred at room temperature for 2 hours. A solution of bromoacetic acid (0.86 g. 6.22 mmoles) in 10 ml of tetrahydrofuran was added over a 1-hour period and the mixture was stirred at room temperature for 4 hours. The mixture was cooled to 0° and ice-water (20 ml) was added dropwise to destroy the unreacted potassium hydride. The tetrahydrofuran was evaporated *in vacuo* and sufficient water was added to dissolve the residue. The alkaline aqueous solution was washed with diethyl ether (3 x 40 ml) and extracted with ethyl acetate (60 ml, then 2 x 30 ml). (The 1-hexynyl product salt was extracted with 80-ml portions of ethyl acetate until no more product could be extracted, as determined by tlc.) To the combined ethyl acetate extracts, water (25 ml) was added and the mixture was acidified to pH 1 with 1 *N* hydrochloric acid. The organic layer was separated, washed with water (2 x 25 ml), dried over magnesium sulfate and evaporated *in vacuo*. The crude product was dissolved in a minimum amount of gently boiling ethyl acetate and hexanes were added to the hot solution until a slight cloudiness persisted. The mixture was heated again to obtain a solution that was allowed to cool to room temperature. Additional hexanes were added to give a total of about 60 ml. The mixture was allowed to stand at room temperature overnight and then was filtered. If further purification was needed, the product was recrystallized from diethyl ether. The yields and physical, spectral and analysis data for compounds **54**-**58** are given in Table 4.

Preparation of Di(aminobenzo)-16-crown-5-oxyacetic Acid (**61**).

Di(nitrobenzo)-16-crown-5-oxyacetic acid (**60**) (10.0 g, 20.2 mmoles) [33] was mixed with 300 ml of ethanol and 2.4 g of 5% Pd/C and then 70 ml of 85% hydrazine hydrate were added. The mixture was refluxed for 24 hours and filtered. The volume of the filtrate was reduced *in vacuo*. After standing overnight, a white solid was filtered and washed with ethanol. The filtrate was reduced in volume and yielded additional product. The yield and physical, spectral and analysis data for very hygroscopic **61** are given in Table 5.

Preparation of *sym*-(Methyl)di[4(5)-*tert*-butylbenzo]-16-crown-5-oxyacetic Acid (**63**).

Under nitrogen, 1.00 g (21.3 mmoles) of sodium hydride (60% dispersion in mineral oil) was washed three times with pentane to remove the mineral oil and was suspended in tetrahydrofuran (50 ml). To the stirred mixture, 5.3 mmoles of *sym*-(hydroxy)-(methyl)dibenzo-16-crown-5 [27] in 50 ml of tetrahydrofuran was added over a 15-minute period and the mixture was stirred for 1 hour. A solution of 1.64 g (11.8 mmoles) of bromoacetic acid in tetrahydrofuran (25 ml) was added dropwise followed by stirring at room temperature for 48 hours and then refluxing for 1 hour. Water (50 ml) was added to the cooled reaction mixture followed by addition of 6 *N* hydrochloric acid to pH 1 and stirring for 2 hours. The tetrahydrofuran was evaporated *in vacuo* and the resultant aqueous mixture was extracted with dichloromethane (3 x 10 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo* to give a crude product that was chromatographed twice on silica gel with dichloromethane-methanol (10:1) as eluent. Recrystallization from ethyl acetate-petroleum ether (bp 30-60°) (1:10) gave a white crystalline solid. The yield and physical, spectral and analysis data for **63** are given in Table 5.

Preparation of *sym*-(Propyl)di(nitrobenzo)-16-crown-5-oxyacetic Acid (**64**).

To a stirred suspension of 8.89 g (19.9 mmoles) of *sym*-(propyl)dibenzo-16-crown-5-oxyacetic acid (**15**) [14] in 80 ml of glacial acetic acid-chloroform (1:1), a solution of 13.5 ml of concentrated nitric acid and 4.5 ml of water was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 2 hours, poured into water (300 ml) and extracted with dichloromethane (2 x 150 ml). The combined dichloromethane extracts were washed with water (6 x 100 ml), dried over magnesium sulfate and evaporated to afford a yellow solid. The yield and physical, spectral and analysis data for **64** are given in Table 5.

Preparation of 1-Cyano-2-(*sym*-dibenzo-16-crown-5-oxy)-ethane (**84**).

Under nitrogen at room temperature with the exclusion of light, *sym*-(hydroxy)dibenzo-16-crown-5 (**82**) (3.00 g, 8.57 mmoles) [35] was dissolved in 30 ml of acrylonitrile. Potassium *tert*-butoxide (0.26 g, 2.34 mmoles) was added and the reaction solution was stirred for 4 hours. Hydrochloric acid (3 *N*, 60 ml) was added. The mixture was filtered and the filtrate was extracted with dichloromethane (3 x 30 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel with diethyl ether as eluent. The resultant clear oil was triturated with 2 drops of methanol to give 2.15 g (63%) of white solid with mp 116-117°: ir (deposit from dichloromethane on a sodium chloride plate): ν 2251 (C≡N), 1132 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.71-2.74 (t, 2H, J = 6Hz), 3.71-4.45 (m, 15H), 6.84-7.26 (m, 8H).

Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 66.14; H, 6.31. Found: C, 65.90; H, 6.41.

Preparation of 1-Cyano-2-(*sym*-di[4(5)-*tert*-butylbenzo]-16-crown-5-oxy)ethane (**85**).

Under nitrogen at room temperature, *sym*-(hydroxy)di[4(5)-*tert*-butylbenzo]-16-crown-5 (**83**) (0.49 g, 1.09 mmoles) [32] and potassium *tert*-butoxide (0.01 g, 0.09 mmoles) were dissolved in tetrahydrofuran (49 ml). A solution of acrylonitrile (0.29 g, 5.44 mmoles) in tetrahydrofuran (20 ml) was added over a 20-minute period. The reaction mixture was stirred for 12 hours at room temperature and the solvent was removed *in vacuo*. The brown residue was dissolved in dichloromethane (30 ml), washed with 6 *N* hydrochloric acid (20 ml), dried over magnesium sulfate and chromatographed on alumina with diethyl ether-ethyl acetate (5:1) as eluent to give 0.27 g (48%) of a clear oil; ir (neat): ν 2251 (C≡N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.14 (s, 18H), 2.51-2.69 (m, 2H), 3.54-4.45 (m, 15H), 6.51-7.02 (m, 6H).

Anal. Calcd. for $C_{30}H_{41}NO_6$: C, 70.42; H, 8.08. Found: C, 70.58; H, 8.28.

General Procedure for the Preparation of Lariat Ether Esters **86** and **87**.

Under nitrogen in a flask equipped with a fritted glass bubbler and an adapter that passed the condensate through a thimble filled with anhydrous sodium sulfate, a solution of lariat ether nitrile **84** or **85** (1.00 mmole) in methanol (100 ml) was brought to reflux. Hydrogen chloride gas was bubbled through the reaction solution for 72 hours for **84** and 12 hours for **85**. At room temperature, water (50 ml) was added. After stirring for 5 minutes, the reaction solution was extracted with dichloromethane (3 x 50 ml). The combined dichloromethane extracts were washed with water (50 ml), dried over magnesium sulfate and evaporated *in vacuo*.

Methyl 3-(*sym*-dibenzo-16-crown-5-oxy)propanoate (**86**).

Compound **86** was obtained in 94% yield as an orange oil after chromatography on silica gel with dichloromethane–diethyl ether (1:1) as eluent; ir (neat): ν 1739 (C=O), 1130 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.69-2.75 (t, 2H, J=6Hz), 3.65-4.41 (m, 18H), 6.75-7.10 (m, 8H). Combustion analyses for lariat ether ester **86** was not performed, but satisfactory combustion analysis results were obtained for lariat carboxylic acid **68**.

Methyl 3-(*sym*-di[4(5)-*tert*-butylbenzo]-16-crown-5-oxy)-propanoate (**87**.

Compound **87** was isolated in 74% yield as a brown oil after chromatography on alumina with diethyl ether as eluent; ir (neat): ν 1739 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (s, 18H), 2.70-2.79 (m, 2H), 3.69 (s, 3H), 3.80-4.48 (m, 15H), 6.78-7.18 (m, 6H).

Anal. Calcd. for $C_{31}H_{44}O_8$: C, 68.37; H, 8.14. Found: C, 68.57; H, 8.18.

General Procedure for the Preparation of Lariat Ether Carboxylic Acids **68** and **69**.

The lariat ether ester **86** or **87** (1.37 mmoles) was dissolved in 70 ml of 95% ethanol at room temperature and a solution of potassium hydroxide (0.15 g, 2.74 mmoles) dissolved in 5 ml of water was added. The reaction solution was stirred for 15 minutes and concentrated hydrochloric acid was added to pH 6. The solution was evaporated *in vacuo* and the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was dried over magnesium sulfate and evaporated *in vacuo*. The residue was recrystallized from benzene to give **68** as a white solid. Compound **69** was obtained as an oil which solidified on standing. The yields and physical, spectral and analysis data for **68** and **69** are given in Table 6.

General Procedure for the Preparation of Lariat Ether Mesylates **91**-**93**.

To a solution of 2.90 mmoles of the appropriate lariat ether alcohol [27] and 0.45 g (4.40 moles) of triethylamine in 100 ml of dichloromethane at 0° under nitrogen was added dropwise methanesulfonyl chloride (0.51 g, 4.40 mmoles) during a 30-minute period. After stirring for an additional 2 hours, water (100 ml) was added. The dichloromethane layer was separated, washed with 5% hydrochloric acid (30 ml), 5% aqueous sodium bicarbonate (30 ml), and brine (50 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the lariat ether mesylate as a colorless oil.

2-[*sym*-(Methyl)dibenzo-16-crown-5-oxy]ethyl mesylate (**91**).

Compound **91** was obtained in 90% yield; ir (neat): ν 1350 (S=O), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50 (s, 3H), 3.03 (s, 3H), 3.38-4.43 (m, 16H), 6.82-6.99 (m, 8H).

Anal. Calcd. for $C_{23}H_{30}SO_9$: C, 57.26; H, 6.27. Found: C, 56.87; H, 6.09.

3-(*sym*-Dibenzo-16-crown-5-oxy)propyl mesylate (**92**).

Compound **92** was isolated in 95% yield; ir (neat): ν 1361, 1176 (SO_2), 1251, 1140 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.85-2.15 (m, 2H), 2.95 (s, 3H), 3.81-4.52 (m, 17H), 6.81-6.98 (m, 8H).

Anal. Calcd. for $C_{23}H_{30}O_9S$: C, 57.25; H, 6.27. Found: C, 57.04; H, 6.10.

3-[*sym*-(Methyl)dibenzo-16-crown-5-oxy]propyl mesylate (**93**).

Compound **93** was obtained in 94% yield; ir (neat): ν 1353, 1174 (S=O), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (s, 3H), 1.93-2.06 (m, 2H), 2.90 (s, 3H), 3.88-4.40 (m, 16H), 6.80-6.96 (m, 8H),

Anal. Calcd. for $C_{24}H_{32}O_9S$: C, 58.06; H, 6.49. Found: C, 58.28; H, 6.25.

General Procedure for the Preparation of Lariat Ether Nitriles **94**-**96**.

To a solution of 4.10 mmoles of lariat ether mesylate **91**, **92** or **93** in dimethyl sulfoxide (30 ml) was added 0.61 g (12.4 mmoles) of sodium cyanide and the reaction mixture was stirred for 2 days at 45° for **91** and **92** and at 90° for **93**. At room temperature, diethyl ether (20 ml) and water (30 ml) were added and the mixture was shaken. The organic layer was separated, washed with water (6 x 30 ml) and brine (3 x 30 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a colorless oil.

3-[*sym*-(Methyl)dibenzo-16-crown-5-oxy]propanonitrile (**94**).

Compound **94** was obtained in 60% yield as a colorless oil after chromatography on silica gel with ethyl acetate-hexanes (1:5) as eluent; ir (neat): ν 2248 (C≡N), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.51 (s, 3H), 2.62-2.65 (t, 2H, J = 6Hz), 3.98-4.43 (m, 14H), 6.82-6.99 (m, 8H).

Anal. Calcd. for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58. Found: C, 66.88; H, 6.77.

4-(*sym*-Dibenzo-16-crown-5-oxy)butanonitrile (**95**).

Compound **95** was isolated in 74% yield as a colorless oil after chromatography on alumina with diethyl ether then diethyl ether-ethyl acetate (5:1) as eluents; ir (neat): ν 2247 (C≡N), 1124 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.99 (p, 2H), 2.55-2.58 (t, 2H, J = 6Hz), 3.70-4.45 (m, 15H), 6.72-7.05 (m, 8H).

Anal. Calcd. for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58. Found: C, 66.84; H, 6.68.

4-[*sym*-(Methyl)dibenzo-16-crown-5-oxy]butanonitrile (**96**).

Compound **96** was obtained in 84% yield as a white solid with mp 109-110° after chromatography on silica gel with ethyl acetate-hexanes (1:5) as eluent; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 2246 (C≡N), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (s, 3H), 1.86-1.97 (m, 2H), 2.50-2.53 (t, 2H, J = 6Hz), 3.85-4.31 (m, 14H), 6.82-6.99 (m, 8H).

Anal. Calcd. for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84. Found: C, 67.51; H, 6.64.

General Procedure for the Preparation of Lariat Ether Esters **97**-**99**.

Into a refluxing solution of the lariat ether nitrile **94**, **95** or **96** (1.69 mmole) in methanol (50 ml) in a flask fitted with a fritted glass bubbler and an adapter to pass the condensate through a thimble containing anhydrous sodium sulfate, hydrogen chloride gas was bubbled for 24 hours. After the methanol was evaporated *in vacuo*, water (20 ml) and ethyl acetate (30 ml) were added to the residue and the mixture was shaken. The organic layer was separated, washed with 5% aqueous sodium bicarbonate (3 x 30 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a colorless oil.

Methyl 3-[*sym*-(methyl)dibenzo-16-crown-5-oxy]propionate (**97**).

Compound **97** was obtained in 65% yield as a colorless oil after chromatography on silica gel with ethyl acetate-hexanes (1:4) as eluent; ir (neat): ν 1737 (C=O), 1122 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.52 (s, 3H), 2.62-2.65 (t, 2H, J = 6Hz), 3.67 (s, 3H), 3.70-4.24 (m, 14H), 6.81-6.99 (m, 8H).

Anal. Calcd. for $C_{23}H_{30}0_8$: C, 64.57; H, 6.77. Found: C, 64.70; H, 6.64.

Methyl 4-(*sym*-dibenzo-16-crown-5-oxy)butanoate (**98**).

Compound **98** was isolated as a tan oil in 79% yield after chromatography on silica gel with dichloromethane then diethyl ether as eluents; ir (neat): ν 1734 (C=O), 1123 (C-O) cm^{-1}; ^1H nmr deuteriochloroform: δ 1.98 (p, 2H), 2.51-2.54 (t, 2H, J = 6Hz), 3.65 (s, 3H) 3.71-4.31 (m, 15H), 6.80-7.00 (m, 8H).

Anal. Calcd. for $C_{24}H_{30}0_8$: C, 64.56; H, 6.77. Found: C, 64.72; H, 6.61.

Methyl 4-[*sym*-(methyl)dibenzo-16-crown-5-oxy]butanoate (**99**).

Compound **99** was obtained in 94% yield as a colorless oil after chromatography on silica gel with ethyl acetate-hexanes (1:4) as eluent; ir (neat): ν 1733 (C=O), 1124 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (s, 3H), 1.95 (m, 2H), 2.47-2.50 (t, 2H, J = 6Hz), 3.62 (s, 3H), 3.79-3.82 (t, 2H, J = 6Hz), 3.91-3.95 (m, 4H), 4.10-4.23 (m, 8H), 6.81-6.96 (m, 8H).

Anal. Calcd. for $C_{24}H_{32}0_8$: C, 65.20; H, 7.00. Found: C, 65.21; H, 6.99.

General Procedure for the Preparation of Lariat Ether Carboxylic Acids **70**-**72**.

A solution of the lariat ether ester **97**, **98** or **99** (102 mmoles), 0.01 g (0.25 mmoles) of potassium hydroxide and 10 ml of 95% ethanol was stirred for 1 hour at room temperature. After evaporation *in vacuo*, ethyl acetate (10 ml) and water (10 ml) were added to the residue. The aqueous layer was separated, washed with ethyl acetate (3 x 10 ml) and acidified to pH 1 with 6 *N* hydrochloric acid followed by addition of dichloromethane (10 ml). The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give a colorless oil. Compounds **70** and **72** were crystallized from benzene, while compound **71** solidified on standing. The yields and physical, spectral and analysis data for **70**-**72** are given in Table 6.

General Procedure for the Preparation of Vinylidene Dibenzo Crown Ethers **102** and **103**.

Procedure A (regular addition).

Under nitrogen, bisphenol **100** [41] or **101** [32] (2.48 mmoles) was dissolved in acetonitrile (11 ml) and cesium carbonate (1.78 g, 5.48 mmoles) was added. The mixture was heated to 80° and a solution of methallyl dichloride (0.47 g, 3.76 mmoles) dissolved in acetonitrile (5.4 ml) was added during a 30-hour period with a

syringe pump. The reaction mixture was stirred for a total of 3 days and then cooled to room temperature. A solution of 3 *N* potassium hydroxide (30 ml) was added and the mixture was extracted with dichloromethane (3 x 30 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with dichloromethane-diethyl ether (varying ratios) as eluent.

Procedure B (simultaneous addition).

The bisphenol (13.92 mmoles) was diluted to 30 ml with acetonitrile and taken up in a syringe. Methallyl dichloride (2.61 g, 20.88 mmoles) was diluted to 30 ml with acetonitrile and taken up in another syringe. The two solutions were simultaneously added with two syringe pumps during a 20-hour period to a stirred suspension of cesium carbonate (9.98 g, 30.71 mmoles) in acetonitrile (40 ml) at 80°. The reaction mixture was stirred for a total of 3 days and cooled to room temperature. A 3 *N* solution of potassium hydroxide (30 ml) was added and the mixture was extracted with dichloromethane (3 x 30 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with dichloromethane-diethyl ether (varying ratios) as eluent.

sym-(Vinylidene)dibenzo-16-crown-5 (**102**).

Compound **102** was obtained as a white solid with mp 94-95° (lit mp [42] 94-95°) in 60% yield by Procedure A and 72% yield by Procedure B; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 1661, 1120 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.83-4.04 (m, 4H), 4.11-4.31 (m, 4H), 4.77-4.80 (d, 4H,J = 8Hz), 5.44 (s, 2H), 6.75-7.10 (m, 8H).

sym-(Vinylidene)di[4(5)-*tert*-butylbenzo]-16-crown-5 (**103**).

Compound **103** was obtained as translucent colorless oil in 74% yield by Procedure A and in 55% yield by Procedure B; ir (neat): ν 1654, 1120 ($R_2C=CH_2$), 1146 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (s, 18H), 3.73-3.92 (m, 4H), 3.97-4.33 (m, 4H), 4.75-4.79 (d, 4H, J = 8Hz), 5.42-5.45 (m, 2H), 6.68-7.12 (m, 6H).

Anal. Calcd. for $C_{28}H_{38}O_5$: C, 73.98; H, 8.42. Found: C, 74.23; H, 8.31.

sym-(Hydroxymethyl)dibenzo-16-crown-5 (**104**).

Under nitrogen at 0°, to a solution of vinylidene crown ether **102** (1.55 g, 4.54 mmoles) in tetrahydrofuran (45 ml), a 1.0 *M* solution of borane-tetrahydrofuran (11.07 ml) was added dropwise over a 10-minute period. The solution was warmed to room temperature and the solution was stirred for 48 hours. After cooling to 0°, 30% hydrogen peroxide (8 ml) and then a 2 *N* sodium hydroxide solution (3 ml) were added. The solution was stirred for 24 hours at room temperature. After adding 2 *N* sodium hydroxide (51 ml), the reaction mixture was refluxed for 48 hours, cooled to room temperature and extracted with dichloromethane (3 x 30 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with ethyl acetate then ethyl acetate-methanol (15:1) as eluents. The colorless residue was recrystallized from heptane-benzene to give 0.99 g (60%) of a white solid with mp 110° (lit mp [42] 110-111°); ir (deposit from a dichloromethane solution on a sodium chloride plate): ν 3600-3200 (OH), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.48 (m, 1H), 2.77 (br s, OH, 1H), 3.71-4.45 (m, 14H), 6.65-6.95 (m, 8H).

sym-(Hydroxymethyl)di[4(5)-*tert*-butylbenzo]-16-crown-5 (**105**).

Under nitrogen at 0°, to a solution of vinylidene crown ether **103** (0.83 g, 1.82 mmoles) in tetrahydrofuran (15 ml) and sodium borohydride (0.07 g, 1.85 mmoles) was added. Then boron trifluoride-diethyl etherate (0.26 g, 18.21 mmoles) was added with a syringe and the reaction mixture was stirred for 2 hours. The mixture was allowed to warm to room temperature and was stirred for 14 hours. The mixture was cooled to 0° and ice was added until hydrogen evolution ceased. A 2 *N* sodium hydroxide solution (0.91 ml) and then 30% hydrogen peroxide (3.59 ml) were added and the mixture was warmed to room temperature. The reaction mixture was stirred for 2 days and the tetrahydrofuran was evaporated *in vacuo*. The resultant aqueous residue was extracted with dichloromethane (3 x 30 ml). The combined dichloromethane extracts were washed with 5% hydrochloric acid (20 ml), dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with diethyl ether then ethyl acetate as eluents to give 0.40 g (45%) of a low-melting, colorless solidified oil (attempted recrystallization from methanol was unsuccessful); ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3518 (OH), 1146 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (s, 18H), 2.41-2.69 (m, 1H), 2.70-2.90 (br s, 1H, OH), 3.62-4.44 (m, 14H), 6.68-7.08 (m, 6H).

Anal. Calcd. for $C_{28}H_{40}O_6 \bullet CH_3OH$: C, 69.02; H, 8.79. Found: C, 69.06; H, 8.77.

sym-(Mesyloxymethyl)dibenzo-16-crown-5 (**106**).

To a solution of lariat ether alcohol **104** (0.89 g, 2.47 mmoles) and triethylamine (0.50 g, 4.94 mmoles) in dichloromethane (22 ml) under nitrogen at -10°, a solution of mesyl chloride (0.57 g, 4.94 mmoles) in dichloromethane (22 ml) was added dropwise during a 30-minute period. The reaction mixture was stirred for 1 hour at 0° and for 15 hours at room temperature and then 5% hydrochloric acid (60 ml) was added. The mixture was extracted with dichloromethane (2 x 20 ml) and the combined dichloromethane extracts were washed with 5% sodium bicarbonate (3 x 40 ml), dried over magnesium sulfate and evaporated *in vacuo* to give 1.06 g (98%) of a cloudy, low melting, solidified oil; ir (neat): ν 1359, 1175 (SO_2), 1124 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.65-2.86 (m, 1H), 3.01 (s, 3H), 3.75-4.00 (m, 4H), 4.00-4.35 (m, 8H), 4.73-4.78 (d, 2H, J = 10Hz), 6.75-7.03 (m, 8H).

Anal. Calcd. for $C_{21}H_{26}O_8S \bullet 0.35\ CDCl_3$: C, 53.39; H, 5.53. Found: C, 53.50; H, 5.47.

(*sym*-Dibenzo-16-crown-5)ethanonitrile (**107**).

Under nitrogen at room temperature, to a solution of lariat ether mesylate **106** (0.68 g, 1.55 mmoles) in dimethyl sulfoxide (11 ml), sodium cyanide (0.23 g, 4.67 mmoles) was added. The mixture was heated to 60°, stirred for 36 hours and cooled to room temperature. Water (20 ml) was added and the solution was extracted with dichloromethane (4 x 20 ml). The dichloromethane extracts were combined, washed with 3 *N* hydrochloric acid (20 ml), dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with dichloromethane-diethyl ether (1:1) as eluent to give 0.56 g (98%) of a white solid with mp

108-109°; ir (deposit from a dichloromethane solution on a sodium chloride plate): ν 2246 (C≡N), 1123 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.55-2.78 (m, 1H), 2.94-2.99 (d, 2H, J = 6Hz), 3.75-4.05 (m, 4H), 4.05-4.37 (m, 8H), 6.69-7.09 (m, 8H).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28. Found: C, 68.19; H, 6.26.

Methyl (*sym*-Dibenzo-16-crown-5)acetate (**108**).

Under nitrogen in a flask equipped with a fritted glass bubbler and an adapter that passed the condensate through a thimble filled with anhydrous sodium sulfate, lariat ether nitrile **107** (0.20 g, 0.73 mmoles) was dissolved in methanol (80 ml). At reflux, hydrogen chloride gas was bubbled through the solution for 16 hours. The solution was cooled to room temperature and water (10 ml) was added. The mixture was stirred for 1 hour and extracted with dichloromethane (3 x 20 ml). The combined dichloromethane extracts were washed with water (10 ml), dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel with dichloromethane-diethyl ether (2:1) as eluent to give 0.29 g (98%) of a cream-colored solid with mp 87-88°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 1732 (C=O), 1122 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.70-3.02 (m, 3H), 3.69 (s, 3H), 3.70-4.05 (m, 4H), 4.05-4.35 (m, 8H), 6.69-7.09 (m, 8H).

Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.66; H, 6.47. Found: C, 65.40; H, 6.52.

(*sym*-Dibenzo-16-crown-5)acetic Acid (**74**).

Under nitrogen at room temperature, lariat ether ester **108** (0.25 g, 0.62 mmoles) was dissolved in 30 ml of 95% ethanol and 3 *N* potassium hydroxide (4.14 ml) was added. The solution was stirred for 1 hour at room temperature and evaporated *in vacuo*. The residue was dissolved in dichloromethane (30 ml) and washed with 6 *N* hydrochloric acid (30 ml). The dichloromethane solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give 0.24 g (99%) of a low-melting, white, solidified oil. Spectral and analysis data for **74** are given in Table 7.

Preparation of *sym*-(Tosyloxy)dibenzo-16-crown-5 (**109**).

Under nitrogen at room temperature, *sym*-hydroxydibenzo-16-crown-5 (**82**) (5.00 g, 14.4 mmoles) [35] and pyridine (2.96 g, 37.4 mmoles) were dissolved in 15 ml of dichloromethane. A solution of tosyl chloride (7.14 g, 37.4 moles) in dichloromethane (7.5 ml) was added over a 30-minute period. The mixture was stirred for 24 hours at room temperature and 6 *N* hydrochloric acid (50 ml) was added. The mixture was extracted with dichloromethane (2 x 30 ml). The combined dichloromethane extracts were washed with water (20 ml), dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with diethyl ether as eluent to give 7.56 g (97%) of white solid with mp 129-130°; ir (deposit): ν 1415, 1363 (SO_2), 1147 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.26 (s, 3H), 3.86-3.91 (d, 4H, J = 10Hz), 4.08-4.13 (d, 4H, J = 10Hz), 4.28-4.33 (dd, 2H, J = 3, 10Hz), 4.42-4.47 (dd, 2H, J = 3, 10 Hz), 5.09 (p, 1H), 6.59-7.05 (m, 8H), 7.31-7.35 (d, 2H, J = 8Hz), 7.90-7.94 (d, 2H, J = 8Hz).

Anal. Calcd. For $C_{26}H_{28}O_8S \bullet 0.5H_2O$: C, 61.29; H, 5.74. Found: C, 61.61; H, 5.75.

Preparation of *sym*-(Bromo)dibenzo-16-crown-5 (**110**).

Under nitrogen, lariat ether tosylate **109** (2.83 g, 5.65 mmoles), lithium bromide (4.91 g, 56.5 moles) and water (3.5 ml) were dissolved in hexamethylphosphoramide (80 ml). The solution was stirred at 100° for 16 hours and then cooled to room temperature. After addition of 6 *N* hydrochloric acid (100 ml), the mixture was extracted with dichloromethane (2 x 40 ml). The combined dichloromethane extracts were washed with 6 *N* hydrochloric acid (2 x 100 ml), dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with dichloromethane as eluent to give 1.91 g (83%) of white solid with mp 83-84°; ir (deposit from a dichloromethane solution on a sodium chloride plate): ν 1126 (C-O), 748 (C-Br) cm^{-1}, ^1H nmr (deuteriochloroform): δ 3.84-3.87 (t, 4H, J = 6Hz), 4.09-4.12 (t, 4H, J = 6Hz), 4.21-4.55 (m, 2H), 4.55-4.68 (m, 3H), 6.79-7.05 (m, 8H).

Anal. Calcd. for $C_{19}H_{21}O_5Br \bullet 1.3CH_2Cl_2$: C, 46.91; H, 4.58. Found: C, 46.84; H, 4.52.

Preparation of 3-(*sym*-Dibenzo-16-crown-5)propanoic Acid (**75**).

Under deoxygenated nitrogen in a 10-ml pyrex flask, lariat ether bromide **110** (0.18 g, 0.43 mmoles) was dissolved in 2 ml of deoxygenated tetrahydrofuran and freshly distilled acrylic acid (0.030 g, 0.43 mmoles) was added. The reaction mixture was irradiated with a 500-watt sun lamp placed 20 cm from the reaction vessel and tributyltin hydride (0.13 g, 0.43 mmoles) was added during a 5-hour period with a syringe pump. The reaction solution was stirred overnight at room temperature in the dark. A solution of acrylic acid (0.030 g, 0.43 mmoles) in tetrahydrofuran (2 ml) was added. The reaction solution was irradiated again and tributyltin hydride (0.13 g, 0.43 mmoles) was added during a 6-hour period with a syringe pump. Dichloromethane (30 ml) was added and the mixture was washed with 5% sodium bicarbonate (25 ml) and 3 *N* hydrochloric acid (25 ml). The solvent was evaporated *in vacuo* and the brown residue was subjected to radial chromatography on a silica gel plate using dichloromethane, diethyl ether-dichloromethane (1:1), diethyl ether, then diethyl ether-methanol (1:1) as eluents to give a white solid. The solid was dissolved in dichloromethane (50 ml) and extracted with 10% sodium hydroxide (5 x 20 ml). The combined sodium hydroxide extracts were acidified with concentrated hydrochloric acid to pH 1 and extracted with dichloromethane (3 x 30 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo* to give a white solid. Spectral and analysis data for **75** are given in Table 7.

General Procedure for the Preparation of Lariat Ether Esters **111** and **112**.

To a solution of lariat ether alcohol **104** or **105** (2.61 mmoles) dissolved in tetrahydrofuran (24 ml) under nitrogen at room temperature was added sodium hydride (0.063 g, 2.61 mmoles, 60% dispersion in mineral oil) suspended in tetrahydrofuran (1 ml). After hydrogen evolution ceased, a solution of ethyl bromoacetate (0.44 g, 2.61 mmoles) in tetrahydrofuran (3 ml) was added dropwise over a 10-minute period. The reaction mixture was stirred for 3 hours, refluxed for 5 minutes and cooled to room temperature. Sodium hydride (0.63 g, 2.61 mmoles, 60% dispersion in mineral oil) and a solution of ethyl bromoacetate (0.44 g, 2.61 mmoles) tetrahydrofuran (3 ml) were added. The reaction mixture was refluxed for 2.5 hours and

then stirred for 15 hours at room temperature. Water (10 ml) was added and the solution was extracted with dichloromethane (3 x 30 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with carbon tetrachloride then diethyl ether-ethyl acetate (20:1) as eluents to give the desired product.

Ethyl α-[*sym*-dibenzo-16-crown-5-methoxy]acetate (**111**).

Compound **111** was obtained in 66% yield as a white solid with mp 96-97°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 1750 (C=O), 1122, 1139 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29-1.32 (t, 3H, J = 6Hz), 2.61-2.83 (m, 1H), 3.82-4.43 (m, 18H), 6.81-7.03 (m, 8H).

Anal. Calcd. for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found: C, 64.80; H, 6.64.

Ethyl α-[*sym*-di[4(5)-*tert*-butylbenzo]-16-crown-5-methoxy]-acetate (**112**).

Compound **112** was isolated in 40% yield as a colorless oil which solidified on standing; ir (neat): ν 1752, 1734 (C=O), 1145 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.08-1.51 (m, 21H), 2.54-2.89 (m, 1H), 3.67-4.57 (m, 18H), 6.77-7.08 (m, 6H).

Anal. Calcd. for $C_{31}H_{46}O_8 \bullet 0.25\ CH_2Cl_2$: C, 66.79; H, 8.08. Found: C, 66.85; H, 8.17.

General Procedure for the Preparation of Lariat Ether Carboxylic Acids **76** and **77**.

To a solution of lariat ether ester **111** or **112** (1.70 mmoles) in 95% ethanol (125 ml) under nitrogen at room temperature, a solution of potassium hydroxide (1.38 g, 24.6 mmoles) in water (10 ml) was added. The solution was stirred for 9 hours at room temperature and then acidified to pH 2 with concentrated hydrochloric acid. The ethanol was evaporated *in vacuo* and dichloromethane (30 ml) was added. The dichloromethane layer was washed with water (20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the desired product. Yields and physical, spectral and analysis data for **76** and **77** are given in Table 7.

General Procedure for the Preparation of Lariat Ether Amines **113** and **114**.

To a solution of lariat ether nitrile **84** or **85** (2.50 mmoles) in tetrahydrofuran (30 ml) under nitrogen, borane-methyl sulfide complex (0.57 g, 7.50 mmoles) was added with a syringe during a 10-minute period. The solution was stirred for 3 hours at room temperature for **84** and refluxed for 3 days for **85**. The methyl sulfide was removed by distillation and the liquid residue was stirred for 48 hours at room temperature. After cooling to 0°, 6 *N* hydrochloric acid (15 ml) was added. The solution was refluxed for 1 hour then cooled to 0° and 20% aqueous sodium hydroxide was added to pH 11. The solution was extracted with dichloromethane (2 x 50 ml) and the combined extracts were washed with 5% hydrochloric acid (30 ml) and 10% aqueous sodium bicarbonate (30 ml) and dried over magnesium sulfate. The solvent was evaporated *in vacuo* to give a waxy solid that was used without further purification.

1-Amino-3-(*sym*-dibenzo-16-crown-5-oxy)propane (**113**).

Compound **113** was obtained in 54% yield as a waxy white solid; ir (neat): ν 3445, 3194, 1595 (NH), 1134 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.87-2.04 (m, 2H), 3.01-3.20 (m, 2H), 3.75-4.35 (m, 15H), 6.51-7.05 (m, 10H).

1-Amino-3-(*sym*-di[4(5)-*tert*-butylbenzo]-16-crown-5-oxy)propane (**114**).

Compound **114** was isolated in 40% yield as a pale green wax; ir (neat) ν 3389, 1600, 805 (NH), 1147 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (s, 18H), 2.01-2.04 (t, 2H, J = 6Hz), 3.15-3.18 (t, 2H, J = 6Hz), 3.71-4.45 (m, 15H), 6.69-7.02 (m, 6H), 7.58 (m, 2H).

Although combustion analyses were not obtained for lariat ether amines **113** and **114**, satisfactory combustion analysis results were obtained for lariat ether diesters **115** and **116**, respectively, which were prepared from these precursors.

General Procedure for the Preparation of Lariat Ether Diesters **115** and **116**.

Under nitrogen, to a solution of lariat ether amine **113** or **114** (2.00 mmoles) and potassium carbonate (1.37 g, 9.94 mmoles) in acetonitrile (83 ml), a solution of ethyl bromoacetate (0.99 g, 5.96 mmoles) in acetonitrile (2 ml) was added during a 10-minute period. The reaction mixture was stirred for 48 hours at room temperature and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (30 ml), washed with water (2 x 50 ml), dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina with diethyl ether-ethyl acetate (1:1) as eluent to give a clear oil.

1-[*N*,*N*-Di(ethylaceto)amino-3-(*sym*-dibenzo-16-crown-5-oxy)]propane (**115**).

Compound **115** was obtained in 98% yield; ir (neat): ν 1747 (C=O), 1147 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25-1.28 (t, 6H, J = 6Hz), 1.84 (p, 2H), 2.91-2.94 (t, 2H, J = 6Hz), 3.58 (s, 4H), 3.79-4.45 (m, 19H), 6.81-7.01 (m, 8H).

Anal. Calcd. for $C_{30}H_{41}NO_{10}$: C, 62.59; H, 7.18. Found: C, 62.50; H, 7.16.

1-[*N*,*N*-Di(ethylaceto)amino-3-(*sym*-di[4(5)-*tert*-butylbenzo]-16-crown-5-oxy)]propane (**116**).

Compound **116** was isolated in 62% yield; ir (neat): ν 1745 (C=O), 1147 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.13-1.19 (m, 24H), 1.77 (p, 2H), 2.83-2.87 (t, 2H, J = 6Hz), 3.49 (s, 4H), 3.65-4.29 (m, 19H), 6.66-6.95 (m, 6H).

Anal. Calcd. for $C_{38}H_{57}NO_{10}$: C, 66.26; H, 8.49. Found: C, 66.38; H, 8.11.

General Procedure for the Preparation of Lariat Ether Dicarboxylic Acids **80** and **81**.

Under nitrogen at room temperature, lariat ether diester **115** or **116** (2.61 mmoles) was dissolved in 95% ethanol (30 ml). A solution of 3 *N* potassium hydroxide (8.71 ml) was added and the solution was stirred for 6 hours at room temperature. After addition of 1 *N* hydrochloric acid (26.1 ml), the solution was extracted with dichloromethane (3 x 30 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated *in vacuo* to give the desired product as an oil which solidified on standing. Yields and physical, spectral and analysis data for **80** and **81** are given in Table 8.

Acknowledgements.

This work was supported by the Division of Chemical Sciences of the Office of Basic Energy Science of the U.S. Department of Energy (Grant DE-FG03-94ER14416 and earlier contracts) and by a Howard Hughes Medical Institute grant through the Undergraduate Biological Sciences Education Program to Texas Tech University.

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