Synthesis of Lipophilic Crown Ethers with Pendant Carboxylic Acid Groups

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Synthetic routes to thirteen highly lipophilic crown ether carboxylic acids are described. Seven contain 12-15-membered crown ether units with four ring oxygens and are designed for lithium ion complexation. Three others possess large ring 24-crown-8, 27-crown-9, and 30-crown-10 units. Six new hydroxymethyl crown ethers are prepared as synthetic intermediates.

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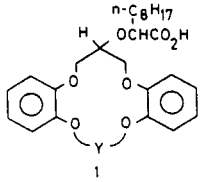
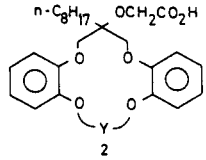
Crown ethers with a pendant ionizable group are efficient reagents for the solvent extraction and transport of alkali metal cations across bulk liquid and liquid surfactant (emulsion) membranes [1-8]. Compared with crown ethers which do not possess such acidic groups, the ionizable crown ethers have the distinct advantage that transport of the metal cation from the aqueous phase into the organic medium does not involve concomitant transfer of the aqueous phase anion [9]. This factor is of immense importance to potential practical applications in which the aqueous phase anions are chloride, nitrate, and sulfate. Such hard anions are very hydrophilic and distribute poorly to organic media.



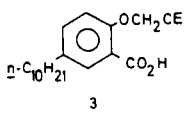
1

(Y = $CH_2CH_2CH_2$, $CH_2CH_2OCH_2CH_2$, $CH_2CH_2OCH_2CH_2OCH_2CH_2$)



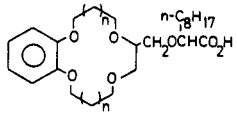
2

(Y = $CH_2CH_2OCH_2CH_2$, $CH_2CH_2OCH_2CH_2OCH_2CH_2$)

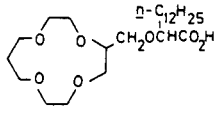


3

(CE = 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7)



n	
4	0
5	1

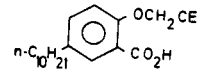


6

Previously we have described the preparation of lipophilic crown ether carboxylic acids **1-3** for which the dominant crown ether ring sizes are 15-21-membered polyether rings [6,10,11]. We now report the synthesis of lipophilic crown ether carboxylic acids **4-16** which incorporate different crown ether ring systems (predominantly smaller and larger) than those prepared earlier.

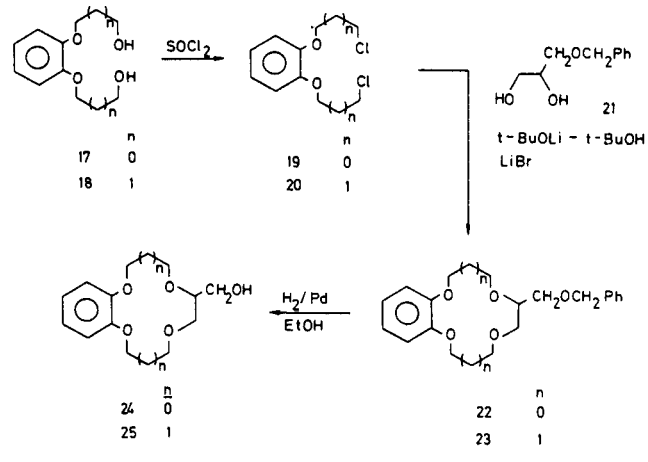
Results and Discussion.

Lipophilic crown ether carboxylic acids **4-11** contain 12-15-membered crown ether rings with four ring oxygens. Such crown ether units should favor complexation of lithium [12-16]. On the other hand, compounds **14-16** incorporate large 24-crown-8, 27-crown-9, and 30-crown-10 rings and should be appropriate for large cation complexation. Compounds **12** and **13** are closely related to previously-prepared **3** with CE = 15-crown-5 and 18-crown-6, respectively, except that one two-carbon bridge in the crown ether rings of the latter is replaced with a three-carbon bridge in the new lipophilic crown ether carboxylic acids.



	CE		CE
7	13-crown-4 (2)	**12**	16-crown-5 (3)
8	13-crown-4 (3)	**13**	19-crown-6 (2)
9	14-crown-4 (2)	**14**	24-crown-8
10	14-crown-4 (3)	**15**	27-crown-9
11	15-crown-4 (3)	**16**	30-crown-10

[(2) or (3) designates attachment through a carbon of a two carbon bridge or the central carbon of a three carbon bridge, respectively]



n	
17	0
18	1

n	
19	0
20	1

n	
24	0
25	1

n	
22	0
23	1

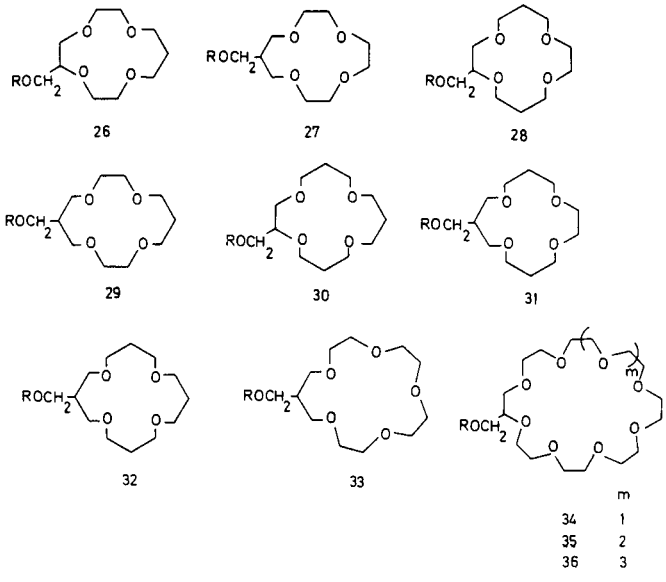
Scheme 1

Appropriate hydroxymethyl-substituted crown ethers and/or their tosylates are precursors to the lipophilic crown ether carboxylic acids **4-16**.

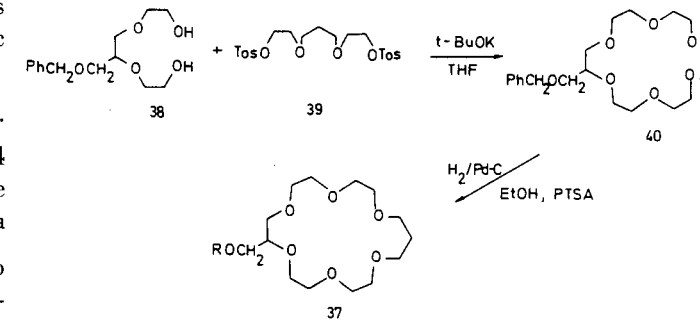
I) Synthesis of Hydroxymethyl-Substituted Crown Ethers.

For the synthesis of monobenzocrown carboxylic acids **4** and **5**, the hydroxymethyl-substituted crown ethers were prepared by the method shown in Scheme 1. The Okahara cyclization [17] of dichlorides **19** and **20** with diol **21** to form the (benzyloxy)methyl crown ethers **22** and **23** was accomplished in yields of 31% and 54%, respectively. Compounds **22** and **23** were deprotected in high yield to provide the crown ether alcohols **24** and **25**.

Hydroxymethyl-substituted crown ethers **26, 28** and **30** (with R = H) were obtained by catalytic hydrogenolysis of the corresponding (benzyloxy)methyl crown ethers (R = CH_2Ph) [15] with palladium on carbon catalyst and a trace of *p*-toluenesulfonic acid. The hydroxymethyl crown ethers **27, 29, 31, 32, 34-36** (with R = H) were available from earlier work [15,18-20]. Compound **33** (with R = H) was prepared according to the literature procedure [21].



The synthetic route to hydroxymethyl-19-crown-6 (**37** with R = H) is depicted in Scheme 2. Cyclization of diol **38** and ditosylate **39** with potassium *t*-butoxide in tetrahydrofuran gave a 52% yield of benzyloxymethyl-19-crown-6 (**40**). Quantitative hydrogenolysis of the protecting benzyl group of **40** was achieved with palladium on carbon catalyst and a trace of *p*-toluenesulfonic acid in ethanol to yield hydroxymethyl-19-crown-6 (**37** with R = H).

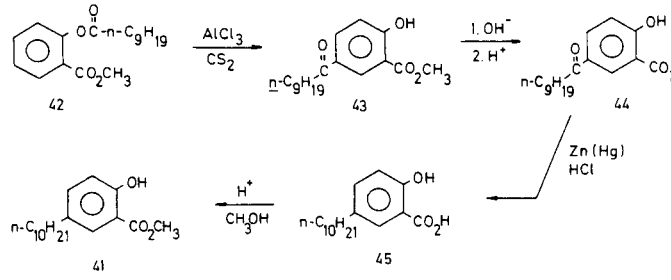


Scheme 2

II) Synthesis of Lipophilic Crown Ether Carboxylic Acids.

Hydroxymethyl crown ethers **24** and **25** (R = H) were converted into lipophilic crown ether carboxylic acids **4** and **5** by reaction with sodium hydride and 2-bromodecanoic acid in tetrahydrofuran in 63 and 47% yields, respectively. Similarly reaction of crown ether alcohol **26** (R = H) with sodium hydride and bromotetradecanoic acid in tetrahydrofuran gave a 27% yield of **6**.

The preparation of methyl 5-(*n*-decyl)salicylate (**41**), a key intermediate for the synthesis of lipophilic crown ether carboxylic acids **7-16**, is summarized in Scheme 3. Although this method was reported previously in preliminary form [6], yields for all steps have now been maximized and complete experimental details are given. Reaction of methyl 2-(*n*-decanoyloxy)benzoate (**42**) with aluminum chloride in carbon disulfide produced a 67% yield of the Fries rearrangement [22] product **43** [23]. Basic hydrolysis of **43** gave a 95% yield of 5-(*n*-decanoyl)salicylic acid [23] (**44**). Clemmensen reduction of **44** afforded 94% of 5-(*n*-decyl)salicylic acid (**45**) which was esterified in 51% yield with sulfuric acid catalyst in methanol to form methyl 5-(*n*-decyl)salicylate (**41**).



Scheme 3

Tosylates **26-36** (R = Tos) were prepared from the corresponding hydroxymethyl crowns (**23-36** with R = H) by reaction with *p*-toluenesulfonyl chloride in pyridine. The water solubility of tosylates **34-36** (R = Tos) required the use of a special work-up procedure.

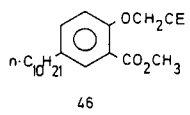
In earlier work, tosylates of hydroxymethyl-12-crown-4, -15-crown-5, -18-crown-6, and -21-crown-7 were coupled with methyl 5-(*n*-decyl)salicylate (**41**) by treatment of the ester with sodium hydride in tetrahydrofuran followed by addition of the hydroxymethyl crown tosylate and reaction at room temperature and then at reflux [6]. Good yields

(58-78%) of the lipophilic crown ether esters **46** (CE = 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7) were obtained [6]. Application of this procedure to tosylates of the large ring crowns **34-36** (R = Tos) gave **46** with CE = 24-crown-8, 27-crown-9, 30-crown-10 in yields of 77, 73, and 74%, respectively.

Although (tosyloxy)methyl-13-crown-4 (**26**, R = Tos) gave a 54% yield of **46** with this procedure, the coupling product yield for the structural isomer **27** (R = Tos), after hydrolysis of **46** to **7**, was only 23%. A significant amount of elimination product **47** was also isolated. Similarly, (tosyloxy)methyl-14-crown-4 (**28**, R = Tos) gave only a 28% yield of coupling product **46** and a 22% yield of the novel methylene-substituted 14-crown-4 compound **48**. (A small amount of the analogous methylene-substituted 15-crown-5 compound **49** was also isolated as a by-product in the previously-reported coupling [6] of salicylate ester **41** with (tosyloxy)methyl-15-crown-5). The problem of competitive elimination was also encountered with (tosyloxy)-methyl-16-crown-5 (**37**, R = Tos) which produced the methylene-substituted 16-crown-5 compound **50** [21] and a 45% yield of coupling product **46**.

We propose that such enhanced propensity for competing elimination results from sodium ion complexation by the polyether portion of the (tosyloxy)methyl crown which acidifies the beta-hydrogen and thereby facilitates the elimination reaction. Since potassium cations should be too large for complexation by the polyether framework, change of the base from sodium hydride to potassium hydride might be expected to favor the coupling process. In agreement, reactions of salicylate ester **41** with potassium hydroxide and then (tosyloxy)methyl-14-crown-4 **29** (R = Tos) or (tosyloxy)methyl-15-crown-4 **31** (R = Tos) gave 45 and 61% yields, respectively, of coupling product **46**. However even with the use of potassium hydride, the coupling of salicylate ester **41** with (tosyloxy)methyl-15-crown-4 (**30**, R = Tos) and with (tosyloxy)methyl-16-crown-4 (**32**, R = Tos) could not be achieved. To demonstrate that substitution could in fact be accomplished for such compounds with a less basic nucleophile, reaction of sodium 1-butanethiolate with **32** (R = Tos) in tetrahydrofuran was conducted and found to produce a 45% yield of substitution product **51**.

Base-catalyzed hydrolysis of the crown ether esters **46** described above with sodium hydroxide in aqueous ethanol followed by acidification proceeded in high yields to give the lipophilic crown ether carboxylic acids **7-16**.



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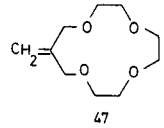

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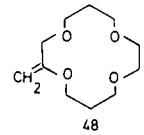

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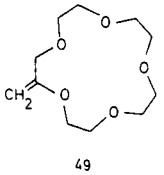

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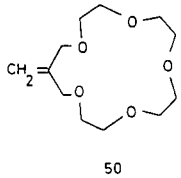

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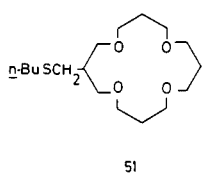

51

EXPERIMENTAL

The ir spectra were obtained on neat samples (unless specified otherwise) with a Nicolet MX-S spectrometer. The ^{1}H nmr spectra were recorded with Varian EM360A or EM360 spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Melting points were taken with either a Mel-Temp or Fisher-Johns melting point apparatus and are uncorrected. Elemental analysis was performed by Galbraith Laboratories, Inc., of Knoxville, Tennessee.

Unless specified otherwise reagent grade reactants and solvents were obtained from chemical suppliers and used as received. Tetrahydrofuran and *n*-pentane were purified by distillation from lithium aluminum hydride. Pyridine was dried over potassium hydroxide pellets. Compounds **17** [24], **20** [25], **21** [26,27], **33** (R = H) [21], **38** [28,29], **39** [30] and 2-bromodecanoic and 2-bromotetradecanoic acids [31] were prepared by known methods. Crown compounds available from earlier work were: **26, 28, 30** (with R = CH_2Ph) [15]; **27, 29, 31, 32** (with R = H) [16], and **34-36** (with R = H) [19-21].

o-Bis[(2-chloroethyl)oxy]benzene (**19**).

Thionyl chloride (16.05 g, 0.135 mole) was added dropwise to a stirred and refluxing solution of *o*-bis[(2-hydroxyethyl)oxy]benzene (**17**) (12.00 g, 0.06 mole) and 10.4 ml of pyridine in 50 ml of dry benzene and the mixture was refluxed for 20 hours. After cooling, the mixture was acidified with 9% hydrochloric acid and the benzene layer was separated. The aqueous solution was extracted with benzene (20 ml) and the combined organic layers were washed with water and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* afforded a crude product which was chromatographed on alumina with 30-60° petroleum ether-ethyl acetate (5:1) as eluent to give 11.50 g (82%) of white crystals: mp 54.5°-56°; ir (deposit): 1257, 1126, 1033 cm^{-1} (C-O); nmr (deuteriochloroform): δ 3.77 (t, 4), 4.23 (t, 4), 6.92 (s, 4).

Anal. Calcd. for $C_{10}H_{12}Cl_2O_2$: C, 51.08; H, 5.14. Found: C, 51.29; H, 5.38.

8-[(Benzyloxy)methyl]-2,3-benzo-12-crown-4 (**22**).

A published procedure for the synthesis of (benzyloxy)methyl-12-crown-4 [17] was adapted. Under nitrogen, lithium metal (1.0 g, 14.4 mmoles) was added to 260 ml of *t*-butyl alcohol. After refluxing for 1 hour, diol **21** (8.50 g, 47.0 mmoles) was added dropwise. To the cloudy heterogeneous mixture, the dichloride **19** (11.05 g, 47.0 mmoles) was added followed by lithium bromide (4.10 g, 47.0 mmoles) and water (1 ml). The reaction mixture was refluxed and stirred for 2 weeks. After removing the solvent *in vacuo*, the residue was neutralized with 6*N* hydrochloric acid and the mixture was extracted with ethyl acetate (3 x 20 ml). The combined extracts gave, after evaporation of the solvent *in vacuo*, the crude product which was chromatographed on alumina with 30-60° petroleum ether-ethyl acetate (5:1) to afford **22** (5.0 g, 31%) as a colorless oil: ir (neat): 1114 cm^{-1} (C-O); nmr (deuteriochloroform): δ 3.13-4.65 (m, 15), 6.76 (s, 4), 7.25 (s, 5).

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.55; H, 7.08.

9-[(Benzyloxy)methyl]-2,3-benzo-14-crown-4 (**23**).

Under the conditions described for the synthesis of **22**, dichloride **20** (12.3 g, 47.0 mmoles) was reacted with diol **21** (8.50 g, 47.0 mmoles). Pure **23** was isolated by column chromatography (alumina, 30-60° petroleum ether-ethyl acetate 20:1) as a colorless oil (9.2 g, 54%); ir (neat): 1116 (C-O); nmr (deuteriochloroform): δ 1.98 (pentet, 4), 3.3-4.4 (m, 13), 4.50 (s,

2), 6.91 (s, 4), 7.28 (s, 5).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.56. Found: C, 70.70; H, 7.75.

2-[(Benzyloxy)methyl]-19-crown-6 (**40**).

To a solution of diol **38** (13.5 g, 50 mmoles) in tetrahydrofuran (480 ml) was added under nitrogen potassium *t*-butoxide (12.2 g, 110 mmoles) and the mixture was stirred at room temperature for 1 hour. A solution of ditosylate **39** (26.0 g, 55 mmoles) in tetrahydrofuran (95 ml) was added dropwise during 1 hour and the reaction was stirred at room temperature for 2 days and then refluxed for an additional 24 hours. The solvent was evaporated *in vacuo* to give a residue which was chromatographed on an alumina column with 30-60° petroleum ether-ethyl acetate (2:1) as eluent. Pure **40** (11.45 g, 57%) was isolated as a colorless, viscous liquid; ir (neat: 1118 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.79 (pentet, 2), 3.3-3.9 (m, 25), 4.49 (s, 2), 7.23 (s, 5).

Anal. Calcd. for $C_{21}H_{34}O_7$: C, 63.30; H, 8.60. Found: C, 63.09; H, 8.60.

General Procedure for the Synthesis of Hydroxymethyl Crown Ethers **24-26, 28, 30, 37** (R = H).

To a solution of the (benzyloxy)methyl-substituted crown ether (13-24 mmoles) in 50 ml of ethanol was added 10% palladium on carbon (100 mg/g of crown ether) and a catalytic amount of *p*-toluenesulfonic acid. After hydrogenolysis with slightly more than 1 atmosphere for 24 hours, the catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give the product which was usually analytically pure. In some cases, final purification by column chromatography on alumina was required with ethyl acetate-methanol (20:1 or 10:1) or 30-60° petroleum ether-ethyl acetate (1:10) as eluent.

8-(Hydroxymethyl)-2,3-benzo-12-crown-4, **24** (mp 39-40°) was obtained from 4.6 g of **22** (R = CH_2Ph) in 86% yield; ir (neat): 3445 cm^{-1} (OH), 1116 cm^{-1} (C-O); nmr (deuteriochloroform): δ 2.8-4.4 (m, 14), 6.90 (s, 4).

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13. Found: C, 61.41; H, 7.31.

9-(Hydroxymethyl)-2,3-benzo-14-crown-4, **25** was prepared from 6.0 g of **23** (R = CH_2Ph) in 96% yield as a colorless oil; ir (neat): 3340 cm^{-1} (OH), 1118 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.5-2.95 (m, 5), 3.3-4.6 (m, 13), 6.90 (s, 4).

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.56; H, 7.68.

2-(Hydroxymethyl)-13-crown-4, **26** (R = H) was synthesized from 7.4 g of **26** (R = CH_2Ph) in 98% yield as a colorless oil; ir (neat): 3430 cm^{-1} (OH), 1128, 1094 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.77 (pentet, 2), 2.85 (br s, 1), 3.4-4.0 (m, 17).

Anal. Calcd. for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.34; H, 9.02.

2-(Hydroxymethyl)-14-crown-4, **28** (R = H) was obtained from 6.8 g of **28** (R = CH_2Ph) in quantitative yield as a viscous colorless liquid: ir (neat): 3435 cm^{-1} (OH), 1124, 1078 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.4-2.2 (m, 4), 2.92 (br s, 1), 2.95-4.2 (m, 17).

Anal. Calcd. for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.26; H, 9.62.

2-(Hydroxymethyl)-15-crown-4, **30** (R = H) was prepared from 4.4 g of **30** (R = CH_2Ph) in 82% yield as a colorless oil; ir (neat): 3430 cm^{-1} (OH), 1116 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.5-2.1 (pentet, 6), 2.46 (s, 1), 3.2-4.3 (m, 17).

Anal. Calcd. for $C_{12}H_{24}O_5$: C, 58.04; H, 9.74. Found: C, 58.14; H, 9.95.

2-(Hydroxymethyl)-19-crown-6, **37** (R = H) was synthesized from 8.9 g of **40** in quantitative yield as a colorless, extremely hygroscopic liquid; ir (neat): 3445 cm^{-1} (OH), 1118 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.83 (pentet, 2), 3.15 (s, 1), 3.3-3.95 (m, 25).

Anal. Calcd. for $C_{14}H_{28}O_7 \cdot 0.75\ H_2O$: C, 52.25; H, 9.24. Found: C, 52.22; H, 8.99.

General Procedure for the Synthesis of (Tosyloxy)methyl-Substituted Crown Ethers **26-33, 37** (R = Tos).

A solution of the hydroxymethyl-substituted crown ether (9-23 mmoles) in 10 ml of pyridine was cooled to -10° and a solution of *p*-toluenesulfonyl chloride (1.25 equivalents) in 10 ml of pyridine was added dropwise. The reaction mixture was kept overnight at 4° and poured over ice. After acidification with cold 6 *N* hydrochloric acid and extraction with dichloromethane, the combined extracts were washed with water and dried over magnesium sulfate. Evaporation of the solvent gave the pure tosylate.

2-[(Tosyloxy)methyl]-13-crown-4, **26** (R = Tos) was obtained from 5.0 g of **26** (R = H) as a viscous colorless liquid in 95% yield; ir (neat): 1359, 1190, 1178 cm^{-1} (SO_2), 1128, 1095 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.77 (pentet, 2), 2.43 (s, 3), 3.4-3.75 (s + m, 15), 4.05 (m, 2), 7.55 (ABq, 4).

Anal. Calcd. for $C_{17}H_{26}O_7S$: C, 54.53; H, 7.00. Found: C, 54.29; H, 7.09.

3-[(Tosyloxy)methyl]-13-crown-4, **27** (R = Tos) was prepared from 4.3 g of **27** (R = H) in 88% yield as a colorless oil: ir (neat): 1359, 1178 cm^{-1} (SO_2), 1134, 1097 cm^{-1} (C-O); nmr (deuteriochloroform): δ 2.0-2.45 (m, 1), 2.42 (s, 3), 3.2-4.2 (m, 18), 7.53 (ABq, 4).

Anal. Calcd. for $C_{17}H_{26}O_7S$: C, 54.53; H, 7.00. Found: C, 54.62; H, 7.16.

2-[(Tosyloxy)methyl]-13-crown-4, **28** (R = Tos) (mp 61-62° after recrystallization from diethyl ether-pentane) was synthesized from 4.3 g of **28** (R = H) in 92% yield: ir (deposit): 1359, 1190, 1176 cm^{-1} (SO_2), 1126, 1097 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.4-2.0 (m, 4), 2.40 (s, 3), 3.25-4.1 (m, 17), 7.55 (ABq, 4).

Anal. Calcd. for $C_{18}H_{28}O_7S$: C, 55.65; H, 7.26. Found: C, 55.52; H, 7.53.

3-[(Tosyloxy)methyl]-14-crown-4, **29** (R = Tos) (mp 79.5-81° after recrystallization from diethyl ether-pentane) was obtained from 3.65 g of **29** (R = H) in 82% yield: ir (deposit): 1359, 1178, 1192 cm^{-1} (SO_2), 1124, 1093 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.5-2.6 (m, 3), 2.43 (s, 3), 3.2-4.35 (s + m, 18), 7.55 (ABq, 4).

Anal. Calcd. for $C_{18}H_{28}O_7S$: C, 55.65; H, 7.26. Found: C, 55.66; H, 7.49.

2-[(Tosyloxy)methyl]-15-crown-4, **30** (R = Tos) (mp 76-77° after recrystallization from ethanol) was prepared from 2.3 g of **30** (R = H) in 42% yield; ir (potassium bromide): 1352, 1165 cm^{-1} (SO_2), 1113 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.4-2.1 (m, 6), 2.46 (s, 3), 3.0-4.2 (m, 17), 7.53 (ABq, 4).

Anal. Calcd. for $C_{19}H_{30}O_7S$: C, 56.70; H, 7.51. Found: C, 56.90; H, 7.75.

3-[(Tosyloxy)methyl-15-crown-4, **31** (R = Tos) (mp 78.5-80.5° after recrystallization from ethanol) was synthesized from 4.7 g of **31** (R = H) in 84% yield; ir (deposit): 1359, 1178, 1190 cm^{-1} (SO_2), 1128 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.4-2.85 (m, 5), 2.42 (s, 3), 3.15-4.35 (m, 18), 7.53 (ABq, 4).

Anal. Calcd. for $C_{19}H_{30}O_7S$: C, 56.70; H, 7.51. Found: C, 56.95; H, 7.78.

3-[(Tosyloxy)methyl]-16-crown-4, **32** (R = Tos) (mp 107-108° after recrystallization from ethanol) was obtained from 1.9 g of **32** (R = H) in 61% yield: ir (deposit): 1346, 1167 cm^{-1} (SO_2), 1114 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.5-2.4 (m, 7), 2.46 (s, 3), 3.1-4.3 (m, 18), 7.55 (ABq, 4).

Anal. Calcd. for $C_{20}H_{32}O_7S$: C, 57.67; H, 7.74. Found: C, 57.42; H, 8.00.

3-[(Tosyloxy)methyl]-16-crown-5, **33** (R = Tos) (mp 35-37° after purification of the crude tosylate by column chromatography on silica gel with dichloromethane-ethanol (50:1) as eluent) was prepared from 7.0 g of **33** (R = H) in 73% yield; ir (neat): 1357, 1190, 1176 cm^{-1} (SO_2), 1120 cm^{-1} (C-O); nmr (deuteriochloroform): δ 2.1-2.8 (m, 1), 2.45 (s, 3), 3.3-3.95 (m, 20), 4.10 (d, 2), 7.25-8.0 (m, 4).

Anal. Calcd. for $C_{19}H_{30}O_8S$: C, 54.53; H, 7.23. Found: C, 54.48; H, 7.20.

2-[(Tosyloxy)methyl]-19-crown-6, **37** (R = Tos) was synthesized from 2.0 g of **37** (R = H) in 91% yield as a pale yellow oil; ir (neat): 1359, 1190 cm^{-1} (SO_2), 1120 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.70 (pentet, 2), 2.42 (s, 3), 3.3-4.2 (m, 25), 7.51 (ABq, 4).

Anal. Calcd. for $C_{21}H_{34}O_9S$: C, 54.53; H, 7.41. Found: C, 54.44; H, 7.54.

General Procedure for the Synthesis of (Tosyloxy)methyl-Substituted Crown Ethers **34-36** (R = Tos).

To a solution of the hydroxymethyl crown ether (3.6-7.5 mmoles) in 10 ml of pyridine at -8° under nitrogen was added dropwise *p*-toluenesulfonyl chloride (1.3 equivalents) in 8 ml of pyridine. After keeping the mixture at 4° for 42 hours, a cold solution of concentrated hydrochloric acid (16 ml) and water (24 ml) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 x 10 ml). The combined extracts were dried over magnesium sulfate and evaporated *in vacuo* to give the tosylate.

2-[(Tosyloxy)methyl]-24-crown-8, **34** (R = Tos) was obtained from 2.9 g of **34** (R = H) as a colorless oil in 75% yield after purification by column chromatography on silica gel with dichloromethane-ethanol (50:1) as eluent: ir (neat): 1352, 1190 cm^{-1} (SO_2), 1114 cm^{-1} (C-O); nmr (deuteriochloroform): δ 2.35 (s, 3), 3.35-4.2 (m, 33), 7.50 (ABq, 4).

Anal. Calcd. for $C_{24}H_{40}O_{11}S$: C, 53.72; H, 7.51. Found: C, 53.47; H, 7.76.

2-[(Tosyloxy)methyl]-27-crown-9, **35** (R = Tos) was prepared from 1.5 g of **35** (R = H) as a pale yellow oil in 90% yield after purification by column chromatography on alumina with ethyl acetate-methanol (49:1) as eluent: ir (neat): 1352, 1170 cm^{-1} (SO_2), 1110 cm^{-1} (C-O); nmr (deuteriochloroform): δ 2.41 (s, 3), 3.2-4.4 (m, 37), 7.55 (ABq, 4).

Anal. Calcd. for $C_{26}H_{26}O_{12}S$: C, 53.78; H, 7.64. Found: C, 53.78; H, 7.62.

2-[(Tosyloxy)methyl]-30-crown-10, **36** (R = Tos) was synthesized from 3.5 g of **36** (R = H) in 96% yield as a pale yellow oil; ir (neat): 1357, 1178 cm^{-1} (SO_2), 1107 cm^{-1} (C-O); nmr (deuteriochloroform): δ 2.44 (s, 3), 3.3-4.3 (m, 41), 7.53 (ABq, 4).

Anal. Calcd. for $C_{28}H_{48}O_{13}S$: C, 53.83; H, 7.74. Found: C, 53.68; H, 7.81.

Crown Carboxylic Acid **4**.

After removal of the protecting mineral oil from 2.5 g (52 mmoles) of sodium hydride by washing with pentane under nitrogen, 40 ml of tetrahydrofuran was added followed by 2.65 g (10.4 mmoles) of **24** and the mixture was stirred at room temperature for 2 hours. A solution of 2-bromodecanoic acid (3.40 g, 13.5 mmoles) in tetrahydrofuran (40 ml) was added dropwise during 3 hours and the mixture was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and water (100 ml) was added to the residue. The mixture was acidified to *p*H 1 with 6 *N* hydrochloric acid and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried over magnesium sulfate and after evaporation of the solvent *in vacuo*, the crude reaction product was purified by column chromatography on silica gel with diethyl ether as eluent and gave 3.56 g of the slightly impure product as an oil which was dissolved in dichloromethane (200 ml). washed with 0.1 *N* sodium hydroxide saturated with sodium chloride (4 x 50 ml) and then with 0.1 *N* hydrochloric acid (100 ml), and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* gave **4** (2.80 g, 63%) as a colorless oil; ir (neat): 3600-2400 cm^{-1} (COOH), 1738 cm^{-1} (C=O), 1120 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.6-2.0 (m, 17), 3.4-4.4 (m, 14), 6.93 (s, 4), 10.10 (s, 1).

Anal Calcd. for $C_{23}H_{36}O_7$: C, 65.07; H, 8.55. Found: C, 65.42; H, 8.63.

Crown Carboxylic Acid **5**.

Under the conditions described above for the preparation of **4**, **25** (2.25 g, 8.0 mmoles) was reacted with 2-bromodecanoic acid (2.50 g, 10.0 mmoles) in the presence of sodium hydride (42 mmoles). The crude reaction product was dissolved in dichloromethane (150 ml), and washed with 0.1 *N* sodium hydroxide saturated with sodium chloride (4 x 50 ml) and then with 0.10 *N* hydrochloric acid (100 ml). The residue obtained after drying over magnesium sulfate and evaporation of the dichloromethane *in vacuo* was chromatographed on a silica gel column with diethyl ether-ethanol (9:1) as eluent and rechromatographed on an alumina column with diethyl ether-ethanol, (9:1), and then methanol as eluents to afford **5** (1.69 g, 47%) as a colorless oil; ir (neat): 3500-2500 cm^{-1} (COOH), 1746 cm^{-1} (C=O), 1114 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.6-2.4 (m, 21), 3.2-4.5 (m, 14), 6.90 (s, 4), 9.70 (br s, 1).

Anal. Calcd. for $C_{25}H_{40}O_7$: C, 66.35; H, 8.91. Found: C, 66.21; H, 8.80.

Crown Carboxylic Acid **6**.

Under the conditions described above for the synthesis of **4**, a solution of 2-bromotetradecanoic acid (22.6 mmoles) in 30 ml of tetrahydrofuran was added dropwise during 12 hours to a mixture of sodium hydride (100 mmoles) and 15 mmoles of **26** (R = H) in 45 ml of tetrahydrofuran at room temperature. After stirring for an additional 10 hours at room temperature, the tetrahydrofuran was evaporated *in vacuo* and water was carefully added to the residue. The mixture was acidified to *p*H = 1 with concentrated hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was purified on a short alumina column using ethyl acetate-methanol (3:1) as eluent to remove unreacted 2-bromotetradecanoic acid and then methanol to elute the product. The methanolic eluent was evaporated *in vacuo* and the residue was extracted with chloroform. The combined extracts were washed several times with water, dried over magnesium sulfate, and evaporated *in vacuo* to give 1.82 g (27%) of **6** as a pale yellow viscous oil; ir (neat): 3670-2350 cm^{-1} (COOH), 1747 cm^{-1} (C=O), 1128 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-2.1 (m, 27), 3.25-4.05 (br s, 18), 9.57 (s, 1).

Anal. Calcd. for $C_{24}H_{46}O_7$: C, 64.54; H, 10.38. Found: C, 64.29; H, 10.26.

Methyl 2-(*n*-Decanoyloxy)benzoate (**42**).

Decanoyl chloride (82 g, 0.43 mole) and methyl salicylate (61 g, 0.40 mole) were heated together at 200° for 6 hours and then left at room temperature overnight. The reaction mixture was dissolved in 400 ml of benzene-diethyl ether (1:1, v/v), washed with 5% aqueous sodium bicarbonate and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* gave a crude product which was vacuum distilled to afford 101 g (82%) of **42** as a colorless oil with bp 142-144°/0.2 Torr (lit [24] 217-219°/12 Torr): ir (neat): 1766, 1730 cm^{-1} (C=O); nmr (deuteriochloroform): δ 0.8-2.35 (m, 19), 2.65 (t, 2), 3.87 (s, 3), 6.95-8.25 (m, 4).

Methyl 5-(*n*-Decanoyl)salicylate **43**.

A literature procedure for the preparation of methyl 5-(*n*-hexanoyl)salicylate [22] was adapted and modified. To a mechanically-stirred suspension of anhydrous aluminum chloride (70 g, 0.52 mole) in 200 ml of carbon disulfide was slowly added 80 g (0.26 mole) of **42**. The mixture was heated to reflux and stirred for 2 hours. The solvent was distilled and the residue was heated at 90-100° for 0.5 hours. After cooling to room temperature, water (150 ml) and diethyl ether (300 ml) were added to the hardened mass. The organic layer was separated and evaporated to half volume which precipitated white crystals. The crystals were filtered and filtrate was evaporated to half volume to give a second crop of white crystals for a 54 g (67%) yield of **4** with mp 65-66° (lit [23] mp 66.5-67.5°): ir (potassium bromide): 3170 cm^{-1} (OH), 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 0.6-2.1 (m, 17), 2.91 (t, 2), 4.00 (s, 3), 7.00 (d, 1), 8.08 (dd, 1), 8.46 (d, 1).

4(*n*-Decanoyl)salicylic Acid (**44**).

To 150 g (0.49 mole) of **43** was added 1.34 liter of 15% aqueous sodium hydroxide and the mixture was refluxed for 20 hours. Upon acidification with 6 *N* hydrochloric acid, the product precipitated. Drying under vacuum produced 153 g (53%) of **44** with mp 120-122° (lit [24] mp 120.5-121.5°); ir (mull): 3400-2600 cm^{-1} (COOH, OH), 1683, 1672 cm^{-1} (C=O); nmr (hexadeuterioacetone): δ 0.6-1.9 (m, 17), 2.95 (t, 2), 6.98 (d, 1), 8.13 (dd, 1), 8.95 (br s, 2).

4-(*n*-Decyl)salicylic Acid (**45**).

Mossy zinc (250 g) was covered with 300 ml of water containing 5.0 g of mercuric chloride. After occasional agitation for 30 minutes, the liquid was decanted and the amalgamated zinc was washed with water. To the amalgamated zinc was added 500 ml of 6 *N* hydrochloric acid followed by a mixture of **44** (54 g, 0.18 mole) and ethanol (200 ml). The mixture was refluxed with stirring for 5 hours. Toluene (200 ml) was added and, after stirring for 10 minutes, the organic layer was separated and washed with water (3 x 200 ml). Evaporation of the solvent *in vacuo* afforded 48 g (95%) of **45** as white crystals with mp 89-91° (from 90-120° petroleum ether) [32].

Methyl 5-(*n*-Decyl)salicylate (**41**).

To 14.5 g (52 mmoles) of **45** dissolved in 150 ml of methanol was added 1 ml of concentrated sulfuric acid and the solution was refluxed over-

night. Most of the solvent was evaporated *in vacuo* and the residue was poured into an ice-water mixture. After extraction with diethyl ether (3 x 50 ml), the combined extracts were washed with saturated aqueous sodium bicarbonate and then water and dried over magnesium sulfate. Evaportion of the solvent *in vacuo* gave the crude ester which was purified on a short silica gel column with benzene as eluent to provide 7.8 g (51%) of **41** with mp 27-28° [32].

General Procedure for Synthesis of Crown Ether Carboxylic Acids **7-16**.

Under nitrogen, sodium hydride (1.25 equivalents) was washed with pentane to remove the protecting mineral oil and 10 ml of tetrahydrofuran was added. To the suspension, 3.4-10.7 mmoles of **41** in 15 ml of tetrahydrofuran was added slowly. After stirring at room temperature for 1 hour, a solution of the crown ether tosylate (1.0 equivalent) in 10 ml of tetrahydrofuran was added and the mixture was refluxed for 72 hours. The solvent was evaporated *in vacuo*, water (10 ml) was added and the mixture was extracted with dichloromethane (2 x 15 ml). The combined extracts were dried over magnesium sulfate, the solvent was evaporated, and the residue was purified by column chromatography on alumina using 30-60° petroleum ether-ethyl acetate as eluent. The resultant methyl ester **46** was dissolved in 20 ml of ethanol and 10 ml of 15% sodium hydroxide was added. The solution was refluxed for 4 hours, the solvent was removed *in vacuo*, and the residue was acidified with 6 *N* hydrochloric acid. The mixture was extracted with dichloromethane (2 x 20 ml) and the combined extracts were washed with water (2 x 10 ml) and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* gave the analytically pure crown carboxylic acid.

Preparation of **7** involved coupling of 10.0 mmoles of **26** (R = Tos) with **41** to give a 54% yield of **46** (CE = 13C4) as a colorless liquid: ir (neat): 1732, 1709 cm^{-1} (C=O), 1132, 1082 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-2.0 (m, 21), 2.53 (t, 2), 3.4-4.3 (m, 20), 6.8-7.7 (m, 3). Basic hydrolysis of **46** (4.0 mmoles) gave **7** (1.77 g, 92%) as a white amorphous solid, mp 46-48° after recrystallization from diethyl ether-pentane: ir (neat): 3500-2400 cm^{-1} (COOH), 1732 cm^{-1} (C=O), 1128, 1086 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-2.0 (m, 21), 2.59 (t, 2), 3.5-3.9 (m, 15), 4.30 (d, 2), 6.9-7.45 (m, 2), 7.98 (d, 2).

Anal. Calcd. for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23. Found: C, 67.24; H, 9.42.

Preparation of **8** by coupling 10.7 mmoles of **27** (R = Tos) with **41** produced **46** (CE = 13C4) in 43% yield as a low melting white solid (mp <30°); ir (neat): 1732, 1709 cm^{-1} (C=O), 1124, 1082 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.65-1.7 (m, 19), 2.15-2.8 (m, 3), 3.2-4.15 (m, 19), 6.7-7.6 (m, 3). Hydrolysis of **46** (2.5 mmoles) gave **8** (0.65 g, 54%) as a pale yellow viscous liquid; ir (neat): 3700-2300 cm^{-1} (COOH), 1728 cm^{-1} (C=O), 1124 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.65-1.75 (m, 19), 2.1-2.7 (m, 3), 3.3-4.35 (m, 18), 6.7-7.45 (m, 2), 7.90 (s, 1), 9.93 (br s, 1).

Anal. Calcd. for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23. Found: C, 67.60; H, 9.00.

Preparation of **9** from 10.0 mmoles of **28** (R = Tos) and **41** produced a 28% yield of **46** (CE = 14C4) as a colorless, viscous liquid: ir (neat): 1732, 1712 cm^{-1} (C=O), 1126 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.65-2.0 (m, 23), 2.50 (t, 2), 3.3-4.15 (m, 20), 6.7-7.65 (m, 3). [In addition, 2-methylene-14-crown-4 (**48**) was isolated in 22% yield as a colorless liquid: ir (neat): 1655, 1626 cm^{-1} (C=C), 1141, 1120, 1095 cm^{-1} (C-O); nmr (deuteriochloroform): δ 1.5-2.15 (m, 4), 3.3-4.2 (m, 16)].

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.25; H, 9.54.

Hydrolysis of 2.4 mmoles of **46** (CE = 14C4) afforded **9** in 94% yield as a pale yellow, viscous oil; ir (neat): 3650-2350 cm^{-1} (COOH), 1734 cm^{-1} (C=O), 1132 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-2.2 (m, 23), 2.60 (t, 2), 3.35-4.35 (m, 17), 6.8-7.5 (m, 2), 7.93 (d, 1), 9.90 (br s, 1).

Anal. Calcd. for $C_{28}H_{46}O_7$: C, 67.99; H, 9.37. Found: C, 68.08; H, 9.55.

Preparation of **10** involved reaction of **29** (R = Tos) (10.0 mmoles), **41** (10.0 mmoles), and potassium hydride (12.5 mmoles) to form **46** (CE = 14C4) in 45% yield as a pale yellow oil which solidified upon storage, mp 34-35°; ir (neat): 1732, 1709 cm^{-1} (C=O), 1126, 1080 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.65-2.75 (m, 24), 2.4-4.2 (m, 21), 6.7-7.65 (m, 3). Hydrolysis of **46** (4.5 mmoles) gave **10** in 90% yield as a pale yellow oil which solidified upon storage, mp 44-46°C; ir (neat): 3600-2300 cm^{-1} (COOH), 1728 cm^{-1} (C=O), 1126 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-2.8 (m, 24), 3.5-4.4 (m, 18), 6.8-8.0 (m, 3), 9.45 (br s, 1).

Anal. Calcd. for $C_{28}H_{46}O_7$: C, 67.99; H, 9.37. Found: C, 68.15; H, 9.50.

Preparation of **11** utilized reaction of **30** (R = Tos) (10.0 mmoles), **41** (10.0 mmoles), and potassium hydride (12.5 mmoles) to produce **46** (CE = 15C4) in 61% yield as a viscous colorless liquid; ir (neat): 1732, 1710 cm^{-1} (C=O), 1126 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-2.8 (m, 26), 3.45-4.35 (m, 21), 6.75-7.55 (m, 3). Hydrolysis of **46** (3.9 mmoles) provided **11** in 86% yield as a viscous, pale yellow oil; ir (neat): 3600-2300 cm^{-1} (COOH), 1730 cm^{-1} (C=O), 1126 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.65-2.7 (m, 26), 3.35-4.35 (m, 18), 6.8-8.0 (m, 3), 10.05 (br s, 1).

Anal. Calcd. for $C_{29}H_{48}O_7$: C, 68.47; H, 9.51. Found: C, 68.38; H, 9.75.

Preparation of **12** involved reaction of **33** (R = Tos) (7.0 mmoles), **41** (7.0 mmoles), and potassium hydride (7.25 mmoles) to give **46** (CE = 16C5) in 45% yield as a viscous colorless oil; ir (neat): 1732, 1709 cm^{-1} (C=O), 1122 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-1.9 (m, 19), 2.3-2.8 (m, 3), 6.75-7.65 (m, 3). Hydrolysis of **46** (2.9 mmoles) gave **12** in 91% yield as a colorless oil; ir (neat): 3600-2400 cm^{-1} (COOH), 1727 cm^{-1} (C=O), 1118 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.65-1.9 (m, 19), 2.3-2.8 (m, 3), 3.5-4.0 (m, 20), 4.35 (d, 2), 6.85-7.5 (m, 2), 7.97 (br s, 1).

Anal. Calcd. for $C_{29}H_{48}O_8$: C, 66.39; H, 9.22. Found: C, 66.40; H, 9.18.

Preparation of **13** by coupling 5.3 mmoles of **37** (R = Tos) with **41** gave **46** (CE = 19C6) in 76% yield as a colorless liquid; ir (neat): 1732, 1709 cm^{-1} (C=O), 1120 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-2.05 (m, 21), 2.55 (t, 2), 3.35-4.2 (m, 28). Hydrolysis of **46** (3.7 mmoles) gave **13** in 94% yield as a pale yellow oil; ir (neat): 3275 cm^{-1} (COOH), 1735 cm^{-1} (C=O), 1120 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-2.05 (m, 21), 2.56 (t, 2), 3.3-4.4 (m, 25), 6.8-7.4 (m, 2), 7.90 (d, 2).

Anal. Calcd. for $C_{31}H_{52}O_9$: C, 65.47; H, 9.22. Found: C, 65.25; H, 9.31.

Preparation of **14** involved coupling of 3.6 mmoles of **34** (R = Tos) with **41** to form **46** (CE = 24C8) in 77% yield as a viscous colorless liquid; ir (neat): 1732, 1709 cm^{-1} (C=O), 1116 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-1.7 (m, 19), 2.53 (t, 2), 3.4-4.2 (m, 36), 6.75-7.65 (m, 3). Hydrolysis of **46** (2.6 mmoles) gave **14** in 90% yield as a pale yellow oil: ir (neat): 3270 cm^{-1} (COOH), 1732 cm^{-1} (C=O), 1116 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-1.8 (m, 19), 2.55 (t, 2), 3.3-4.4 (m, 33), 6.8-7.9 (m, 3), 10.00 (br s, 1).

Anal. Calcd. for $C_{34}H_{58}O_{11}$: C, 63.53; H, 9.09. Found: C, 63.29; H, 9.20.

Preparation of **15** utilized coupling of 3.4 mmoles of **35** (R = Tos) with **41** to give **46** (CE = 27C9) in 73% yield as a colorless oil; ir (neat): 1732 cm^{-1} (C=O), 1113 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-1.8 (m, 19), 2.60 (t, 2), 3.4-4.2 (m, 40), 6.84 (d, 1), 7.19 (dd, 1), 7.53 (d, 1). Hydrolysis of **46** (2.45 mmoles) give **15** in quantitative yield as a colorless oil; ir (neat): 3269 cm^{-1} (COOH), 1732 cm $^{-1}$ (C=O), 1113 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-1.8 (m, 19), 2.4-2.8 (m, 2), 3.3-4.5 (m, 37), 6.96 (d, 1), 7.30 (dd, 1), 7.90 (d, 1).

Anal. Calcd. for $C_{36}H_{62}O_{12}$: C, 62.95; H, 9.10. Found: C, 62.97; H, 9.38.

Preparation of **16** involved coupling of 4.8 mmoles of **36** (R = Tos) with **41** to produce **46** (CE = 30C10) as a colorless oil in 74% yield; ir (neat): 1730 cm^{-1} (C=O), 1113 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-1.8 (m, 19), 2.55 (t, 2), 3.2-4.3 (m, 44), 6.83 (d, 1), 7.19 (dd, 1), 7.51 (d, 1). Hydrolysis of **46** (3.6 mmoles) gave crude **16** which was purified on an alumina column with ethyl acetate-methanol (3:1) as eluent to afford **16** as a colorless oil in 71% yield; ir (neat): 3273 cm^{-1} (COOH), 1732 cm^{-1} (C=O), 1113 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.7-1.8 (m, 19), 2.60 (t, 2), 3.3-4.5 (m, 41), 6.96 (d, 1), 7.29 (dd, 1), 7.89 (d, 1).

Anal. Calcd. for $C_{38}H_{66}O_{13}$: C, 62.44; H, 9.10. Found: C, 62.13; H, 9.26.

Methylene-15-crown-5 (**49**).

Compound **49** was isolated as the elimination product in the previously-reported [6] reaction of **41**, (tosyloxy)methyl-15-crown-5, and sodium hydride in 12% yield as a colorless liquid; ir (neat): 1633 cm^{-1} (C=C), 1114 cm^{-1} (C-O); nmr (deuteriochloroform): δ 3.35-4.2 (s + m, 2).

Anal. Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.67; H, 8.86.

3-(*n*-Butylthio)methyl-16-crown-4 (**51**).

To sodium hydride (50% dispersion in mineral oil, 0.06 g, 1.32 mmoles) in 4 ml of tetrahydrofuran was added 0.11 g (1.22 mmoles) of

n-butanethiol dissolved in 4 ml of tetrahydrofuran. After stirring for 2 hours, 0.50 g (1.20 mmoles) of **31** (R = Tos) dissolved in 4 ml of tetrahydrofuran was added dropwise during 20 minutes and the mixture was refluxed for 50 hours. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was chromatographed on two alumina columns with 30-60° petroleum ether-ethyl acetate (90:10 and then 98:2) as eluents to give **51** (0.18 g, 45%) as a colorless oil; ir (neat): 1124 cm^{-1} (C-O); nmr (deuteriochloroform): δ 0.6-2.2 (m, 14), 2.2-2.8 (m, 4), 3.0-4.0 (m, 16).

Anal. Calcd. for $C_{17}H_{34}O_4S$: C, 61.04; H, 10.24. Found: C, 61.28; H, 10.07.

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