Synthesis of New Proton-Ionizable and Neutral Macrocyclic, Macrobicyclic and Macrotricyclic Crown Compounds Containing Dibenzo-16-crown-5 Units

Sadik Elshani*[a,b], Michael X. B. Xia [a], Chien M. Wai [a], and N. R. Natale [a], Rexford W. Widener [c], and Richard A. Bartsch [b]

[a] Department of Chemistry, University of Idaho, Moscow, ID 83844-2343
[b] Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061
[c] College of Southern Idaho, 315 Falls Avenue, PO Box 1238, Twin Falls, ID 83383

Received January 22, 1997
Revised August 10, 1998

Fifteen new macrocyclic, macrobicyclic and macrotricyclic crown ether compounds with *sym*-dibenzo-16-crown-5 units have been prepared. The series includes macrocyclic polyether and bis(crown ether) compounds with proton-ionizable carboxylic or phosphonic acid monoethyl ester groups and bis(crown ether) and macrotricyclic polyether compounds with two *sym*-dibenzo-16-crown-5 units linked by amide, diamide, or diester functions.

J. Heterocyclic Chem., **35**, 1381 (1998).

Introduction.

Lariat ethers are based on crown ethers and have secondary coordination sites bound to the macroring by flexible side arms. Lariat ethers have been designed to enhance the cation binding ability of crown ethers and also partly to mimic the dynamic complexation processes shown by natural macrocyclic ligands [1]. In addition, side arms have been attached to crown ethers to provide additional lipophilicity or as a linkage to a support or polymer [2-7]. The ^{13}C nmr spectroscopic studies [1,8] and X-ray diffraction analysis [1,9] provide evidence for participation of the lariat ether side arms in metal ion complexation.

Recently there has been considerable interest in macrocyclic compounds which contain protonionizable functional groups [10]. When a proton-ionizable group is incorporated into the side arm of a lariat ether, the molecule is both a cation exchanger and a chelator [11]. Such an arrangement can provide an extraction system with greater selectivity and efficiency than one in which an organophilic acid is simply mixed with a crown ether [11]. A very important advantage of these proton-ionizable lariat ethers is that the ionized group on the side arm provides the counteranion necessary for the transport of a metal ion into an organic layer during separations by solvent extraction or transport across liquid membranes. Bartsch and coworkers have prepared a series of dibenzo crown ethers with pendant carboxylic acid groups [12,13] and we have reported a series of macrocyclic polyether compounds with hydroxamic acid groups in the side arms [14]. These macrocyclic ligands have been shown to be very efficient ligands for the extraction of alkali, alkali earth and lanthanide ions [15-28]. The selectivity and the *p*H range of extraction are influenced by the structure of the ligand.

The observation that some crown ethers form complexes involving two ligands per metal ion led several research groups to prepare and examine the properties of macrobicyclic polyethers or bis(crown ethers) [29-35], as well as macropolycyclic polyethers [36]. These macrocylces exhibit somewhat different cation-complexing properties than the corresponding monocyclic analogues. Bis(crown ethers) are able to form intramolecular sandwich complexes in which the adjacent crown ether units cooperate [30-34]. As a result of sandwich complex formation, they may exhibit remarkable selectivity toward some metal ions in crown ether-based, ion-selective electrodes [31]. Bis(crown ether) ester derivatives with a short aliphatic chain may complex particular metal cations very strongly and selectively by formation of intramolecular complexes in which the cation is sandwiched between the two adjacent crown ether rings [29-32]. Zavada and coworkers prepared a series of bis(monoazacrown ethers) and studied the effects of linker length and ring size on the stability and selectivity in their formation of sandwich complexes with alkali metal cations [33]. They noted that not only the macrocyclic polyether ring size but also the bridge length had a remarkable influence on the ligand selectivities toward alkali metal cations [33a]. Introduction of a (benzyoxy)methyl, (1-naphthyloxy)methyl, or hydroxymethyl substituent into the alkyl bridge gave a surprisingly large destabilizing effect due to symmetry violation [33b].

The present work describes the synthesis of new cyclic, bicyclic, and tricyclic crown ether compounds **1-15** which contain *sym*-dibenzo-16-crown-5 units (Figure 1). Lariat ethers are prepared with pendant alcohol, amide, amine, bromide, *O*-benzylhydroxylamine, carboxylic acid, phosphonic acid diester and monoethyl ester, or tosylate groups. The macrobicyclic polyethers include bis(crown ether) carboxylic acid **11** and bis(crown ethers) in which the bridge contains one amide group (in **12**), two amide groups (in **13**), and two ester groups (in **15**). In the

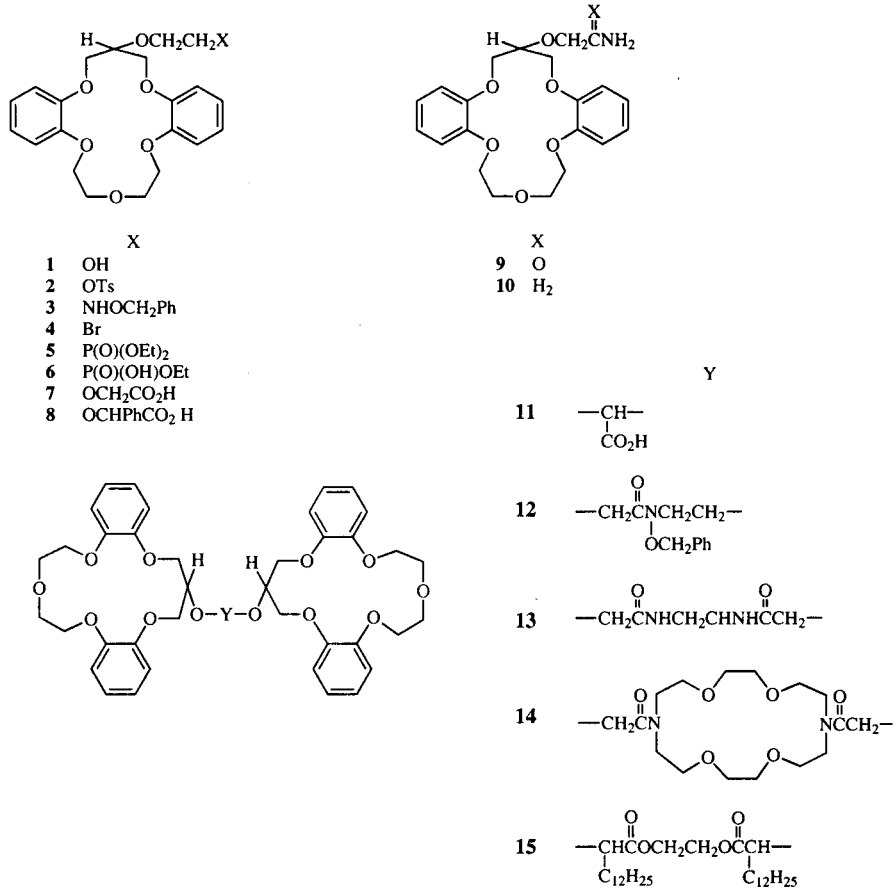
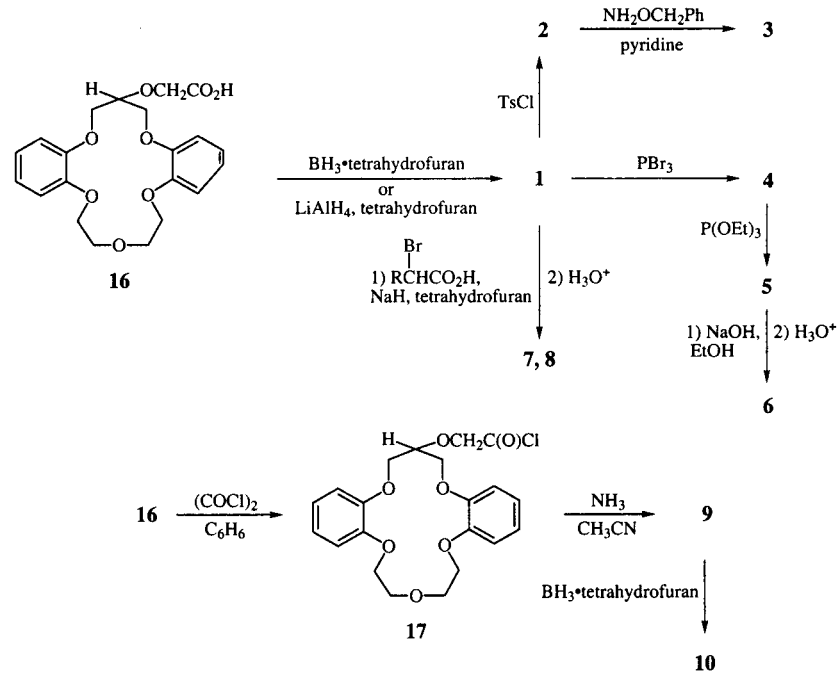


Figure1. Structures of New Compounds.

Scheme I



macrotricyclic compound **14**, two crown ether units are joined by a 1,10-diaza-18-crown-6 diamide linkage.

Results and Discussion.

The preparation of the new lariat ether compounds **1-10** is shown in Scheme I. In some cases, these lariat ethers were synthetic intermediates for the preparation of bis(crown ether) compounds.

The length of the side arm that connects the polyether ring to the ionizable group is an important parameter for proton-ionizable lariat ethers. Lariat ether carboxylic acids **7** and **8** contain two ether oxygens in the chain between the polyether ring and the carboxylic group. This compares with a single ether oxygen and a shorter chain for reported lariat ether carboxylic acids based upon *sym*-dibenzo-16-crown-5-oxyacetic acid (**16**) [15].

Lariat ether carboxylic acid **16** was reduced with borane-tetrahydrofuran complex (Method A) or lithium aluminum hydride (Method B) to produce lariat ether alcohol **1** in 90-95% yields. Reaction of **1** with the appropriate 2-bromocarboxylic acid gave lariat ether carboxylic acids **7** and **8** in 60 and 65% yields, respectively .

The multi-step synthesis of lariat ether phosphonic acid monoethyl ester **6** involved the initial preparation of lariat ether bromide **4** in 88% yield from lariat ether alcohol **1** and phosphorus tribromide. Subsequently, the lariat ether bromide **4** was reacted with triethyl phosphite to produce a 92% yield of lariat ether phosphonic acid diethyl ester **5** which, upon basic hydrolysis, gave a 46% yield of lariat ether phosphonic acid monoethyl ester **6**.

Lariat ether tosylate **2** was prepared from lariat ether alcohol **1** and *p*-toluenesulfonyl chloride in 76% yield and then reacted with *O*-benzylhydroxylamine to provide lariat ether *O*-benzylhydroxylamine **3** in 69% yield.

Reaction of known lariat ether carboxylic acid **16** with oxalyl chloride gave the corresponding lariat ether acid chloride **17** which was treated with ammonia in acetonitrile to give a 95% yield of lariat ether amide **9**. Reduction of **9** with borane-tetrahydrofuran complex produced a 68% yield of lariat ether amine **10**.

The macrobicyclic and macrotricyclic crown ether compounds were prepared as shown in Scheme II.

The bis(crown ether) carboxylic acid **11** was realized in 17% yield from the reaction of known *sym*-(hydroxy)-dibenzo-16-crown-5 (**18**) with sodium hydride and dibromoacetic acid.

Bis(crown ether) **12** with an amide group-containing linker was prepared in 65% yield from lariat ether acid chloride **17** and the lariat ether *O*-benzylhydroxylamine **3**.

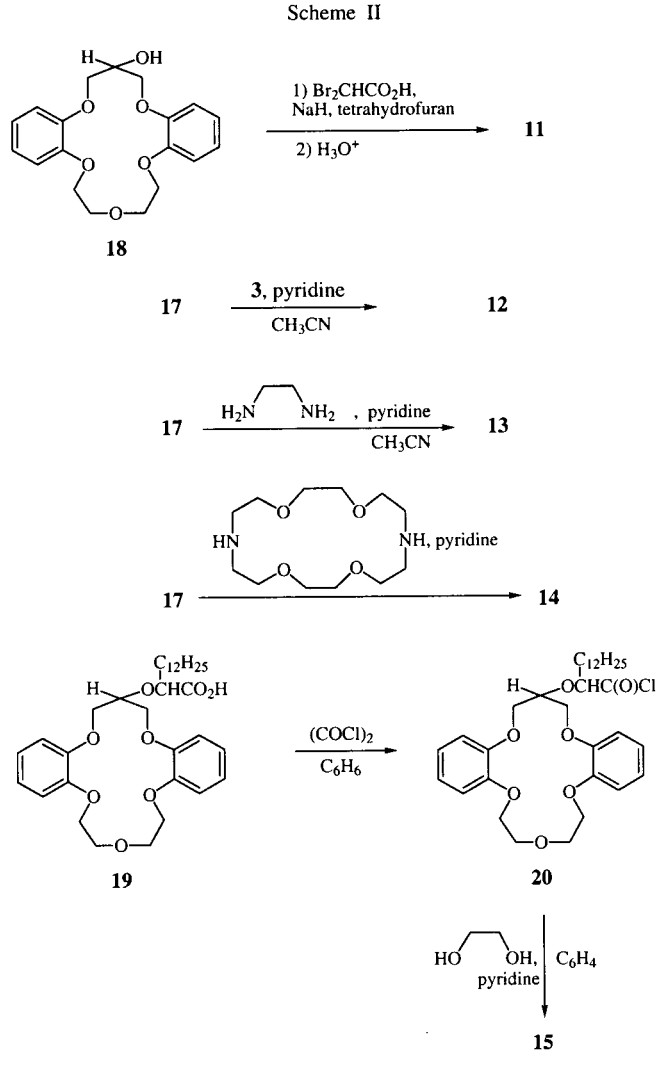
Reaction of lariat ether acid chloride **17** with ethylenediamine and 1,10-diaza-18-crown-6 gave bis(crown ether) **13** and tricyclic polyether ligand **14** in 72 and 62% yields, respectively.

Conversion of known 2-(*sym*-dibenzo-16-crown-5-oxy)tetradecanoic acid (**19**) into its acid chloride **20** with oxalyl chloride followed by reaction with ethylene glycol gave an 85% yield of bis(crown ether) **15** which has two ester groups in the linker.

Structures of the new macrocyclic, macrobicyclic, and macrotricyclic compounds were verified by their nmr spectra and by combustion analysis. Structural verification by ir spectra was included for some compounds.

Lariat ether carboxylic acids, hydroxamic acids, and phosphonic acid monoethyl esters have proven to be effective agents for the extraction of a variety of metal ions [14-28]. Our preliminary investigations indicate that lariat ether carboxylic acids **7** and **8**, bis(crown ether) carboxylic acid **11**, and lariat ether phosphonic acid monoethyl ester **6** exhibit high efficiency for extraction of lanthanide and radium ions. Further studies concerning the extraction efficiency of these ligands and complexation properties of macrocyclic, macrobicyclic and macrotricyclic compounds are ongoing in our laboratory and our progress will be reported in due course.

Scheme II



EXPERIMENTAL

Commercial reagents were obtained from Aldrich and Fluka (dibromoacetic acid) and were used as received. Tetrahydrofuran was distilled from sodium and benzophenone. Acetonitrile was dried over and distilled from calcium hydride. Benzene was dried over sodium. Starting materials **16** [12], **18** [37], and **19** [14] were prepared by the reported methods.

The proton nuclear magnetic resonance (nmr) spectra were obtained with a Bruker AF200 200 MHz spectrometer. Infrared (ir) spectra were taken with a Digilab Qualimatic FTIS-80 spectrophotometer. Mass spectra were obtained with a VG Micro Mass 70/70HS mass spectrometer. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

Preparation of 2-(*sym*-Dibenzo-16-crown-5-oxy)ethanol (**1**).

Method A.

Borane-tetrahydrofuran complex (17 ml, 17 mmoles) was slowly added to a solution of 4.04 g (10 mmoles) of lariat ether carboxylic acid **16** dissolved in 30 ml of tetrahydrofuran at 0° under nitrogen. The solution was stirred at 25° for 6 hours and the excess hydride was destroyed with 6 ml of aqueous tetrahydrofuran (1:1). The aqueous phase was saturated with potassium carbonate. The tetrahydrofuran was evaporated *in vacuo* and the aqueous residue was extracted with dichloromethane, washed with water and dried over magnesium sulfate. The solvent was evaporated *in vacuo* to give 3.70 g (95% yield) of a white solid with mp 126-127°; ir (potassium bromide): ν 3471, 3379 (OH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.01 (br s, 1H), 3.80-4.30 (m, 17H), 6.80-6.99 (m, 8H); ^{13}C nmr (deuteriochloroform): δ 62.1, 67.6, 69.6, 71.8, 72.0, 77.9, 113.3, 118.7, 121.3, 123.2, 148.2, 150.4; ms: m/z 390 (M^+, Cl, 34.70%; EI, 56.79 % relative intensity).

Anal. Calcd. For $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.40; H, 6.66.

Method B.

Carboxylic acid **16** (4.04 g, 10.0 mmoles) was dissolved in 150 ml of freshly distilled tetrahydrofuran and the solution was cooled to 0° under nitrogen. Lithium aluminum hydride (pellets, 0.38 g, 10.0 mmoles) was added. The reaction mixture was stirred at 0° for 2 hours, allowed to warm to room temperature, and stirred overnight. Aqueous sodium sulfate was added carefully to destroy the excess lithium aluminum hydride. Filtration through Celite and distillation of the filtrate *in vacuo* gave a crude product which was purified by recrystallization with hexane-ethyl acetate (1:1) to give 3.63 g (93% yield) of **1**.

Preparation of 2-(*sym*-Dibenzo-16-crown-5-oxy)ethyl Tosylate (**2**).

To a cooled solution of **1** (1.25 g, 3.19 mmoles) in 5 ml of dichloromethane and 30.3 mmoles of triethylamine, *p*-toluenesulfonyl chloride (3.5 mmoles) in 5 ml of dichloromethane was slowly added and the reaction mixture was stirred overnight. The mixture was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel with dichloromethane and then diethyl ether as eluents to give 1.32 g (76% yield) of a white solid with mp 89-90°; ^1H nmr (deuteriochloroform): δ 2.37 (s, 3H), 3.83-4.53 (m, 17H), 6.80-6.98 (m, 8H), 7.25-7.29 (d, 2H, J = 8 Hz), 7.77-7.82 (d, 2H, J = 10 Hz).

Anal. Calcd. for $C_{28}H_{32}O_9S$: C, 61.76; H, 5.88. Found: C, 61.75; H, 5.68.

Preparation of *O*-Benzyl 2-(*sym*-Dibenzo-16-crown-5-oxy)ethyl Hydroxylamine (**3**).

Tosylate **2** (1.29 g, 2.37 mmoles) dissolved in 10 ml of dioxane was added to 7.0 mmoles of *O*-benzylhydroxylamine (prepared from *O*-benzylhydroxylamine hydrochloride by neutralization with potassium hydroxide) and the reaction mixture was refluxed for 3 days at 95-100°. After cooling the mixture to room temperature, the precipitate was filtered and washed with diethyl ether. The filtrate was acidified with concentrated hydrochloric acid which precipitated the hydrochloride salt of the unreacted *O*-benzylhydroxylamine. This was also filtered and washed with diethyl ether. The combined filtrate and washings were evaporated to near dryness. The residue was dissolved in dichloromethane and extracted with 2.5 *M* hydrochloric acid and then with 1 *M* sodium bicarbonate solution, washed with water, and dried over sodium sulfate. Evaporation *in vacuo* gave a crude product which was purified by column chromatography on silica gel with dichloromethane and then dichloromethane-methanol (9:1) as eluents to provide 0.81 g (69% yield) of an oil; ^1H nmr (deuteriochloroform): δ 3.84-4.30 (m, 17H), 4.71 (s, 2H), 6.81-6.96 (m, 8H), 7.26-7.34 (m, 5H), 9.92 (s, 1H, NH). Compound **3** was an intermediate for the preparation of bis(crown ether) **12** which gave satisfactory combustion analysis.

Preparation of 2-(*sym*-Dibenzo-16-crown-5-oxy)ethyl Bromide (**4**).

To a solution of 3.90 g (10.0 mmoles) of alcohol **1** in 100 ml of benzene was added 1.0 ml (10.0 mmoles) of phosphorus tribromide. The reaction mixture was stirred at room temperature for 14 hours and then stirred with 200 ml of diethyl ether and 200 ml of saturated aqueous sodium bicarbonate. The organic layer separated and washed with saturated sodium bicarbonate and brine and dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel with hexane-ethyl acetete (2:1) as eluent to give 4.00 g (88% yield) of a white solid with mp 108-110°; ^1H nmr (deuteriochloroform): δ 3.56 (t, 2H, J = 6.3 Hz, CH_2Br), 3.84-4.34 (m, 15H), 6.81-7.01 (m, 8H); ms: m/z 452 (CI: M^+ 38.3% relative intensity).

Anal. Calcd. for $C_{21}H_{25}BrO_6$: C, 55.68; H, 5.59. Found: C, 55.64; H, 5.56.

Preparation of Diethyl 2-(*sym*-Dibenzo-16-crown-5-oxy)ethylphosphonate (**5**).

Bromide **4** (4.00 g, 8.80 mmoles) and 3.0 ml (17.5 mmoles) of triethyl phosphite were stirred at 150° for 10 hours. The excess triethyl phosphite was removed by vacuum distillation and the residue was purified by flash chromatography on silica gel with hexane-ethyl acetate-ethanol (10:10:1) as eluent to give 4.15 g (92% yield) of **5** as a colorless oil; ^1H nmr (deuteriochloroform): δ 1.25 (t, 6H, J = 7.0 Hz), 2.16 (d of t, 2H, J = 18.5, 7.5 Hz), 3.78-4.29 (m, 19H), 6.76-6.95 (m, 8H); ^{13}C nmr (deuteriochloroform): δ 16.4 (d, J = 6.25 Hz), 27.4 (d, J = 137.75 Hz), 61.6 (d, J = 16.4 Hz), 64.7, 67.5, 69.5, 71.5, 77.5, 113.1, 118.7, 121.1, 123.0, 148.2, 150.4; ^{31}P nmr (deuteriochloroform): δ 28.77; ms: m/z 511 (CI, M^++1, 45.8% relative intensity).

Anal. Calcd. for $C_{25}H_{35}O_9P \cdot 0.5H_2O$: C, 57.79; H, 6.98. Found: C, 57.92; H, 6.83.

Preparation of Monoethyl 2-(*sym*-Dibenzo-16-crown-5-oxy)ethylphosphonate (**6**).

Diethyl phosphonate **5** was refluxed with 0.50 g of sodium hydroxide in 50 ml of ethanol overnight under nitrogen. The solution was cooled to room temperature and acidified to *p*H <1 with 6 *M* hydrochloric acid. Extraction with dichloromethane, drying over magnesium sulfate, and evaporation *in vacuo* gave 1.80 g (46% yield) of white solid with mp 55-57°; ^{1}H nmr (deuteriochloroform): δ 1.32 (t, 3H, J = 7.0 Hz), 2.08-2.30 (m, 2H), 3.87-4.35 (m, 17H), 6.81-7.20 (m, 8H), 9.25 (br s, 1H).

Anal. Calcd. for $C_{23}H_{31}O_9P \cdot 0.5H_2O$: C, 56.21; H, 6.56. Found: C, 56.35; H, 6.67.

Preparation of Lariat Ether Carboxylic Acids **7** and **8**.

Tetrahydrofuran (15 ml) was added to 0.50 g (21.0 mmoles) of dry sodium hydride under nitrogen and the mixture was stirred for 30 minutes at room temperature. Alcohol **1** (3.0 mmoles) dissolved in 15 ml of tetrahydrofuran was added dropwise over 1 hour and the mixture was stirred at room temperature for 1 hour. The appropriate 2-bromocarboxylic acid (6.0 mmoles) dissolved in 15 ml of tetrahydrofuran was added dropwise over a 4-hour period. The reaction mixture was refluxed for several hours for **7** or stirred at room temperature for 12 hours for **8**. Careful addition of water to destroy the excess sodium hydride was followed by evaporation of the tetrahydrofuran *in vacuo*. To the residue, 20 ml of water were added and the mixture was extracted with diethyl ether to remove the unreacted alcohol. The aqueous layer was acidified with aqueous 6 *M* hydrochloric acid and extracted with dichloromethane. The combined organic layers were washed with water and dried over magnesium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with dichloromethane-methanol (9:1) as eluent to give **7** and **8** as follows.

5-(*sym*-Dibenzo-16-crown-5-oxy)-3-oxapentanoic Acid (**7**).

A white solid with mp 90-92° was obtained in 60% yield; ir (sodium chloride plate): ν 3410 (COOH), 1735 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.54-4.34 (m, 13H), 4.54 (s, 4H), 4.63 (s, 2H), 6.70-6.91 (m, 8H).

Anal. Calcd. for $C_{23}H_{28}O_9$: C, 61.60; H, 6.25. Found: C, 61.39; H, 6.23.

5-(*sym*-Dibenzo-16-crown-5-oxy)-3-oxa-2-phenylpentanoic Acid (**8**).

A pale yellow solid with mp 53-55° was obtained in 65% yield; ir (sodium chloride plate): ν 3430 (COOH), 1739 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.48-4.40 (m, 13H), 4.92 (s, 4H), 5.26 (s, 1H), 6.82-7.67 (m, 13H).

Anal. Calcd. for $C_{29}H_{32}O_9 \cdot 0.25H_2O$: C, 65.84; H, 6.15. Found: C, 65.88; H, 6.09.

Preparation of *sym*-Dibenzo-16-crown-5-oxyacetamide (**9**).

Carboxylic acid **16** (2.0 mmoles) was added to 10 ml of dry benzene under nitrogen. After cooling to 0°, oxalyl chloride (8.0 mmoles) was added dropwise and the mixture was stirred at room temperature for 1 hour and then warmed to 60° for 1 hour. The mixture was evaporated *in vacuo* and the resultant acid chloride **17** was used directly in the next step.

Anhydrous ammonia was introduced into a cooled acetonitrile solution of **17**. The mixture was allowed to warm to room temperature, stirred for 12 hours, and evaporated *in vacuo*. The residue was dissolved in ethyl acetate and the solution was washed with 0.6 *M* hydrochloric acid, water, 0.6 *M* aqueous sodium bicarbonate, and water and dried over magnesium sulfate. Evaporation of the solution *in vacuo* gave amide **9** as a white solid with mp 54-56° in 65% yield; ir (potassium bromide): ν 3348 (NH), 1689 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.90-4.31 (m, 15H), 6.81-7.02 (m, 8H), 7.66 (br s, 2H).

Anal. Calcd. for $C_{21}H_{25}NO_7$: C, 62.53; H, 6.20, N, 3.47. Found; C, 62.64; H, 6.44; N, 3.27.

Preparation of 2-(*sym*-Dibenzo-16-crown-5-oxy)ethylamine (**10**).

A solution of compound **9** (0.25 g, 0. 62 mmole) in 10 ml of dry tetrahydrofuran was cooled at 0° under nitrogen and 5.0 ml of borane-tetrahydrofuran complex (1.0 *M* solution in tetrahydrofuran) was added dropwise over a period of 15 minutes. The cooling bath was removed and the reaction mixture was kept at room temperature for 30 minutes and then refluxed for 6-8 hours. The solution was cooled to 0°, and the excess borane was destroyed by the addition of water. The white solid was filtered and dissolved in concentrated hydrochloric acid-water-methanol (2:3:10) and refluxed for 5 hours. The reaction mixture was evaporated *in vacuo* and the residue was treated with a strongly alkaline solution and extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and evaporated *in vacuo*. The crude product was recrystallized from absolute ethanol to give 0.16 g (68%) of a white solid with mp 103-104°; ir (potassium bromide): ν 3379 (NH_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.22 (s, 2H), 3.80-4.33 (m, 17H), 6.81-6.99 (m, 8H).

Anal. Calcd. for $C_{21}H_{27}NO_6 \cdot 0.2H_2O$: C, 64.18; H, 6.98; N, 3.56. Found: C, 64.30; H, 7.32; N, 3.08.

Preparation of Bis(crown ether) Carboxylic Acid **11**.

To a suspension of sodium hydride (0.72 g, 30.0 mmoles) in 20 ml of dry tetrahydrofuran under nitrogen, a solution of 1.04 g (3.0 mmoles) of alcohol **18** in 10 ml of dry tetrahydrofuran was added. The mixture was stirred for 30 minutes at room temperature and dibromoacetic acid (1.30 g, 6.0 mmoles) in 10 ml of dry tetrahydrofuran was added dropwise during a 30-minute period. The reaction mixture was stirred at room temperature for 24 hours. The excess sodium hydride was destroyed by careful addition of water and the mixture was evaporated *in vacuo*. To the oily residue was added 50 ml of dichloromethane and the mixture was acidified to *p*H 1 with 6 *M* hydrochloric acid. The organic layer was separated, washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel with dichloromethane and dichloromethane-methanol (19:1) as eluents and then recrystallized from absolute ethanol to give 0.30 g (17% yield) of a white solid with mp 168-170°; ir (potassium bromide): ν 3429 (COOH), 1751 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.87-4.71 (m, 26H), 5.79 (s, 1H), 6.80-7.01 (m, 16H).

Anal. Calcd. for $C_{40}H_{44}O_{14}$: C, 64.16; H, 5.92. Found: C, 63.96; H, 5.79.

General Method for the Preparation of Macrobicyclic Amide **12**, Diamide **13** and Macrotricyclic Diamide **14**.

Lariat ether acid chloride **17** (2.0 mmoles) was prepared as described above in the synthesis of amide **9**. The corresponding amine (2.0 mmoles) or diamine (1.0 mmoles) was dissolved or suspended in 10 ml of dry acetonitrile and 2.0 mmoles of pyridine was added. The mixture was cooled to 0° and an acetonitrile solution of **17** was added dropwise. The mixture was allowed to warm to room temperature and stirred for 12 hours. The mixture

was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with 0.6 *M* hydrochloric acid, water, 0.6 *M* aqueous sodium bicarbonate, and water and dried over anhydrous magnesium sulfate. Evaporation of the solution *in vacuo* gave the macrobicyclic and macrotricyclic amide or diamide.

Bis(crown ether) Amide **12**.

A white solid with mp 54-56° was obtained in 65% yield; ir (potassium bromide): ν 1678 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.89-4.92 (m, 34H), 6.79-7.33 (m, 21H).

Anal. Calcd. for $C_{49}H_{55}NO_{14}•H_2O$: C, 65.40; H, 6.34; N, 1.55. Found: C, 65.53; H, 6.71; N, 1.19.

Bis(crown ether)diamide **13**.

A white solid with mp 174-175° was realized in 72% yield; ir (potassium bromide): ν 3352 (NH), 1674 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.41 (s, 4H), 3.86-4.28 (m, 30H), 6.80-6.97 (m, 16H), 7.81 (br s, 2H).

Anal. Calcd. for $C_{44}H_{52}N_2O_{14}•1.25H_2O$: C, 61.79; H, 6.37; N, 3.27. Found: C, 61.56; H, 6.27; N, 3.13.

Macrotricyclic Diamide **14**.

A white solid with mp 53-55° was obtained in 62% yield; ir (potassium bromide): ν 1651 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.50-4.36 (m, 50H), 4.59 (s, 4H), 6.79-6.97 (m, 16H).

Anal. Calcd. for $C_{54}H_{70}N_2O_{18}•0.5H_2O$: C, 62.12; H, 6.80; N, 2.68. Found: C, 62.18; H, 6.61; N, 2.56.

Preparation of Bis(crown ether) Diester **15**.

Lariat ether acid chloride **20** (2.0 mmoles) was prepared as described above to prepare lariat ether acid chloride **17** in the synthesis of amide **9**. A solution of ethylene glycol (0.062 g, 1.00 mmoles) in 2 ml of dry benzene was added to a solution of acid chloride **20** (1.18 g, 2.00 mmoles) and pyridine (0.158 g, 2.00 mmoles) in 10 ml of dry benzene. The solution was refluxed overnight under nitrogen and evaporated *in vacuo* to give an oil that was dissolved in dichloromethane. The dichloromethane solution was washed with 5% aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated *in vacuo* to give a crude product, which was chromatographed on silica gel with dichloromethane and dichloromethane-methanol (9:1) as eluents to afford 0.95 g (81% yield) of **15** as a colorless oil; ir (sodium chloride plate): ν 1747 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.82-0.88 (t, 6H, J = 6 Hz), 1.22 (s, 36H), 1.41-1.78 (m, 8H); 3.83-4.59 (m, 32H), 6.76-6.99 (m, 16H).

Anal. Calcd. for $C_{68}H_{98}O_{16}$: C, 69.74; H, 8.37. Found: C, 69.72; H, 8.37.

Acknowledgments.

The research conducted at the University of Idaho was generously supported by the National Science Foundation's EPSCoR Program, Grant #R11-8902065. Portions of the research performed at Texas Tech University were supported by the Division of Chemical Sciences of the Office of Basic Energy Sciences of the US Department of Energy through grant DE-FG03-9414416.

REFERENCES AND NOTES

[1] For review of lariat ethers, their cation complexation properties and applications see: [a] G. W. Gokel and J. E. Trafton, Cation Binding by Macrocycles, Y. Inoue and G. W. Gokel, eds, Marcel Dekker, New York, 1990, p 253; [b] G. W. Gokel, *Chem. Soc. Rev.*, **39** (1992); [c] G. W. Gokel and O. F. Schall, Comprehensive Supramolecular Chemistry, Vol **1**, G. W. Gokel, ed, Pergamon, New York, 1996, p 97.

[2] J. Smid and R. Sinta, *Top. Curr. Chem.*, **121**, 105 (1984).

[3] J. S. Bradshaw, K. E. Krakowiak, R. L. Bruening, B. J. Tarbet, P. B. Savage and R. M. Izatt, *J. Org. Chem.*, **53**, 3190 (1988).

[4] L. Collie, J. E. Denness, D. Parker, F. O'Carroll and C. Tachon, *J. Chem. Soc., Perkin Trans. 2*, 1747 (1993).

[5] R. M. Izatt, *J. Inclusion Phenom.*, **29**, 197 (1997).

[6] J. S. Bradshaw and R. M. Izatt, *Acc. Chem. Res.*, **30**, 338 (1997).

[7] A. Favre-Reguillon, N. Dumont, B. Dunjic and M. Lemaire, *Tetrahedron*, **53**, 1343 (1997).

[8a] A. Kaifer, L. Echegoyen, H. D. Durst, R. A. Schultz, D. M. Dishong, D. M. Goli and G. W. Gokel, *J. Am. Chem. Soc.*, **106**, 5100 (1984); [b] H. Tsukube, T. Inoue and K. Hori, *J. Org. Chem.*, **59**, 8047 (1994).

[9a] F. R. Fronczek, V. J. Gatto, R. A. Schultz S. J. Jungk, W. J. Golucci, R. D. Gandour and G. W. Gokel, *J. Am. Chem. Soc.*, **105**, 6717 (1983); [b] F. R. Fronczek and R. D. Gandour, Cation Binding by Macrocylces, Y. Inoue and G. W. Gokel, eds. Marcel Dekker, New York, 1990, p 311.

[10a] C. W. McDaniel, J. S. Bradshaw and R. M. Izatt, *Heterocycles*, **30**, 665 (1990); [b] J. S. Bradshaw, *J. Inclusion Phenom.*, **29**, 221 (1997).

[11] W. J. McDowell, *Sep. Sci. Technol.*, **23**, 1251 (1988).

[12] R. A. Bartsch, G. S. Heo, S. I. Kang, Y. Liu and J. Strzelbicki, *J. Org. Chem.*, **47**, 457 (1982).

[13] R. A. Bartsch, Y. Liu, S. I. Kang, B. Son, G. S. Heo, P. G. Hipes and L. J. Bills, *J. Org. Chem.*, **48**, 4864 (1983).

[14] S. Elshani, N. Noriyuki, C. M. Wai, N. R. Natale and R. A. Bartsch, *J. Heterocyclic Chem.*, **35**, 875 (1998).

[15] J. Strzelbicki and R. A. Bartsch, *Anal. Chem.*, **53**, 1894 (1981).

[16] J. Strzelbicki and R. A. Bartsch, *Anal. Chem.*, **53**, 2247 (1981).

[17] J. Strzelbicki and R. A. Bartsch, *Anal. Chem.*, **53**, 2251 (1981).

[18] R. A. Bartsch, G. S. Heo, S. I. Kang, Y. Liu and J. Strzelbicki, *J. Anal. Chem.*, **47**, 457 (1982).

[19] M. J. Pugia, G. Ndip, H. K. Lee, I.-W. Yang and R. A. Bartsch, *Anal. Chem.*, **58**, 2723 (1986).

[20] W. Walkowiak, W. A. Charewicz, S. I. Kang, I.-W. Yang, M. J. Pugia and R. A. Bartsch, *Anal. Chem.*, **62**, 2018 (1990).

[21] T. Hayashita, M. J. Goo, J. C. Lee, J. S. Kim, J. Krzykawski and R. A. Bartsch, *Anal. Chem.*, **62**, 2283 (1990).

[22] T. Hayashita, J. J. Lee, S. Chen and R. A. Bartsch, *Anal. Chem.*, **63**, 1844 (1991).

[23] T. Hayashita, J. H. Lee, J. C. Lee, J. Krzykawski and R. A. Bartsch, *Talanta*, **39**, 857 (1992).

[24] T. Hayashita, J. H. Lee, M. G. Hankins, J. C. Lee, J. S. Kim, J. M. Knobeloch and R. A. Bartsch, *Anal. Chem.*, **64**, 815 (1992).

[25] J. Tang and C. M. Wai, *Anal. Chem.*, **58**, 3233 (1986).

[26] J. Tang and C. M. Wai, *Analyst*, **114**, 451 (1989).

[27] J. Tang and C. M. Wai, *J. Membr. Sci.*, **35**, 339 (1988).

[28] J. Tang and C. M. Wai, *J. Radioanal. Nucl. Chem. Letters*, **128**, 61 (1988).

[29] M. Bourgoin, K. H. Wong, J. Y Hui and J. Smid, *J. Am. Chem. Soc.*, **97**, 3462 (1975).

[30] Y. Takeda, *Top. Curr. Chem.*, **121**, 1 (1984).

[31] K. Kimura and T. Shono, Cation Binding by Macrocycles, Y. Inoue and G. W. Gokel, eds, Marcel Dekker, New York, 1990, p 429 and references cited therein.

[32] M. J. Pugia, B. E. Knudsen and R. A. Bartsch, *J. Org. Chem.*, **52**, 2617 (1987).

[33a] P. Holy, J. Koudelka, M. Belohradsky, I. Stibor and J. Zavada, *Collect. Czech. Chem. Commun.*, **56**, 1482 (1991); [b] M. Belohradsky, P.

Holy, J. Koudelka and J. Zavada, *Collect. Czech. Chem. Commun.*, **58**, 153 (1993).

[34] A. S. Craig, R. Kataky, R. C. Matthews, D. Parker, G. Ferguson, A. Lough, H. Adams, N. Bailey and H. Schneider, *J. Chem. Soc., Perkin Trans. 2*, 1523 (1990).

[35] R. A. Bissell, E. Calle, A. P. de Silva, S. A. de Silva, H. Q. N. Gunaratne, J. L. Habib-Jiwan, S. L. A. Peiris, R. A. D. D. Rupasinghe, T. K. S. D. Samarasinghe, K. R. A. S. Sandanayake and J. P. Sournillion, *J. Chem. Soc., Perkin Trans. 2*, 1559 (1992).

[36] For a review on macropolycyclic polyethers and related compounds see: H. An, J. S. Bradshaw and R. M. Izatt, *Chem. Rev.*, **92**, 5431 (1992).

[37] G. S. Heo, R. A. Bartsch, L. L. Schlobohm and J. G. Lee, *J. Org. Chem.*, **46**, 3574 (1981).