Synthesis of Lariat Ethers with Pendent Amine, Amide, *O*-Benzylhydroxamate, and Urethane Groups

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Synthetic routes to twenty-six new crown ether compounds with pendent amine, amide, *O*-benzylhydroxamate, and urethane groups are reported. The new lariat ether compounds are based on *sym*-dibenzo-16-crown-5, *sym*-dicyclohexano-16-crown-5, and 14-crown-4 scaffolds.

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Introduction.

For over three decades, macrocyclic polyether compounds (crown ethers) have been prepared and utilized in alkali and alkaline earth metal cation determination and separation due to their superior binding ability for these metal ions [1]. Attachment of one or more side arms with potential metal ion coordination sites produces complexing agents that are known as lariat ethers [2]. Lariat ethers are designed to enhance the cation binding ability of crown ethers and also partly to mimic the dynamic complexation processes exhibited by natural macrocyclic ionophores [3]. The coordinating properties of amide groups are well documented [4], and we and other researchers have prepared crown ether, monoazacrown ether and diazacrown ether compounds with pendent amide, *N*-alkylamide and *N*,*N*-dialkylamide functionalities [5-11].

We reported earlier the synthesis of a large number of lariat ether compounds with pendent oxyacetamide, *N*-alkyl oxyacetamide and *N*,*N*-dialkyl oxyacetamide groups attached to *sym*-(R)dibenzo-13-crown-4, *sym*-(R)dibenzo-14-crown-4, *sym*-(R)dibenzo-16-crown-5, and *sym*-(propyl)dicyclohexano-16-crown-5 scaffolds [10,11]. Subsequently, responses of these ionophores toward alkali and alkaline earth metal cations, protons, and ammonium ions in solvent polymeric membrane electrodes were assessed [12,14]. Dibenzo-16-crown-5 compounds with an *N*,*N*-dipentyloxyacetamide group attached to the central carbon of the three-carbon bridge and a geminal alkyl group of two or more carbon atoms have been found to be excellent ionophores for Na^+-selective electrodes.

We also reported previously the preparation of a series of lariat ether *O*-benzylhydroxamates [15,16]. Beside their use as valuable intermediates for the preparation of lariat ether hydroxamic acids, the responses of these ionophores toward alkali and alkaline earth metal cations in solvent polymeric membrane electrodes were assessed [16,17].

For further investigation of the influence of structural variation for lariat ether amide and *O*-benzylhydroxamate ionophores in solvent polymeric membrane electrodes, new lariat ether compounds with pendent *N*-alkylamide, *N*,*N*-dialkylamide and *O*-benzylhydroxamate groups have now been synthesized. New lipophilic lariat ether amines were prepared as precursors for the synthesis of some of the new lariat ether amides. Two lariat ethers with pendent urethane groups were also prepared for comparison.

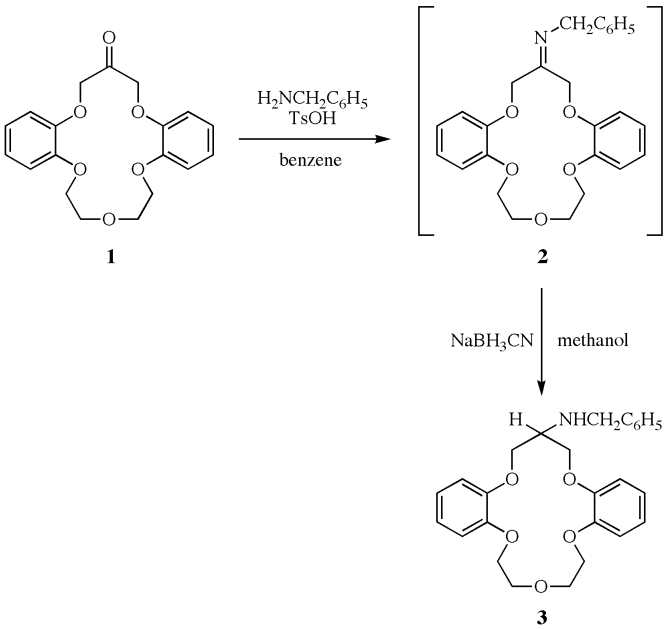
When combined with the previously reported compounds, these lariat ethers provide systematic variation of several structural features. The synthesis of these twenty-six new compounds is now described.

Results and Discussion.

Synthesis of Lariat Ether Amines.

For the synthesis of lipophilic lariat ether amines, reductive amination [18,19] of *sym*-(keto)dibenzo-16-crown-5 (**1**) *via* a lariat ether imine intermediate **2**, as shown in Scheme 1, was envisioned. In attempted preparation of **2**, crown ether ketone **1** was treated with benzylamine and *p*-toluenesulfonic acid in benzene with the co-product water being removed by benzene azeotropic distillation with a Dean-Stark apparatus. It was found that crown ether imine

Scheme 1

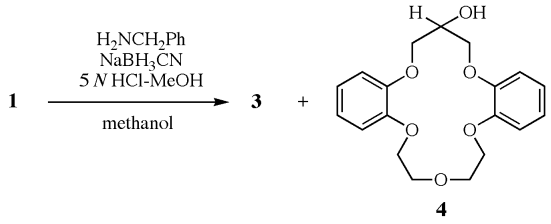


1 **2** **3**

2 could not be isolated due to its ready reaction with moisture to reform **1**. Without isolation, the imine intermediate was treated with sodium cyanoborohydride in methanol at pH 4 to give a low yield (2%) of desired amine **3**.

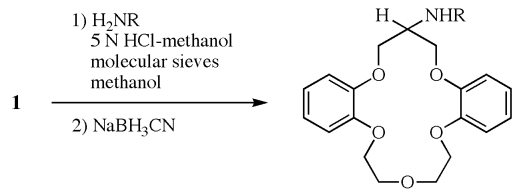
A one-step reductive amination [20] of crown ether ketone **1** with benzylamine, sodium cyanoborohydride, and 5 *N* hydrochloric acid-methanol in methanol gave a 51% yield of amine **3** (Scheme 2). However, lariat ether alcohol **4** was formed as a by-product and found to be difficult to separate from the desired product.

Scheme 2



We believe that there is an equilibrium between ketone **1** and imine intermediate **2**. Thus, reduction of the imine to give the desired product **3** is in competition with reduction of ketone **1** to give alcohol **4**. If this rationalization is correct, a shift of the equilibrium to the imine intermediate **2** by removal of water produced in the imine-forming reaction with a drying agent should increase the proportion of desired product **3**. In agreement, treatment of ketone **1** with benzylamine and 5 *N* hydrochloric acid-methanol in methanol in the presence of 4 Å molecular sieves as the drying agent followed by reduction with sodium cyanoborohydride produced an 81% yield of the lariat ether secondary amine **3** that was free from by-product **4** (Scheme 3). Subsequently, the same reaction conditions were utilized with other primary amines to produce lariat ether secondary amines **5-7** in good to very good yields.

Scheme 3

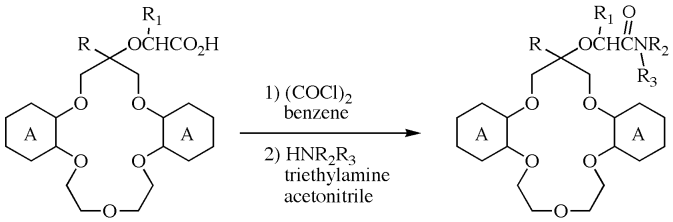


	R
3	C_6H_5
5	C_4H_9
6	C_8H_{17}
7	$C_{12}H_{23}$

Synthesis of Lariat Ether Amides.

For the synthesis of lariat ether amides **15-24** (Scheme 4), the corresponding carboxylic acids **8-13** were available

Scheme 4



	R	R_1	A	R_2	R_3	
8	H	H	benzo	H	C_6H_{13}	**15**
8	H	H	benzo	CH_3	C_6H_{13}	**16**
8	H	H	benzo	H	$C_{12}H_{25}$	**17**
8	H	H	benzo	H	C_6H_5	**18**
9	$C_{10}H_{21}$	H	benzo	H	H	**19**
10	$C_{10}H_{21}$	C_6H_5	benzo	C_5H_{11}	C_5H_{11}	**20**
11	$CH_2C(CH_3)_3$	H	benzo	C_5H_{11}	C_5H_{11}	**21**
12	C_6H_5	H	benzo	H	$CH_2C_6H_5$	**22**
13	C_6H_5	C_6H_5	benzo	C_5H_{11}	C_6H_5	**23**
14	H	H	cyclohexano	H	C_6H_{13}	**24**

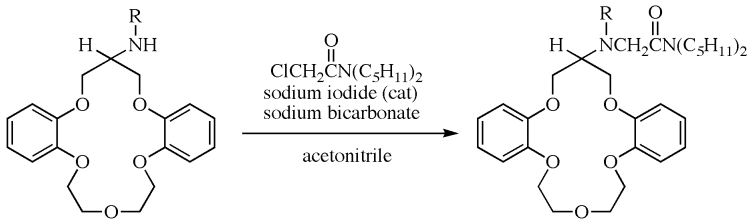
from earlier work. By catalytic hydrogenation of **8**, *sym*-dicyclohexano-16-crown-5-oxyacetic acid (**14**) was prepared. The *sym*-(R)dibenzo(or dicyclohexano)-16-crown-5-oxyacetic acids were converted into the corresponding acid chlorides by reaction with oxalyl chloride in benzene. Subsequent treatment of the lariat ether acid chlorides with the appropriate amine (ammonia for **19**) in acetonitrile gave the desired lariat ether amides **15-24** in very good yields.

In expansion of the previously reported lariat ether amide series in which the structural change in geminal R group was from hydrogen to linear alkyl groups of increasing length to a branched alkyl group [10,11], this series adds an aryl (phenyl) group. Lariat ether amides **20** and **23**, in addition to containing R = decyl and phenyl group, respectively, possess an additional phenyl group α to the carboxamide function. Lariat ether amides **18** and **22** contain phenyl and benzyl groups, respectively, on the amide nitrogen instead of linear alkyl groups.

Amides **25** and **26** (Scheme 5) differ from previously described lariat ether amides in that they contain a *N*-alkylamino group in addition to a *N*,*N*-dipentylamido function. In the lariat ether amides described above and those reported earlier [10,11], an oxygen atom connects the functional side arm to the polyether ring. In contrast, for **25** and **26**, a nitrogen atom links the sidearm to the dibenzo-16-crown-5 unit. Lariat ether amines **6** and **7** were reacted with *N*,*N*-dipentylchloroacetamide in acetonitrile at reflux in the presence of sodium bicarbonate and a catalytic amount of sodium iodide to form amides **25** and **26**, respectively. In contrast, reactions of **6** and **7** with *N*,*N*-dipentylchloracetamide and sodium hydride in tetrahydrofuran gave only recovered starting materials.

Another objective was to prepare potential Li^+-selective lipophilic lariat ether 14-crown-4 amides **29** and **30**

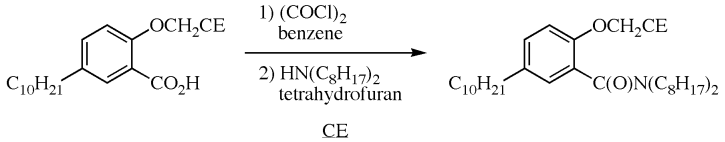
Scheme 5



	R	
6	C_8H_{17}	**25**
7	$C_{12}H_{25}$	**26**

(Scheme 6) for evaluation in polymeric membrane electrodes. Reaction of lipophilic salicylic acid lariat ethers **27** and **28** with oxalyl chloride in benzene followed by reaction with dioctylamine in tetrahydrofuran gave the lipophilic ether amides **29** and **30** in high yields.

Scheme 6



CE

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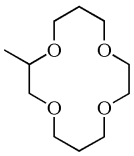
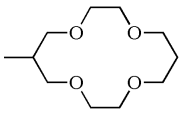


29

28



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Synthesis of Lariat Ether *O*-Benzylhydroxamates.

The lariat ether *O*-benzylhydroxamates **37**-**42** were prepared from the corresponding lariat ether carboxylic acids as shown in Scheme 7. First, the lariat ether carboxylic acids **31**-**36** were converted into the corresponding acid chlorides by reaction with oxalyl chloride in benzene at 0°, followed by stirring at room temperature and finally at 60-70°. Treatment of the lariat ether acid chlorides with *O*-benzylhydroxylamine hydrochloride and triethylamine in dry acetonitrile [15] afforded the lariat ether *O*-benzylhydroxamates **37**-**42**.

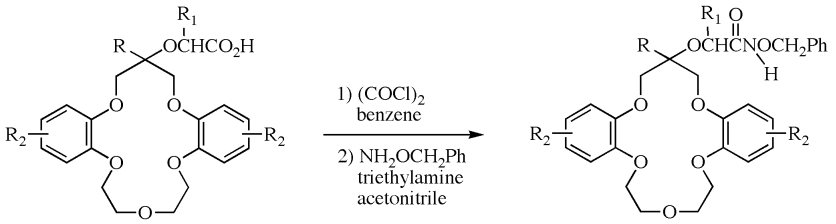
In earlier work, we reported the preparation of lariat ether *O*-benzylhydroxamates with an alkyl or phenyl group attached α to the *O*-benzylhydroxamate function or on the polyether ring carbon geminal to the *O*-benzylhydroxamate-containing side arm or to both positions [15,16]. For further investigation of the influence of structural variation for lariat ether *O*-benzylhydroxamate ionophores in solvent polymeric membrane electrodes, new lariat ether compounds with an octyl group α to the *O*-benzylhydroxamato group (**37**), a *tert*-butyl group on each benzene ring (**38**), tolyl groups on the central carbon of the three-carbon bridge (**39**-**41**), and a cyclohexyl group in the same position (**42**) have been synthesized. Lariat ethers **39**-**41** with tolyl groups were prepared for comparison of their potentiometric selectivities with those of (trifluoromethyl)phenyl analogues in solvent polymeric membrane electrodes [16]. This series will also allow the influence of different methyl group positions in **39**-**41** upon their potentiometric selectivities in solvent polymeric membrane electrodes to be determined.

Synthesis of Lariat Ether Urethanes.

Two new crown ether compounds with pendent urethane groups were synthesized by treating the lariat ether alcohol with phenyl isocyanate as shown in Scheme 8. Such lariat ether urethanes are of interest for comparison of their metal ion-binding properties with those of lariat ether amides and esters.

Structures of the twenty-six new lariat ether compounds reported in this study were confirmed by ^{1}H nmr and ir spectra and by elemental analysis. In the ^{1}H nmr spectra of

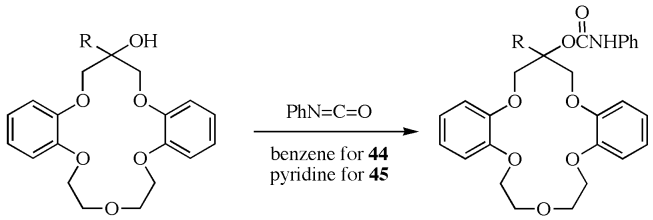
Scheme 7



	R	R_1	R_2	
31	H	C_8H_{17}	H	**37**
32	H	H	$C(CH_3)_3$	**38**
33	2-$(CH_3)C_6H_4$	H	H	**39**
34	3-$(CH_3)C_6H_4$	H	H	**40**
35	4-$(CH_3)C_6H_4$	H	H	**41**
36	c-C_6H_{11}	H	H	**42**

lariat ethers with a geminal alkyl or aryl group on the central carbon of the three-carbon bridge in dibenzo-16-crown-5 lariat ethers, clearly discernable AB patterns were evident for the diastereotopic methylene group hydrogens on the three-carbon bridges which demonstrate conformational restrictions of this structural unit on the nmr time scale [10].

Scheme 8



	R	
4	H	**44**
43	C_3H_7	**45**

Further investigation of the potentiometric selectivities of these lariat ether compounds in solvent polymeric membrane electrodes, are in progress in our laboratories and the results will be reported elsewhere.

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. Benzene was dried over sodium. Acetonitrile was dried over and distilled from calcium hydride. Starting materials **1** [21], **4** [22], **8** [23], **9** and **10** [15], **11** [24], **12** and **13** [15], **27** and **28** [25], **31** [24], **32** [26], **33**-**35** [24], **36** [15], **43** [27] and *N,N*-dipentyl-2-chloroacetamide [10] were prepared by reported procedures.

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, Arizona.

General Procedure for the Synthesis of *sym*-(*N*-Alkylamino)-dibenzo-16-crown-5 Compounds **3** and **5**-**7**

To a solution of 0.50 g (1.56 mmole) of crown ether ketone **1**, a primary amine (8.7 mmole), and 1.0 g of molecular sieves (4 Å) in absolute methanol (25 ml) was added 0.57 ml (2.9 mmole) of 5 *N* hydrochloric acid-methanol. The reaction mixture was stirred at room temperature for 4 hours and cooled to -78°. Sodium cyanoborohydride (55 mg, 0.90 mmole) was added and the mixture was slowly warmed to -10° and stirred at -10° for 2 hours and then at room temperature for 1 hour. The insoluble material was filtered and the solvent was evaporated from the filtrate *in vacuo*. Most of the excess of primary amine was removed *in vacuo* with some heating. The residue was dissolved in dichloromethane (20 ml) and washed with 5% aqueous sodium hydroxide (10 ml), water (10 ml), and brine (10 ml). The organic layer was dried over magnesium sulfate and evaporated *in vacuo*. Column chromatography on silica gel with ethyl acetate/hexanes (1:2) as eluent gave the product.

sym-(*N*-Benzylamino)dibenzo-16-crown-5 (**3**).

This compound was obtained in 81% yield as a white solid with mp 110-111°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3330 (NH), 1257, 1219, and 1121 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.31 (br s, 1H), 3.45-3.51 (p, 1H), 3.78-4.31 (m, 14H), 6.79-6.96 (m, 8H), 7.20-7.43 (m, 5H).

Anal. Calcd. for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.44; H, 6.73; N, 3.25.

sym-(*N*-Butylamino)dibenzo-16-crown-5 (**5**).

This compound was obtained in 50% yield as a white solid with mp 83-84°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3332 (NH), 1257, 1224, and 1122 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.95 (t, 3H, *J* = 6 Hz); 1.40-1.62 (m, 4H); 2.00 (br s, 1H); 2.77 (t, 2H, *J* = 6 Hz); 3.42-3.45 (p, 1H); 3.93-4.31 (m, 12H); 6.83-7.00 (m, 8H).

Anal. Calcd. for $C_{23}H_{31}NO_5$: C, 68.81; H, 7.78; N, 3.49. Found: C, 68.57; H, 7.78; N, 3.39.

sym-(*N*-Octylamino)dibenzo-16-crown-5 (**6**).

This compound was obtained in 74% yield as a white solid with mp 57-58°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3324 (NH), 1257, 1225, and 1140 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.87 (t, 3H, *J* = 6 Hz); 1.12-1.32 (m, 10H), 1.55-1.58 (m, 2H); 1.97 (br s, 1H); 2.75 (t, 2H, *J* = 6 Hz); 3.38-3.44 (p, 1H); 3.86-3.97 (m, 4H); 4.00-4.30 (m, 8H); 6.82-7.00 (m, 8H).

Anal. Calcd. for $C_{27}H_{39}NO_5$: C, 70.87; H, 8.59; N, 3.06. Found: C, 70.70; H, 8.53; N, 3.46.

sym-(*N*-Dodecylamino)dibenzo-16-crown-5 (**7**).

This compound was obtained in 67% yield as a white solid with mp 72-73°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3324 (NH), 1259, 1231, and 1124 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.88 (t, 3H, *J* = 6 Hz); 1.26 (br s, 18H), 1.55-1.58 (m, 2H); 1.97 (br s, 1H); 2.75 (t, 2H, *J* = 6 Hz); 3.39-3.45 (p, 1H); 3.87-4.31 (m, 12H); 6.82-7.00 (m, 8H).

Anal. Calcd. for $C_{31}H_{47}NO_5$: C, 72.48; H, 9.22; N, 2.73. Found: C, 72.58; H, 9.48; N, 2.71.

Preparation of *sym*-Dicyclohexano-16-crown-5-oxyacetic Acid (**14**).

A mixture of lariat ether carboxylic acid **8** (6.60 g, 16.3 mmole), 0.70 g of 5% rhodium on alumina catalyst, 1.0 g of glacial acetic acid and 320 ml of 1-butanol was hydrogenated at 65 °C under 500 psi of hydrogen for 16 hours. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo* to give 6.80 g (100%) of **14** as a colorless oil; ir (neat): ν 3650-2200 (OH), 1748 (C=O), 1267 and 1148 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00-2.10 (m, 16H), 3.10-4.63 (m, 19H).

Anal. Calcd for $C_{21}H_{36}O_8$: C, 60.56; H, 8.71. Found: C, 60.41; H, 8.73.

General Procedure for the Preparation of Lariat Ether Amides **15**-**24**, **29** and **30**.

The lariat ether carboxylic acid (5.0 mmole) was added to 10 ml of dry benzene under nitrogen. After cooling to 0°, oxalyl chloride (20 mmole) 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 was dissolved in acetonitrile and the solution was added dropwise to the corresponding amine (5.0 mmole) and triethylamine (5.0 mmole) in acetonitrile at 0° under nitrogen. (For **19** anhydrous ammonia was introduced into a cooled acetonitrile solution of the corresponding acid chloride.) 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 *in vacuo* gave the crude lariat ether amide that was purified by column chromatography or recrystallization.

N-Hexyl *sym*-Dibenzo-16-crown-5-oxyacetamide (**15**).

Column chromatography on silica gel with dichloromethane as eluent gave an 81% yield of white solid with mp 102-104°; ir (potassium bromide): ν 3333 (NH), 1668 (C=O), 1120 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.88-1.41 (m, 11H), 2.85-3.30 (m, 2H), 3.75-4.32 (m, 13H), 4.36 (s, 2H), 6.75-6.95 (m, 8H), 7.58 (br s, 1H).

Anal. Calcd. for $C_{27}H_{37}NO_7 \bullet H_2O$: C, 64.72; H, 7.74. Found: C, 64.86; H, 7.45.

N-Hexyl *N*-Methyl *sym*-Dibenzo-16-crown-5-oxyacetamide (**16**).

Column chromatography on alumina with dichloromethane as eluent gave a 46% yield of colorless oil; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 1645 (C=O), 1261, 1120 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.80-1.31 (m, 13H), 2.92 (s, 3H), 2.90-3.27 (m, 2H), 3.67-4.34 (m, 13H), 4.41 (s, 2H), 6.73-6.94 (m, 8H).

Anal. Calcd. for $C_{29}H_{41}NO_7 \bullet CH_2Cl_2$: C, 60.49; H, 7.16. Found: C, 60.89; H, 7.27.

N-Dodecyl *sym*-Dibenzo-16-crown-5-oxyacetamide (**17**).

Column chromatography on silica gel with dichloromethane as eluent gave a 79% yield of white solid with mp 99-100°; ir (potassium bromide): ν 3390 (NH), 1675 (C=O), 1261, 1110 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.82-1.39 (m, 23H), 3.00-3.34 (m, 2H), 3.75-4.32 (m, 15H), 4.30 (s, 2H), 6.76-6.97 (m, 8H), 7.50 (br s, 1H)).

Anal. Calcd. for $C_{33}H_{49}NO_7 \bullet H_2O$: C, 67.21; H, 8.71. Found: C, 67.09; H, 8.41.

N-Phenyl *sym*-Dibenzo-16-crown-5-oxyacetamide (**18**).

Recrystallization from methanol produced a white solid in 93% yield with mp 164-165°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3339 (NH), 1677 (C=O), 1257, 1121 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.85-4.03 (m, 5H), 4.09-4.16 (m, 4H), 4.31 (s, 4H), 4.36 (s, 2H), 6.84-7.04 (m, 8H), 7.19-7.30 (m, 2H), 7.55-7.68 (m, 3H), 9.47 (s, 1H).

Anal. Calcd. for $C_{27}H_{29}NO_7$: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.48; H, 6.06; N, 2.95.

sym-(Decyl)dibenzo-16-crown-5-oxyacetamide (**19**).

To the oily product, hexanes were added. Stirring for 2 hours at room temperature to gave a white solid with mp 60-62° in 96% yield; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3471 (NH), 1686 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.85 (t, 3H, J = 6Hz), 1.28 (s, 16H), 1.88-1.93 (m, 2H), 3.83-4.16 (m, 12H), 4.52 (d, 2H, *J* = 10 Hz), 4.57 (s, 2H), 5.57 (br s, 2H), 6.80-6.99 (m, 8H).

Anal. Calcd. for $C_{31}H_{45}NO_7$: C, 68.48; H, 8.34; N, 2.58. Found: C, 68.26; H, 8.41; N, 2.64.

N,*N*-Dipentyl α-[*sym*-(Decyl)dibenzo-16-crown-5-oxy]phenylacetamide (**20**).

Column chromatography on silica gel with dichloromethane-ethyl acetate (9:1) as eluent gave an oil in 96% yield; ir (deposit from dichloromethane on a sodium chloride plate): ν 1748 (C=O) 1256, 1122 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.88 (t, 6H, *J* = 6 Hz), 1.10 (t, 3H, J = 7Hz), 1.24 (s, 20H), 1.26-1.29 (m, 8H), 2.04-2.09 (m, 6H), 3.88-4.04 (m, 8H), 4.11-4.27 (m, 2H), 4.49 (d, 1H, *J* = 10 Hz), 5.88 (s, 1H), 6.73-6.93 (m, 8H), 7.25-7.33 (m, 3H), 7.52-7.55 (m, 2H).

Anal. Calcd. for $C_{47}H_{69}NO_7$: C, 74.27; H, 9.15; N, 1.84. Found: C, 74.42; H, 8.91; N, 1.85.

N,*N*-Dipentyl *sym*-(2,2-Dimethylpropyl)dibenzo-16-crown-5-oxyacetamide (**21**).

Column chromatography on silica gel with dichloromethane then ethyl acetate as eluent gave an 83% yield of white solid with

mp 75-76°; ir (deposit from dichloromethane on a sodium chloride plate): ν 1645 (C=O) 1256, 1121 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.76-0.90 (m, 6H), 1.14-1.51 (m, 21H), 2.52-2.64 (m, 1H), 3.21-3.36 (m, 4H), 3.88-3.92 (m, 4H), 4.13-4.16 (m, 4H), 4.22-4.55 (q, 4H), 4.67 (s, 2H), 6.79-6.97 (m, 8H).

Anal. Calcd. for $C_{36}H_{55}NO_7$: C, 70.44; H, 9.03. Found: C, 70.49; H, 8.99.

N-Benzyl *sym*-(Phenyl)dibenzo-16-crown-5-oxyacetamide (**22**).

Column chromatography on silica gel with dichloromethane then dichloromethane-ethyl acetate (9:1) as eluents and recrystallization from ethyl acetate-hexanes produced a white solid in 70% yield with mp 55-57°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3414 (NH), 1673 (C=O) 1256, 1124 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.86-3.96 (m, 2H), 3.97-4.03 (m, 2H), 4.04-4.18 (m, 4H), 4.36 (d, 2H, J = 10 Hz), 4.48 (d, 2H, J = 6 Hz), 4.74 (t, 4H, J = 4.5 Hz), 6.68-6.93 (m, 8H), 7.15-7.35 (m, 5H), 7.38-7.43 (m, 3H), 7.62-7.65 (m, 2H), 10.01 (s, 1H).

Anal. Calcd. for $C_{34}H_{35}NO_7$: C, 71.68; H, 6.19; N, 2.46. Found: C, 71.41; H, 6.04; N, 2.45.

N,N-Dipentyl α-[*sym*-(Phenyl)dibenzo-16-crown-5-oxy)phenylacetamide (**23**).

An 87% yield of white solid with mp 69-71° was realized after recrystallization from ethyl acetate-hexanes; ir (deposit from dichloromethane on a sodium chloride plate): ν 1647 (C=O), 1256, 1138 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.70 (t, 6H, *J* = 6 Hz), 0.81-1.04 (m, 8H), 1.13-1.41 (m, 4H), 2.97-3.11 (m, 4H), 3.84-3.97 (m, 4H), 4.01-4.15 (m, 4H), 4.30 (d, 1H, *J* = 10 Hz), 4.59 (d, 1H, *J* = 10 Hz), 4.70 (d, 1H, *J* = 10 Hz), 4.78-4.82 (d, 1H, *J* = 10 Hz), 5.84 (s, 1H), 6.72-6.91 (m, 8H), 7.28-7.36 (m, 6H), 7.53 (d, 2H, J = 1.6 Hz), 7.93 (d, 2H, J = 1.5 Hz).

Anal. Calcd. for $C_{43}H_{53}NO_7$: C, 74.22; H, 7.67; N, 2.01. Found: C, 74.19; H, 7.28; N, 1.99.

N-Hexyl *sym*-Dicyclohexano-16-crown-5-oxyacetamide (**24**).

Column chromatography on silica gel with dichloromethane as eluent gave a 56% yield of yellowish oil; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3361 (NH), 1645 (C=O) 1261, 1120 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.72-1.51 (m, 27H), 3.15-4.24 (m, 17H), 7.67 (s, 1H).

Anal. Calcd. for $C_{27}H_{45}NO_7$: C, 63.13; H, 9.67. Found: C, 62.90; H, 9.22.

Lipophilic Lariat Ether Amide **29**.

This compound was obtained in 95% yield as a colorless oil; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 1640 (C=O), 1125 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.82-2.00 (m, 53H), 2.52 (t, 2H, *J* = 6 Hz), 2.80-3.30 (m, 3H), 3.47-4.01 (m, 18H), 6.80 (d, 1H, *J* = 3 Hz), 6.99 (d, 1H, *J* = 3 Hz), 7.1 (dd, 1H, *J* = 4 Hz).

Anal. Calcd. for $C_{44}H_{79}NO_6$: C, 73.59; H, 11.09. Found: C, 73.54; H, 11.14.

Lipophilic Lariat Ether Amide **30**.

This compound was obtained in 96% yield as a colorless oil; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 1640 (C=O), 1124 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.80-2.10 (m, 51H), 2.30 (m, 1H), 2.51 (t, 2H, *J* = 6 Hz), 3.08 (m, 3H), 3.62-3.97 (m, 19H), 6.70 (d, 1H, *J* = 3 Hz), 6.99 (br s, 1H), 7.00 (d, 1H, *J* = 3 Hz).

Anal. Calcd. for $C_{44}H_{79}NO_6$: C, 73.59; H, 11.09. Found: C, 73.81; H, 11.24.

General Procedure for the Preparation of Lariat Ether Amides **25** and **26.**

A mixture of lariat ether amine **6** or **7** (0.98 mmole), *N,N*-dipentylchloroacetamide (0.35 g, 1.50 mmole), sodium bicarbonate (0.13 g, 1.55 mmole), and a catalytic amount of sodium iodide in dry acetonitrile (20 ml) was refluxed for 48 hours. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in dichloromethane (30 ml), and the solution was washed with water (30 ml) and then with brine (30 ml), dried over magnesium sulfate, and evaporated *in vacuo*. Column chromatography on silica gel with ethyl acetate-hexanes (1:4) and then with ethyl acetate-hexanes (1:2) gave the product as a colorless oil.

N,N-Dipentyl [*N*-Octyl *sym*-amino)dibenzo-16-crown-5]-acetamide (**25**).

This compound was obtained as a colorless oil in 86% yield; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 1634 (C=O) 1256, 1142 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.80-0.92 (m, 9H), 1.27 (m, 18H), 1.53 (m, 6H), 2.85 (t, 2H, *J* = 6 Hz), 3.29 (t, 2H, *J* = 6 Hz), 3.44 (t, 2H, *J* = 6 Hz), 3.59-3.65 (m, 1H), 3.77 (s, 2H), 3.86-3.98 (m, 4H), 4.12-4.16 (m, 4H), 4.30-4.33 (m, 4H), 6.80-6.99 (m, 8H).

Anal. Calcd. for $C_{39}H_{62}N_2O_6$: C, 71.52; H, 9.54; N, 4.28. Found: C, 71.30; H, 9.35; N, 4.33.

N,N-Dipentyl [*N*-Dodecyl *sym*-(amino)dibenzo-16-crown-5]-acetamide (**26**).

This compound was isolated as a colorless oil in 84% yield; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 1641 (C=O) 1256, 1139, 1121 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.80-0.92 (m, 9H), 1.25 (m, 26H), 1.53 (m, 6H), 2.85 (t, 2H, *J* = 6 Hz), 3.27 (t, 2H, *J* = 6 Hz), 3.45 (t, 2H, *J* = 6 Hz), 3.59-3.65 (m, 1H), 3.76 (s, 2H), 3.89-3.95 (m, 4H), 4.12-4.16 (m, 4H), 4.31-4.34 (m, 4H), 6.80-6.99 (m, 8H).

Anal. Calcd. for $C_{43}H_{70}N_2O_6$: C, 72.64; H, 9.92; N, 3.94. Found: C, 72.5.3; H, 9.70; N, 3.96.

General Procedure for the Preparation of Lariat Ether *O*-Benzylhydroxamates **37-42**.

The lariat ether carboxylic acid (5.0 mmole) was added to dry benzene (10 ml) under nitrogen. After cooling to 0°, oxalyl chloride (2.50 g, 20 mmole) was added dropwise. The solution was stirred at room temperature for one hour, heated at 60° for one hour, and evaporated *in vacuo* to give the corresponding lariat ether acid chloride that was used immediately in the next step. *O*-Benzylhydroxylamine hydrochloride (800 mg, 5.0 mmole) was suspended in dry acetonitrile (10 ml) and pyridine (0.80 ml, 10 mmole) was added. The mixture was cooled to 0° and an acetonitrile solution of the lariat ether acid chloride was added dropwise. The mixture was allowed to warm to room temperature and then stirred at room temperature for 24 hours. The mixture was evaporated *in vacuo* and the residue dissolved in ethyl acetate. The solution was washed with 0.6 *N* hydrochloric acid, water, 0.6 *M* aqueous sodium bicarbonate, and water, dried over magnesium sulfate, and evaporated *in vacuo* to produce the lariat ether *O*-benzyl-hydroxamate.

O-Benzyl 2-(*sym*-Dibenzo-16-crown-5-oxy)decanohydroxamate (**37**).

Column chromatography on silica gel with dichloromethane-ethyl acetate (9:1) as eluent and then recrystallization from methanol gave a 76% yield of a white solid with mp 96-98°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3288 (NH), 1689 (C=O) 1258, 1124 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.87 (t, 3H, *J* = 6 Hz), 1.26 (s, 10H), 1.67-1.91 (m, 4H), 3.82-3.98 (m, 4H), 4.01-4.19 (m, 8H), 4.65 (d, 1H, *J* = 10 Hz), 4.90 (s, 2H), 6.81-7.06 (m, 8H), 7.26-7.34 (m, 5H), 10.55 (s, 1H).

Anal. Calcd. for $C_{36}H_{47}NO_8$: C, 69.61; H, 7.63; N, 2.25. Found: C, 69.22; H, 7.85; ; N, 2.44.

O-Benzyl (*sym*-Di[4(5)-*tert*-butylbenzo]-16-crown-5-oxy)acetohydroxamate (**38**).

Recrystallization from pentane provided a white solid with mp 55-57° in 75% yield; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3276 (NH), 1695 (C=O) 1267, 1145 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (s, 18H), 3.88-3.90 (m, 4H), 4.11-4.28 (m, 8H), 4.35 (s, 2H), 4.92 (s, 2H), 6.77-6.88 (m, 4H), 6.98-7.00 (m, 2H), 7.22-7.34 (m, 5H), 10.40 (s, 1H).

Anal. Calcd. for $C_{36}H_{47}NO_8$: C, 69.61; H, 7.63; N, 2.25. Found: C, 69.32; H, 7.62; ; N, 2.22.

O-Benzyl [*sym*-(2-Tolyl)dibenzo-16-crown-5-oxy]acetohydroxamate (**39**).

Column chromatography on silica gel with dichloromethane-ethyl acetate (9:1) as eluent and then recrystallization from ethyl acetate-hexanes gave a 68% yield of a white solid with mp 68-70°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3327 (NH), 1685 (C=O) 1256, 1123 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H), 3.84-3.88 (m, 2H), 3.99-4.06 (m, 4H), 4.12-4.16 (m, 4H), 4.48 (d, 2H, *J* = 10 Hz), 4.72 (d, 2H, *J* = 10Hz), 4.74 (s, 2H), 6.73-6.95 (m, 8H), 7.19-7.31 (m, 8H), 7.58 (m, 1H), 9.50 (s, 1H).

Anal. Calcd. for $C_{35}H_{37}NO_8$: C,70.10; H, 6.22; N, 2.34. Found: C, 70.32; H, 6.27; ; N, 2.14.

O-Benzyl [*sym*-(3-Tolyl)dibenzo-16-crown-5-oxy]acetohydroxamate (**40**).

Column chromatography on silica gel with dichloromethane-ethyl acetate (9:1) as eluent and recrystallization from ethyl acetate-hexanes produced a 52% yield of white solid with mp 118-120°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3340 (NH), 1693 (C=O) 1255, 1124 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H), 3.84-3.88 (m, 2H), 4.03-4.17 (m, 6H), 4.25 (d, 2H, *J* = 12 Hz), 4.72 (d, 2H, *J* = 10 Hz), 4.82 (s, 2H), 4.89 (s, 2H), 6.67-6.94 (m, 8H), 7.23-7.35 (m, 9H), 9.51 (s, 1H).

Anal. Calcd. for $C_{35}H_{37}NO_8$: C,70.10; H, 6.22; N, 2.34. Found: C, 70.09; H, 6.34; N, 2.27.

O-Benzyl [*sym*-(4-Tolyl)dibenzo-16-crown-5-oxy]acetohydroxamate (**41**).

Column chromatography on silica gel with dichloromethane-ethyl acetate (9:1) as eluent and then recrystallization from ethyl acetate-hexanes provided a 64% yield of a white solid with mp 66-68°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3335 (NH), 1686 (C=O) 1256, 1124 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.39 (s, 3H), 3.85-3.88 (m, 2H), 4.03-4.16 (m, 6H), 4.25 (d, 2H, *J* = 12 Hz), 4.69 (d, 2H, *J* = 12 Hz), 4.89 (s, 2H), 4.92 (s, 2H), 6.69-6.96 (m, 8H), 7.21-7.35 (m, 9H), 9.47 (s, 1H).

Anal. Calcd. for $C_{35}H_{37}NO_8$: C,70.10; H, 6.22; N, 2.34. Found: C, 70.32; H, 6.27; N, 2.14.

O-Benzyl [*sym*-(Cyclohexyl)dibenzo-16-crown-5-oxy]acetohydroxamate (**42**).

Column chromatography on silica gel with dichloromethane-ethyl acetate (9:1) as eluent and then recrystallization from ethyl acetate-hexanes gave a 62% yield of white solid with mp 125-127°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3336 (NH), 1696 (C=O) 1256, 1122 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.83-1.34 (m, 6H), 1.81-2.09 (m, 5H), 3.81-3.92 (m, 4H), 4.01-4.16 (m, 6H), 4.57 (d, 2H, *J* = 11 Hz), 4.85 (d, 4H, *J* = 15 Hz), 6.79-6.98 (m, 8H), 7.26-7.32 (m, 5H), 9.35 (s, 1H).

Anal. Calcd. for $C_{34}H_{41}NO_8$: C, 69.02; H, 6.93; N, 2.37. Found: C, 69.23; H, 6.97; N, 2.22.

General Procedure for the Preparation of Lariat Ether Urethanes **44** and **45**.

To a solution of the lariat ether alcohol (2.0 mmole) in 15 ml of benzene (for **44**) or pyridine (for **45**) was added phenyl isocyanate (0.26 g, 2.2 mmole) in 5 ml of pyridine. The reaction mixture was stirred at 115° for 5 hours. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel with dichloromethane then dichloromethane-ethyl acetate (3:1) as eluents. Since the ^1H nmr spectrum showed the presence of residual diphenylurea, the product was washed with cold diethyl ether (3x10 ml) to give the pure lariat ether urethane.

N-Phenyl *sym*-Dibenzo-16-crown-5 Carbamate (**44**).

This compound was obtained in 89% yield as a white solid with mp 133-135°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3352 (NH), 1695 (C=O) 1257, 1125 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.89-3.93 (m, 4H), 4.12-4.16 (m, 4H), 4.43-4.46 (m, 4H), 6.80-7.07 (m, 8H), 7.28-7.42 (m, 5H), 10.2 (s, 1H).

Anal. Calcd. for $C_{26}H_{27}NO_7 \bullet CH_2Cl_2$: C, 66.13; H, 5.79. Found: C, 66.19; H, 5.61.

N-Phenyl *sym*-(Propyl)dibenzo-16-crown-5 Carbamate (**45**).

This compound was isolated in 92% yield as a white solid with mp 119-121°; ir (deposit from dichloromethane solution on a sodium chloride plate): ν 3349 (NH), 1692 (C=O) 1255, 1121 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.99 (t, 3H, *J* = 6 Hz), 1.48-1.60 (m, 2H), 2.25-2.34 (m, 2H), 3.90-3.95 (m, 4H), 4.12-4.16 (m, 4H), 4.45 (d, 2H, *J* = 10 Hz), 4.70 (d, 2H, *J* = 10 Hz), 6.79-7.05 (m, 8H), 7.27-7.36 (m, 5H), 10.24 (s, 1H).

Anal. Calcd. for $C_{29}H_{37}NO_7$: C, 68.62; H, 6.55. Found: C, 68.77; H, 6.43.

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REFERENCES AND NOTES

[1] For recent reviews: [a] G. W. Gokel, *Chem. Soc. Rev.*, 39 (1992); [b] Y. Inoue and G. W. Gokel, Cation Binding by

Macrocycles, Marcel Dekker, New York, 1990; [c] R. D. Hancock and A. E. Martell, *Chem. Rev.*, **89**, 1875 (1989); [d] R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, *Chem. Rev.*, **91**, 1721 (1991); [e] R. M. Izatt, J. S. Bradshaw, K. Pawlak, R. L. Bruening and B. J. Tarbet, *Chem. Rev.*, **92**, 1261 (1992); [f] R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, *Chem. Rev.*, **95**, 2529 (1995); [g] J. S. Bradshaw, R. M. Izatt, A. V. Bordunov, C. Y. Zhu and J. K. Hathaway, Comprehensive Supramolecular Chemistry, Vol. **1**, G. W. Gokel, ed., Pergamon, New York, 1996, p 35.

[2] G. W. Gokel, D. M. Dishong and C. J. Diamond, *J. Chem. Soc., Chem. Commun.*, 1053 (1980).

[3] 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 and O. F. Schall, Comprehensive Supramolecular Chemistry, Vol. **1**, G. W. Gokel, ed., Pergamon, New York, 1996, p 97.

[4] H. Sigel and R. B. Martin, *Chem. Rev.*, **82**, 385 (1982).

[5] J. P. Behr, J.-M. Lehn, A. C. Dock and D. Moras, *Nature*, **295**, 526 (1982).

[6] R. Kataky, P. E. Nicholson and D. Parker, *Tetrahedron Lett.* **30**, 4559 (1989).

[7] H. Tsukube, H. Adachi and S. Morosawa, *J. Chem. Soc., Perkin Trans. 1*, 89 (1989).

[8] H. Tsukube, H. Adachi and S. Morosawa, *J. Chem. Soc., Perkin Trans. 1*, 1537 (1989).

[9] J. C. Hernandez, J. E. Trafton and G. W. Gokel, *Tetrahedron Lett.*, **32**, 6269 (1991).

[10] S. P. Kasprzyk and R. A. Bartsch, *J. Heterocyclic Chem.*, **30**, 119 (1993).

[11] X. Huang, Y. Jang, J. J. Collier, H.-S. Hwang and R. A. Bartsch, *J. Heterocyclic Chem.*, **33**, 223 (1996).

[12] A. Ohki, J. P. Lu and R. A. Bartsch, *Anal. Chem.*, **66**, 651 (1994).

[13] A. Ohki, S. Maeda, J. P. Lu and R. A. Bartsch, *Anal. Chem.*, **66**, 1743 (1994).

[14] A. Ohki, J. P. Lu, X. Huang and R. A. Bartsch, *Anal. Chem.*, **66**, 4332 (1994).

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

[16] S. Elshani, H. Du, K. E. Laintz, N. R. Natale, C. M. Wai, N. S. A. Elkarim and R. A. Bartsch, *Tetrahedron*, **56**, 4651 (2000).

[17] N. S. A. Elkarim, Doctoral Dissertation, Texas Tech University, pp 94-102 (1998).

[18] R. O. Hutchins, W. Y. Su, R. Sivakumar, F. Cistone and Y. P. Stercho, *J. Org. Chem.*, **48**, 3412 (1983).

[19] J. E. Wrobel and G. Ganem, *Tetrahedron Lett.*, **22**, 3447 (1981).

[20] R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2987 (1971).

[21] 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).

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

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

[24] R. A. Bartsch, C. L. Cowey, S. Elshani, M.-J. Goo, V. J. Huber, S. N. Ivy, R. J. Johnson, J. S. Kim, E. Luboch, J. A. McDonough, M. J. Pugia, B. Son and Q. Zhao, *J. Heterocyclic Chem.*, **38**, 311 (2001).

[25] B. P. Czech, A. Czech, B. Son, H. K. Lee and R. A. Bartsch, *J. Heterocyclic Chem.*, **23**, 465 (1986).

[26] W. A. Charewicz, G. S. Heo and R. A. Bartsch, *Anal. Chem.*, **54**, 2094 (1982).

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