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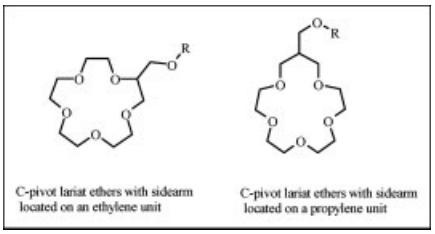
Received January 2, 2009
DOI 10.1002/jhet.225
Published online 12 November 2009 in Wiley InterScience (www.interscience.wiley.com).



This review covers the main strategies for the synthesis of *C*-pivot lariat ethers as well as their specific syntheses.

J. Heterocyclic Chem., **46**, 1035 (2009).

Contents

1. INTRODUCTION

In 1967, Charles Pedersen, who was a chemist working at Du Pont, discovered a simple method for synthesizing a crown ether when he was trying to prepare a complexing agent for divalent cations [1]. Crown ethers are heterocyclic compounds that consist of a ring containing several ether groups. Pedersen realized that the cyclic polyethers presented a new class of complexing agents that were capable of binding alkali metal cations. The fields of organic synthesis, phase transfer catalysis, and other emerging disciplines benefited from the discovery of crown ethers. Pedersen shared the 1987 Nobel Prize in Chemistry for the discovery of the synthetic routes to and binding properties of crown ethers. Since Pedersen's discovery, there has been great interest in the synthesis of crown compounds in an attempt to find molecules with superior properties and proper applications in various areas [2–12].

Lariat ethers are a class of macrocyclic polyether compounds having one or more donor-group-bearing sidearms [13]. Functionalization of macrocyclic polyether compounds with such additional donating centers is a good way to increase their complexing ability and selectivity [14]. Lariat ethers should achieve a somewhat higher level of cation binding than generally observed with simple macrocyclic crown ethers by presenting a cation with a three-dimensional intramolecular array of binding sites as do the cryptands. Moreover, a higher degree of flexibility and dynamics characteristic of ionophores could be achieved. Thus, they combine characteristics of podands, corands, and cryptands [10,15].

The concept of lariat ethers has been extended to include molecules having sidearms that contain ionizable, lipophilic, or chromogenic groups. Functionalization of crown ethers with ionizable sidearms opened access to switchable lariat ethers [16]. Furthermore, lariat ethers with chromogenic sidearms offer distinct advantages in detection of cations when compared with the other available analytical methods. The color changes associated with complexation of different cations could make such sensors more versatile. Changes in potential or other properties could also be useful in sensing, but they would be less apparent. It is noteworthy that Takagi *et al*. pioneered chromogenic lariat ether complexation [17].

Moreover, macrocyclic ligands with one or more fluorine-containing sidearms have potential applications in metal ion separations involving a fluorous phase or supercritical carbon dioxide. Also, macrocycles with a fluoride label on the macrocyclic framework have potential applications as ^{19}F NMR probes [18]. Macrocycles with longer spacers between the macro ring and the perfluoroalkyl group were found to exhibit greater extraction efficiencies than analogues with shorter spacers.

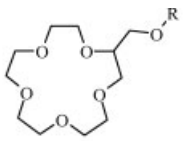
This review casts light on the main strategies for the synthesis of *C*-pivot lariat ethers as well as their specific syntheses. A number of other reviews [10,15,19] that have appeared concerning lariat ethers did not cover the synthesis of these compounds in an organized manner. We have concentrated on the crown compounds containing at least 12-membered rings.

2. NOMENCLATURE

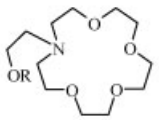
The physical resemblance of CPK molecular models of these compounds to rope lassoes coupled with the concept of ''roping and tying'' a cation suggested the name lariat ethers [13].

Lariat ethers are divided according to the point at which the sidearm and the macro ring meet (pivot atom), into two main classes:

(i) *C*-pivot lariat ethers **1** [20]: Systems in which sidearms are attached to a carbon of the macro ring.
(ii) *N*-pivot lariat ethers **2** [21]: Systems in which sidearms are attached to a nitrogen of the macro ring.



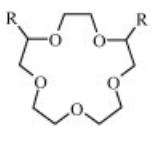
1
A carbon-pirvot lariat ether



2
A nitrogen-pivot lariat ether

When more than one sidearm is attached, the number of them is designated using standard prefix and the Latin word brachium which means arm.

Two-armed compounds **3** and **4** are thus bibracchial lariat ether and the name is abbreviated BiBLEs [22,23]. A three-armed compound **5** is tribracchial lariat ether and the name is abbreviated TriBLEs, *etc*.



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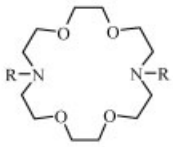
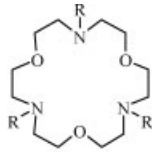


4
Bibracchial lariat ether



5
Tribracchial lariat ether

3. LARIAT ETHER COMPLEXATION PROCESS

The lariat ether idea is represented schematically in Figure 1. The sidearm which contains one or more donor groups placed in appropriate position would provide a third dimension of solvation to a ring-bound cation (binding of Type A) [15].

Two armed crown ethers have various kinds of cation binding modes (Fig. 2) [22]

(a) Only one sidearm interacts with guest metal cation (Type B).
(b) Two side arms provide coordination from the same or opposite sides (Type C or Type D).

It is noteworthy to mention that carbon pivot lariat ethers proved to be more chemically stable but less dynamic than the *N*-pivot counterparts. The greater flexibility of the latter is due to the facile inversion of the nitrogen atom, a property not shared by carbon.

In comparison with ordinary crown ethers extractants, a crown ether with a proton-ionizable group has the advantage that metal ion transport into the organic phase does not require concomitant transport of an ion (or ions) from the aqueous phase (Fig. 3). This feature is of immense importance to potential practical applications of crown ether-type extractants in which the hard aqueous phase anions of chloride, nitrate, and sulfate would be involved [24].

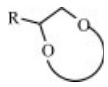
An additional advantage of proton-ionizable crown ethers is that a mechanism for cation release has been incorporated (Fig. 4). Following the extraction step, shaking of the separated organic phase with aqueous hydrochloric acid strips the extracted metal ions into an aqueous phase and regenerates the neutral form of the extractant [24].

The attachment of sufficient lipophilic groups to the proton-ionizable ionophores allows it to remain completely in the organic phase during extraction of alkali-metal cations from alkaline aqueous phases.

4. MAIN CLASSES OF *C*-PIVOT LARIAT ETHERS

C-Pivot lariat ethers are classified into two main classes A and B according to the point of attachment of the sidearm to the macro ring.

4.1. Attachment of the sidearm to an ethylenoxy unit of the macro ring.



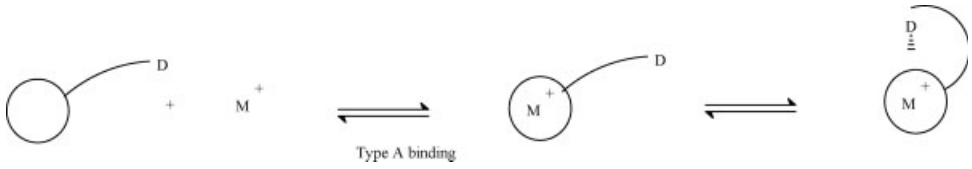


Figure 1. Cation binding by a single sidearmed crown ether.

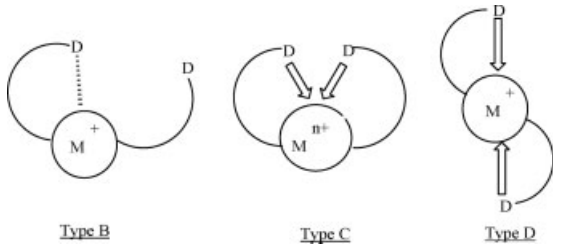
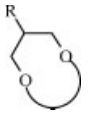


Figure 2. Various modes of cation binding by two armed crown ethers.

4.2. Attachment of the sidearm to the middle carbon of a trimethylene unit of the macro ring.



5. GENERAL AND SPECIFIC SYNTHESIS OF *C*-PIVOT LARIAT ETHERS

5.1. Synthesis of lariat ethers in which the sidearm is attached to an ethylenoxy unit of the macro ring.

5.1.1. Synthesis of C-pivot lariat ethers. There are different methods by which the pivot carbon could be incorporated into the macrocycle.

5.1.1.1. Incorporation of the pivot carbon via a glycerol unit. When the pivot carbon is incorporated *via* a glycerol unit the primary and secondary hydroxyl groups could be used as nucleophiles for formation of the ring. The remaining primary hydroxyl group must be protected by a group which could be removed after cyclization leaving a free hydroxy-methyl group for attachment of the sidearm. In other cases, the sidearm is incorporated into the glycerol unit before cyclization.

Glycerol units needed for the synthesis of *C*-pivot lariat ethers are prepared using one of the following routes:

Route 1: Reactions of alcohols or phenols **6** with epichlorohydrin (**7**). In the case of alcohol precursors, the chlorohydrin was isolated and then treated with 50% NaOH to give the glycidyl ether **8**. In the case of phenolic precursors, the conversion to the glycidyl ether could be accomplished in a single step. Hydrolysis with dilute perchloric acid afforded the corresponding diol **9**, as illustrated in Scheme 1 [25].

Route 2: Reactions of alcohols or phenols **6** with allyl chloride (**10**) to give the corresponding allyl ether **11** followed by bishydroxylation of the ethylene unit to furnish the corresponding diol **9** upon reaction with alkaline OsO_4 and *N*-methylmorpholine *N*-oxide (Scheme 2) [26].

Route 3: Bis(hydroxylation) of acrolein diethyl acetal **12** on treatment with $KMnO_4$ to give 1,2-dihydroxy-3,3-diethoxypropane (**13**) (Scheme 3) [27].

In the above three routes, cyclization of the diol is accomplished in the standard fashion by using NaOH or NaH as the base in concert with the appropriate oligoethylene glycol ditosylate, dimesylate, or dihalide in THF. In some cases, *t*-BuOLi/*t*-BuOH or NaOH/dioxane are used as bases. The reactions were typically heated overnight, although longer reaction times were required in some cases. Purification was usually accomplished by chromatography followed by crystallization in case when the *C*-pivot crown was a solid rather than an oil.

When the protecting group (R) is benzyl or allyl, they can be easily removed after cyclization with the appropriate ditosylates to give the corresponding hydroxymethyl derivative upon treatment with 10% Pd/C and a catalytic amount of *p*-toluenesulfonic acid [28,29] (PTSA) in ethanol under 3.4 atmosphere of H_2 at room temperature.

Yields were not appreciably altered by the presence of an aliphatic rather than an aromatic sidearm [20] (alcohols *vs*. phenol precursors), but the presence of donor group at a distance from the crown's cavity suitable for secondary interaction was important.

It was postulated by Greene [30] that a template effect was responsible for the high yields observed in these ring-formation reactions. Evidence for the template effect has accumulated [31], although there have also been skeptics of this theory [32]. In any event in molecules designed with sidearm capable of secondary binding through donor groups in them, one might anticipate that yields would be high (more organization in the transition state leading to a cycle) when such donor groups are present in contrast to the situation prevailing in their absence.

An example of this is shown in Scheme 4 in which the cyclization of 2-methoxyphenyloxypropanediol (**14**) with

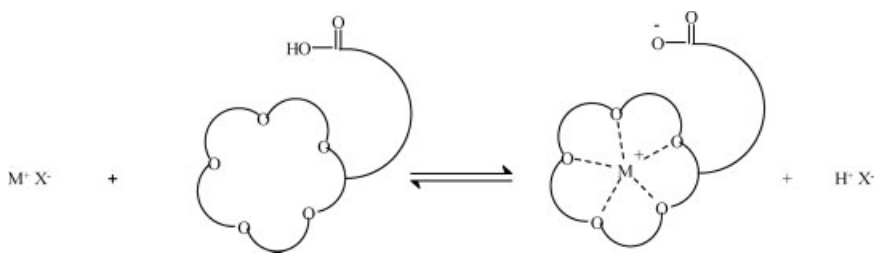


Figure 3. Metal ion extractant by a proton-ionizable crown ether.

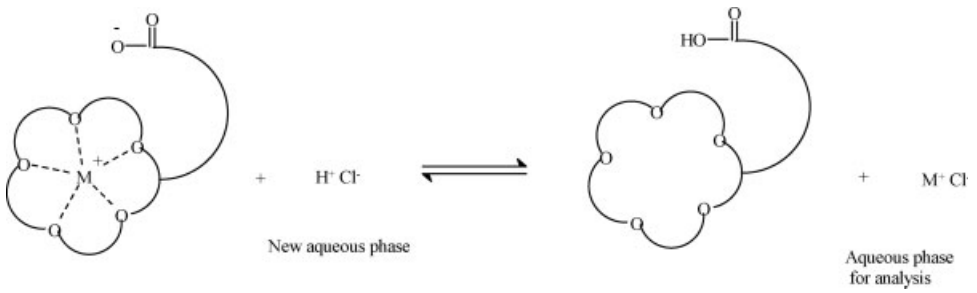


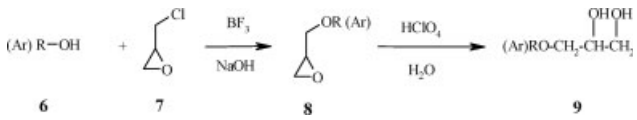
Figure 4. Metal ion stripping from an ionized crown ether-metal ion complex.

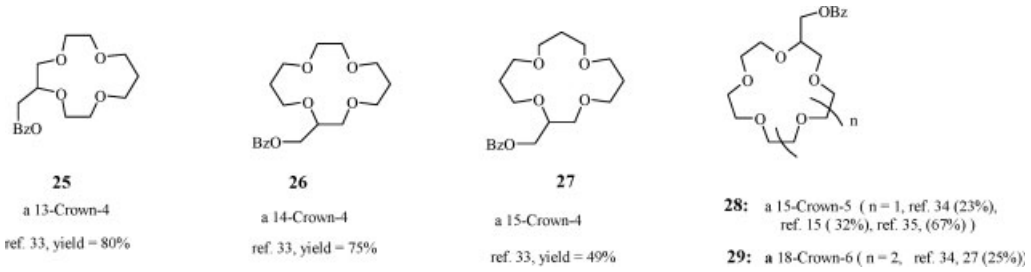
tetraethylene glycol ditosylate (**15**) to yield the corresponding 15-crown-5 **16** is illustrated. When the 2-methoxy group is present, the cycle is formed in about 70%, where in its absence the yield of the cyclization decreases to 34%. The yield of cyclization also decreases to 57% and 29%, respectively, when the methoxy group is present in the 3-(*meta*) or 4-(*para*) positions [13,20].

Using route 1 Gokel *et al*. [13] reported the synthesis of a series of 15-crown-5 ether derivatives **18–24** by treatment of the appropriate diols **17** with tetraethylene glycol ditosylates **15a** or dimesylates **15b** in the presence of NaH in THF (Scheme 5).

Similarly, a variety of benzyloxymethyl crown ethers of different cavity sizes **25–29** have been prepared.

Scheme 1





The latter compounds can be converted to the corresponding hydroxymethyl derivatives on treatment with H_2 over Pd/C.

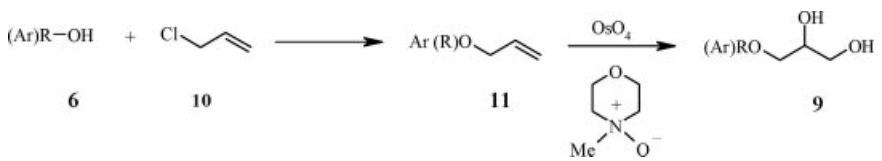
Gokel *et al*. [36] used the same approach for the synthesis of olefinic crown ethers **30**. The latter compounds were used as starting materials for the synthesis of epoxy lariat crown ethers **34** and **35** as outlined in Scheme 6.

Olefinic crown ethers **30** were converted to the corresponding diols **32** by treatment of the olefins with *N*-methylmorpholine *N*-oxide (**31**) in the presence of catalytic osmium tertraoxide. The diols thus obtained were converted to the monotosylates **33** on treatment with *p*-toluenesulfonyl chloride in pyridine. The latter compound underwent ring closure under basic condition to the desired epoxy crown ethers **34** and **35**.

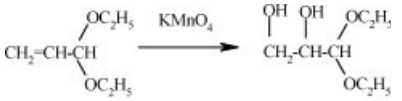
Bradshaw *et al*. [37] reported the synthesis of bis-allyloxymethyl-18-crown-6 **37** by the 2 + 2 cycloaddition reaction of the commercially available allyloxymethyl ethylene glycol **9** and diethylene glycol ditosylate **36** (Scheme 7).

Gokel *et al*. [26] used route 2 for the synthesis of the cholestanyl lariat ether **41** as shown in Scheme 8. Commercially available 3β-cholestanol (**38**) was *O*-allylated under phase transfer catalytic conditions to give the

Scheme 2



Scheme 3



12 **13**

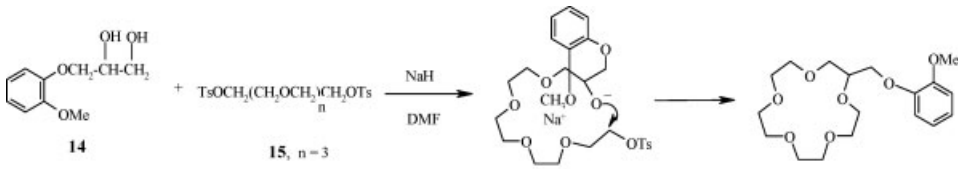
crystalline allyl cholestanyl ether **39**. Catalytic bishydroxylation of **39** using OsO_4 and *N*-methylmorpholine *N*-oxide afforded the diol **40**. Reaction of dialkoxide derived from diol **40** and NaH in THF with tetraethylene glycol ditosylate **15** gave after chromatography, cholestanyl lariat ether **41**.

Fukunishi *et al*. [27] used route 3 for the synthesis of hydroxylmethyl-18-crown-6 **45**. Thus, cyclization of **13** with pentaethylene glycol ditosylate **42** gave **43**. Hydrolysis of the latter to the aldehde derivative **44** and subsequent reduction produced **45** in 32% yield (Scheme 9).

5.1.1.2. Incorporation of the pivot carbon via a thioglycerol unit. Nabeshima *et al*. [38] used this approach to synthesize thiolariat ethers **50–55** as outlined in Scheme 10. Alkyl halides or benzyl chloride **47** was treated with thioglycerol **46** to give *S*-alkylated diols **48**. Cyclization of diols **48** with the appropriate oligoethylene glycol ditosylates **15**, **36,** and **49** in a THF suspension of NaH afforded thiolariat ethers **50–55**. Subsequent cleavage of the benzyl moiety of **50, 51, 54** gave the corresponding mercaptomethyl crown ethers **56a–c** in moderate yields.

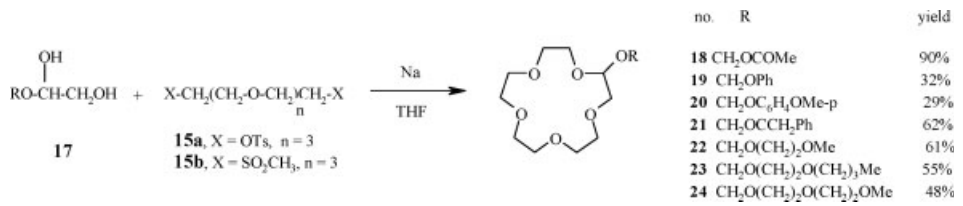
Crown ethers containing a sulfur atom outside the ring have fascinating features for ion and molecular

Scheme 4



14 **15**, n = 3 **16**

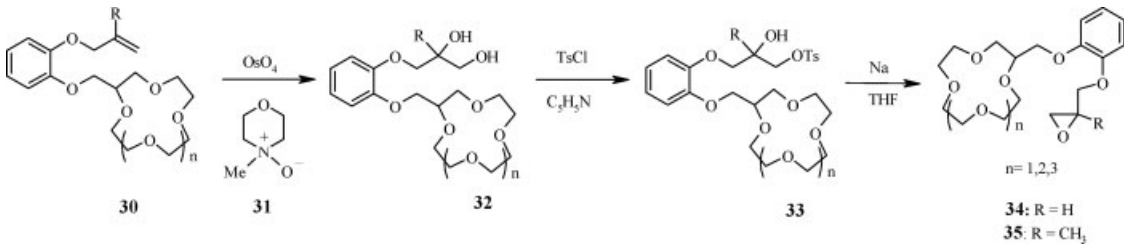
Scheme 5



no.	R	yield
18	CH_2OCOMe	90%
19	CH_2OPh	32%
20	$CH_2OC_6H_4OMe$-p	29%
21	CH_2OCCH_2Ph	62%
22	$CH_2O(CH_2)_2OMe$	61%
23	$CH_2O(CH_2)_2O(CH_2)_2Me$	55%
24	$CH_2O(CH_2)_2O(CH_2)_2OMe$	48%

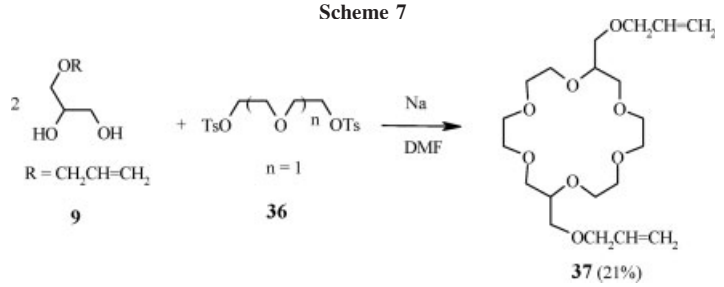
17 **15a**, X = OTs, n = 3; **15b**, X = SO_2CH_3, n = 3

Scheme 6



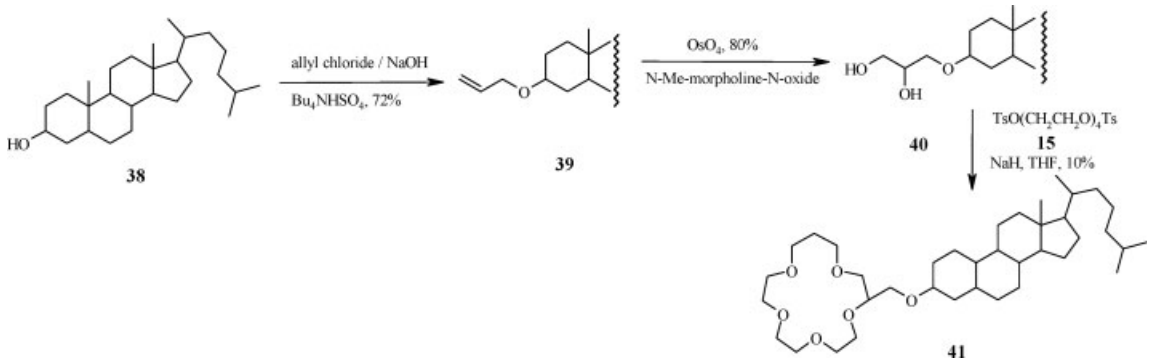
30 **31** **32** **33** **34:** R = H; **35**: R = CH_3, n = 1,2,3

Scheme 7

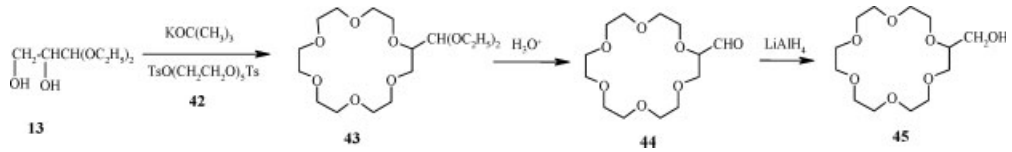


9 **36** **37** (21%)

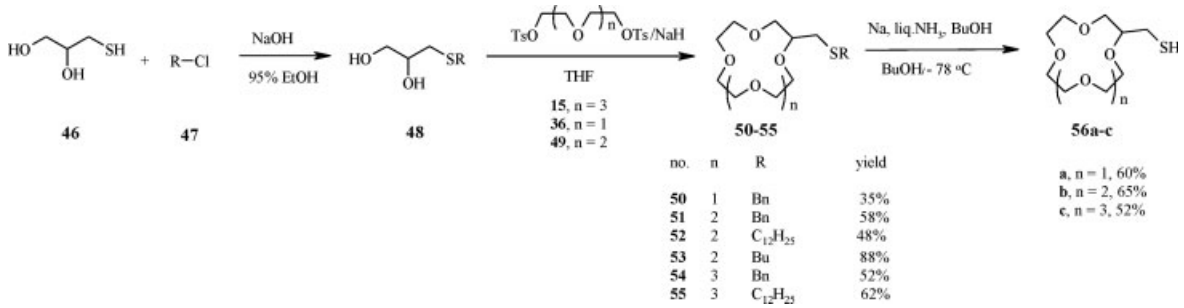
Scheme 8



Scheme 9



Scheme 10



no.	n	R	yield
50	1	Bn	35%
51	2	Bn	58%
52	2	$C_{12}H_{25}$	48%
53	2	Bu	88%
54	3	Bn	52%
55	3	$C_{12}H_{25}$	62%

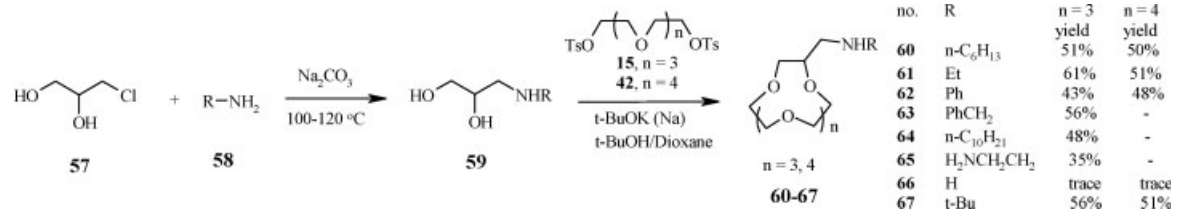
recognition. Crown ethers bearing a mercapto group as a side chain are considered to be key compounds in host–guest chemistry. These mercapto crowns can be used as precursors for various thiolariat ethers whose side chain contain a substituent unstable under basic cyclization reaction conditions. The mercapto crown may also be useful for polymer-support thiolariat ethers and for functionalization of surfaces of electrode and other solid materials [38,39].

5.1.1.3. Incorporation of the pivot carbon via a 3-(N-substituted amino)-1,2-propanediol. Okahara *et al.* [40] reported the synthesis of various *N*-substituted or unsubstituted aminomethyl crown ethers **60–67** from the reaction between 3-amino-1,2-propanediols **59** and the oligoethylene glycol ditosylates **15** and **42** as outlined in Scheme 11.

The starting material, 3-(*N*-substituted amino)-1,2-propanediols (**59**) were prepared from 3-chloro-1,2-propanediol (**57**) and the appropriate primary amine **58**.

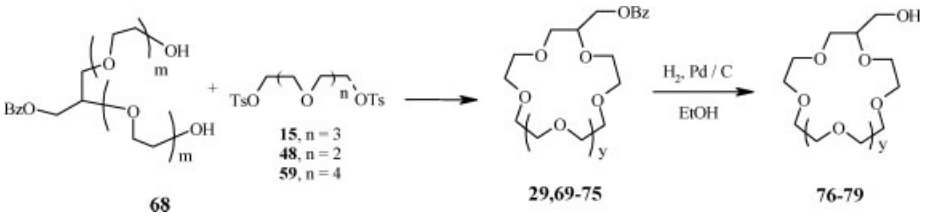
5.1.1.4. Incorporation of the pivot carbon via benzyloxy(alkoxy)methyl oligoethylene glycols or their ditosylates derivatives. Reaction of benzyloxyoligoethylene glycol **68** with the appropriate oligoethylene glycol ditosylate **15**, **48**, and **59** in THF in presence of CsOH, KOH, or *t*-BuOK gave the corresponding benzyloxymethyl 18-crown-6 **29** [35], 21-crown-7 **69** and **71** [41], 24-crown-8 [41] **70** and **72**, 27-crown-9 [41] **74**, and 30-

Scheme 11



no.	R	n = 3 yield	n = 4 yield
60	n-C_6H_{13}	51%	50%
61	Et	61%	51%
62	Ph	43%	48%
63	$PhCH_2$	56%	-
64	n-$C_{10}H_{21}$	48%	-
65	$H_2NCH_2CH_2$	35%	-
66	H	trace	trace
67	t-Bu	56%	51%

Scheme 12

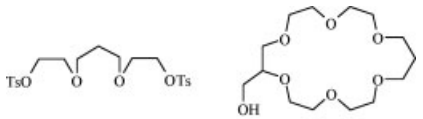


crown-10 **73** and **75** [41]. Debenzylation of **69, 70, 74,** and **75** afforded the hydroxymethyl derivatives **76–79** (Scheme 12) (Table 1) [41,42].

Montanari and Tundo [44] used a similar approach for the synthesis of *t*-butoxymethyl-18-crown-6 in an 38% yield from *t*-butoxymethyldiethylene glycol and triethylene glycol ditosylate followed by conversion into the corresponding hydroxymethyl-18-crown-6 on reaction with HBF_4 in CH_2Cl_2.

The diol **68** ($m = 1$) was obtained by the reaction of (benzyloxymethyl)ethylene glycol with chloroacetic acid followed by reduction. The diols **68** ($m = 2, 3$) were obtained by the reaction of 3-*O*-benzylglycerol with THP-blocked oligoethylene glycol monochloride in the presence of lithium *t*-butoxide in *t*-butyl alcohol followed by deprotection upon treatment with HCl in CH_2Cl_2—MeOH [29,43].

Hydroxymethyl 19-crown-6 **81** was obtained by cyclization of diol **68** ($m = 1$) and ditosylate **80** with potassium *t*-butoxide in THF, followed by debenzylation [45].



Gandour *et al*. [28] reported the synthesis of alkoxymethyl 18-crown-6 **84–87** by cyclization of 1-(alkoxymethyl)-3,6,9-trioxaundecane-1,11-diol **83** with diethylene glycol ditosylate in the presence of KH. The hydroxymethyl derivative **44** can be easily liberated by removal of the allyl group on treatment of **87** with Pd/C and *p*-toluenesulfonic acid (Scheme 13).

The diol **83** can be obtained by the reaction of (alkoxymethyl) oxirane **8** with excess 3,7-dioxaoctane-1,8-diol **82** in the presence of catalytic amount of NaH.

5.1.1.5. Incorporation of the pivot carbon via bis(aminomethyl) oligoethylene glycols. Okahara *et al*. [46] reported the synthesis of bis(aminomethyl)oligoethylene glycols **89** by treatment oligoethylene glycol diglycidyl ethers **88** with excess amine. Reaction of bis diols **89** with the oligoethylene glycol ditosylates **36** and **48** gave the corresponding bis(aminomethyl) crown ethers **90–98** (Scheme 14).

5.1.1.6. Incorporation of the pivot carbon via 2-methylallyl ether derivatives by a one-step or two-step bromination-cyclization sequence. Okahara *et al*. [25,47,48] reported the synthesis of 2-methyl-2-bromomethyl 12-, 13-, 14-, 15-, 16-crown ethers using two methods, A and B.

In method A, the appropriate 2-methylallyl ether **99** (obtained upon treatment of methallyl chloride with excess of the appropriate oligoethylene glycol) undergo intramolecular bromoalkoxylation with *N*-bromosuccinimide (NBS) using $LiBF_4$ as the template in 1,2-dichloroethane. In this instance, NBS acts as a bromating agent toward the double bond rather toward the allylic position. Bromination occurs, as expected from the less substituted side of the alkene with formation of the more stable carbocation [49]. The tertiary carbocation is intercepted intramolecularly by the hydroxyl group. This reaction is probably favored by the templating effect of sodium cation which is also present in this solution as the tetrafluoroborate salt [15,50].

Using this method Okahara *et al*. [25,47] prepared bromomethyl-substituted lariat ethers having a 12-, 14-crown-4 **100** and **101** as well as 15-crown-5 **102** rings (Scheme 15).

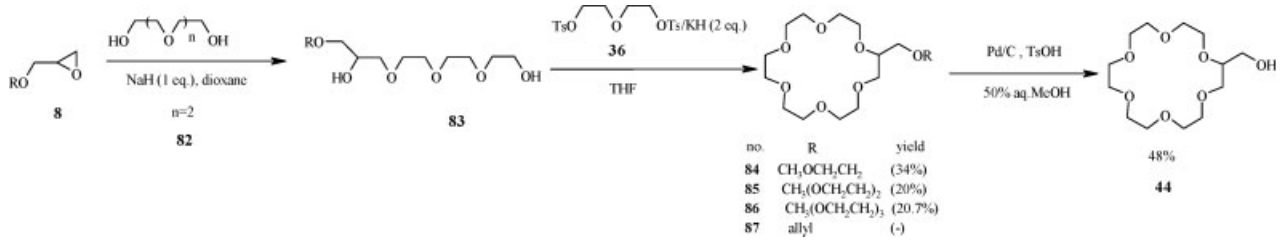
In method B, 2-methylallyl ethers **99** undergo intermolecular bromoalkoxylation with NBS and the appropriate oligoethylene glycol **82** and **103** followed by intramolecular cyclization with benzenesulfonyl chloride using lithium *tert*-butoxide as the base in *tert*-butyl

Table 1

Compounds **29**, **60–79**.

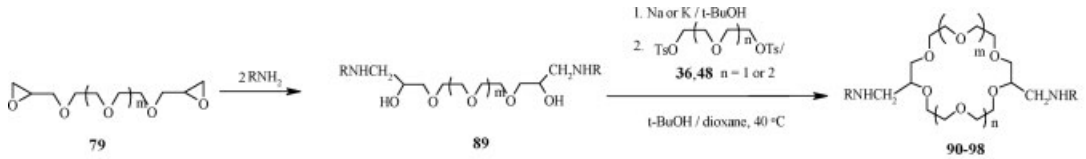
Comp. no.	*m*	*n*	*y*	Ref. (yield)
29	1	2	2	35 (73)
69	1	3	3	41 (27)
70	1	4	4	41 (14)
71	1	3	3	43 (44)
72	1	4	4	43 (35)
73	3	2	6	43 (39)
74	2	3	5	42 (38)
75	2	4	6	42 (35)
76	1	3	3	41 (81)
77	1	4	4	41 (72)
78	2	3	5	42 (97)
79	2	4	6	42 (86)

Scheme 13



no.	R	yield
84	$CH_3OCH_2CH_2$	(34%)
85	$CH_3(OCH_2CH_2)_2$	(20%)
86	$CH_3(OCH_2CH_2)_3$	(20.7%)
87	allyl	(-)

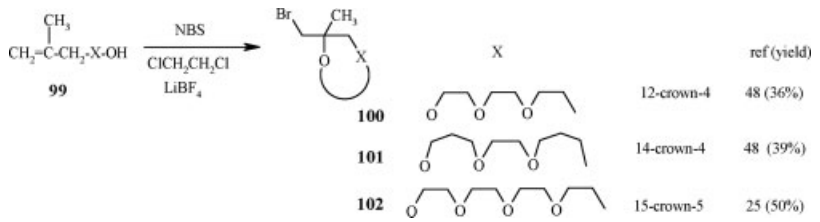
Scheme 14



88a, m = 0; **b**, m = 1; **c**, m = 2

no.	R	m	n		yield
90	H	0	1	15-crown-5	trace
91	CH_3	1	1	18-crown-6	63%
92	C_2H_5	0	1	15-crown-5	60%
93	C_2H_5	0	2	18-crown-6	58%
94	C_2H_5	1	1	18-crown-6	70%
95	C_2H_5	1	2	21-crown-7	53%
96	C_6H_{13}	0	1	15-crown-5	54%
97	C_6H_{13}	1	1	18-crown-6	65%
98	C_6H_{13}	2	1	21-crown-7	40%

Scheme 15



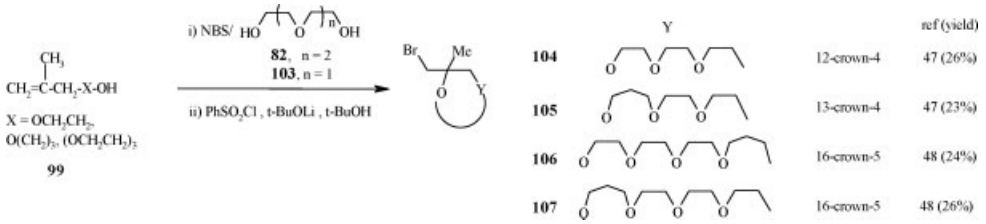
	X		ref (yield)
100		12-crown-4	48 (36%)
101		14-crown-4	48 (39%)
102		15-crown-5	25 (50%)

alcohol [47,48]. Using this approach, methyl lariat ether based on 12-crown-4 **104**, 13-crown-4 **105**, and 16-crown-5 **106** and **107** have been prepared as depicted in Scheme 16.

Nakatsuji *et al*. [51] and Okahara *et al*. [52] reported the synthesis of two kinds of positional isomers of the *C*-pivot type of double-armed 15-crown-5 ethers **109** and **111** by bromoalkoxylation reaction of the appropriate bis(2-methylallyl)ethers **108** and **110** with triethylene glycol and ethylene glycol, respectively, in the presence of $NaBF_4$ as the template ion (method A) (Scheme 17).

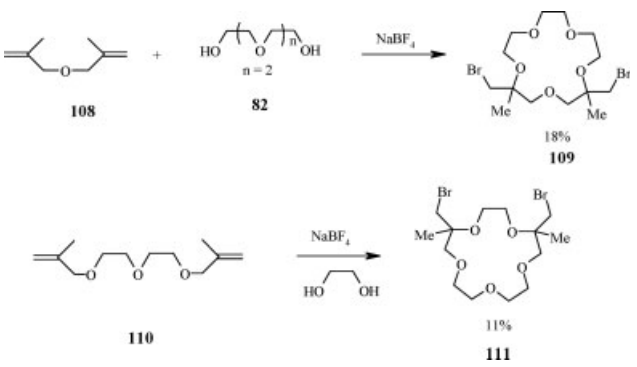
The same authors [51,52] used (method B) to prepare another positional isomer of double-armed 15-crown-5

Scheme 16



	Y		ref (yield)
104		12-crown-4	47 (26%)
105		13-crown-4	47 (23%)
106		16-crown-5	48 (24%)
107		16-crown-5	48 (26%)

Scheme 17



ether **114** as well as some positional isomers of bis(bromomethyl)dimethyl 18-crown-6 **115** and **116** and 21-crown-7 **117** and **118** by intramolecular cyclization reaction of the diols **113**, which were obtained by bromoalkoxylation reaction of bis(2-methylallyl)ether **112** with the appropriate oligoethylene glycol, by using benzenesulfonyl chloride under basic conditions as depicted in Scheme 18.

5.1.2. Synthesis of C-pivot lariat benzocrown ethers. Bartsch *et al*. [45,53] used route 1 (Incorporation of the pivot carbon *via* a glycerol unit, Section 5.1.1.1) for the synthesis of hydroxymethylbenzo-12-crown-4, 14-crown-4 [45] and hydroxymethylbenzo-18-crown-6 [53] by reaction of the appropriate benzyloxymethy diol with the corresponding ditosylates and subsequent debenzylation.

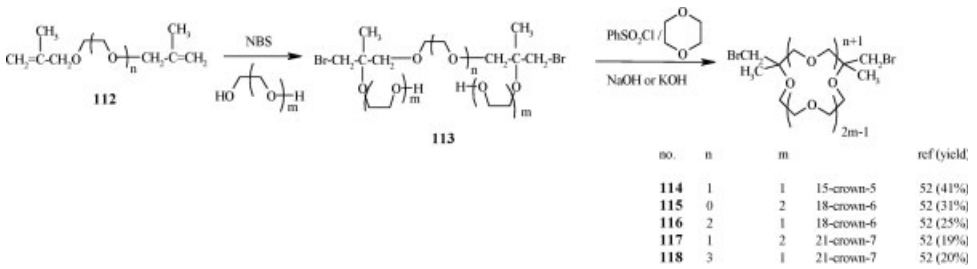
Bartsch *et al*. [53] used the strategy reported in Section 5.1.1.4 (Incorporation of the pivot carbon *via* benzyloxy(alkoxy)methyl oligoethylene glycols or their ditosylate derivatives) for the synthesis of hydroxymethyl benzo-18-crown-6 **120**. Thus, cyclization of the diol **68** ($m = 1$) and ditosylate **119** with KOH in THF/H_2O and subsequent debenzylation gave an 96% yield of **120** (Scheme 19).

The ditosylate **119** was obtained from catechol by initial treatment with 2-chloroethanol to give 1,2-bis(2-hydroxyethoxy)benzene and subsequent reaction with *p*-toluenesulfonyl chloride in pyridine.

The hydroxymethyl benzo-18-crown-6 **120** ($n = 1$) was alternatively obtained in 70% yield by the reaction of catechol **122** with the ditosylate **121** and cesium fluoride in acetonitrile followed by debenzylation (Scheme 20) [43].

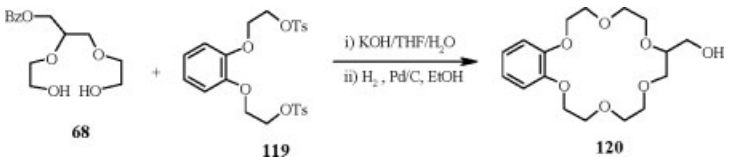
Using a similar approach, Reinhoudt *et al*. [29] reacted benzyloxymethylnonaethylene glycol ditosylate **121** ($n = 3$) with the cesium salt of catechol in acetonitrile followed by debenzylation to furnish 94% of the corresponding hydroxymethylbenzo-30-crown-10 **123**.

Scheme 18

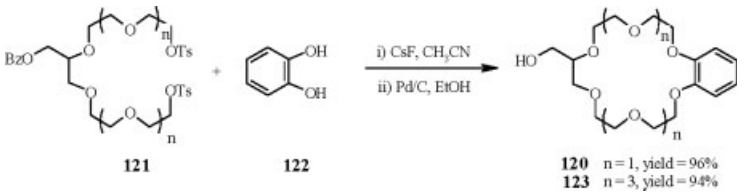


no.	n	m		ref (yield
114	1	1	15-crown-5	52 (41%)
115	0	2	18-crown-6	52 (31%)
116	2	1	18-crown-6	52 (25%)
117	1	2	21-crown-7	52 (19%)
118	3	1	21-crown-7	52 (20%)

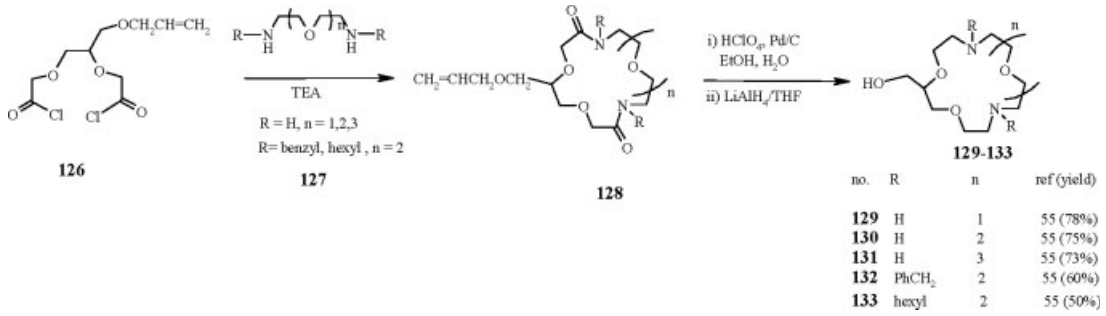
Scheme 19



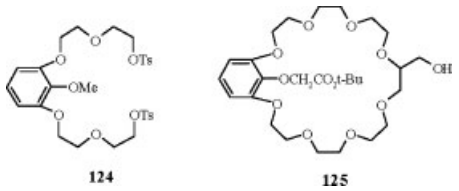
Scheme 20



Scheme 21



Similarly, Bartsch *et al*. [54] reported the synthesis of resorcinol-25-crown-8 **125** with an intraanular oxyacetic acid ester group and a pendant hydroxymethyl function in 99% yield starting from diol **68** ($n = 1$) and ditosylate **124**.



5.1.3. Synthesis of C-pivot lariat azacrown ethers. Preparation of such systems are classified depending on the starting materials as follows.

5.1.3.1. Action of diacid dichloride on diamines. Bartsch *et al*. [55,56] reported the synthesis of hydroxymethyl-substituted diazacrowns in which the cavity sizes are systematically varied as depicted in Scheme 21.

Thus, reaction of 3,6-dioxa-4-(allyloxymethyl)-1,8-octanedioic acid dichloride **126** with the appropriate diamines **127** under high dilution conditions in the presence of TEA afforded the allyloxymethyl-substituted cyclic diamides **128**. The latter compound underwent deprotection by isomerizatrion of the allyl group with palladium on carbon followed by acid-catalyzed cleavage and subsequent reduction with $LiAlH_4$ to give the hydroxymethyl-substituted diazacrowns **129–133** in good yields (50–78%).

5.1.3.2. Reaction of diamines with diiodide or dimesylate. Bradshaw *et al*. [56] reported the synthesis of [(allyloxy)methyl]-diaza-18-crown-6 **136** and **137** by the reaction of the appropriate diamine **127** with diiodide **135** in CH_3CN containing Na_2CO_3 or dimesylate **134** in hexane containing *n*-butyl lithium (Scheme 22).

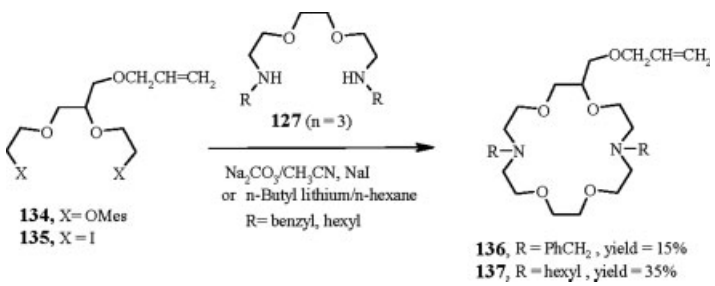
The diacid dichloride **126** as well as the diiodide **135** were prepared as outlined in Scheme 23. Thus, reaction of diol **9** with chloroacetic acid afforded the diacid **138**. The latter underwent chlorination on treatment with oxalyl chloride to give the corresponding diacid dichloride **115**. Reduction of **126** with $LiAlH_4$ afforded the diol **139**. The dimesylate **134** could be obtained from **139** upon treatment with MesCl in pyridine. The diiodide **135** was obtained from **134** by the reaction with NaI in acetone [55].

5.1.3.3. Ring closure of the appropriate diazadiols. The most convenient method to prepare **136** as well as **142** is shown in Scheme 24 [56]. Thus, reaction of diamines **140** with epoxide **8** gave the diazadiol **141**. The Okahara ring closure of **141** using tosyl chloride gave good yields of diaza-18-crown-6 lariat ethers **136** and **142**.

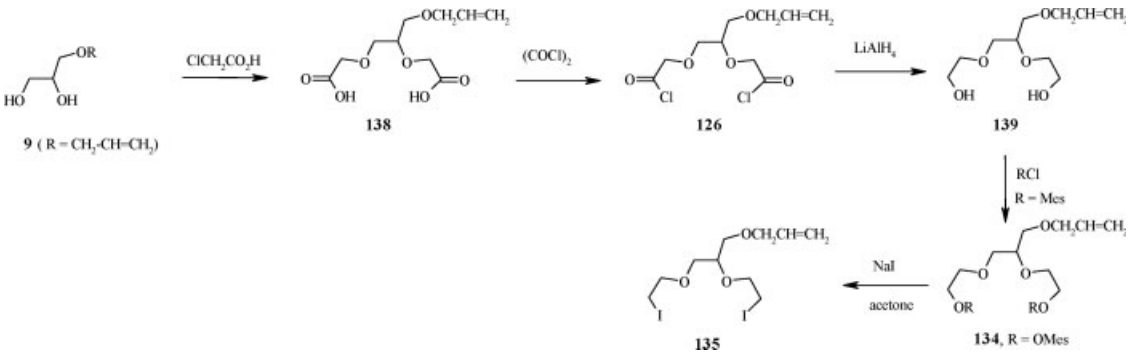
Bradshaw *et al*. [57] prepared *N*,*N*-diethyl- and *N*,*N*-dibenzyldiazapentaethylene glycol **140** in high overall yield from the reaction of *N*-ethyl- or *N*-benzyl-substituted-ethanaolamine **143** with the dihalide **144** (Scheme 25).

Bradshaw [57] reported the synthesis of allyloxymethyl-substituted triaza- and tetraazacrown compounds **146** and **148** by the reaction of the appropriate diamines **145** and **147** with 4-(allyloxymethyl)-1,8-diiodo-3,6-

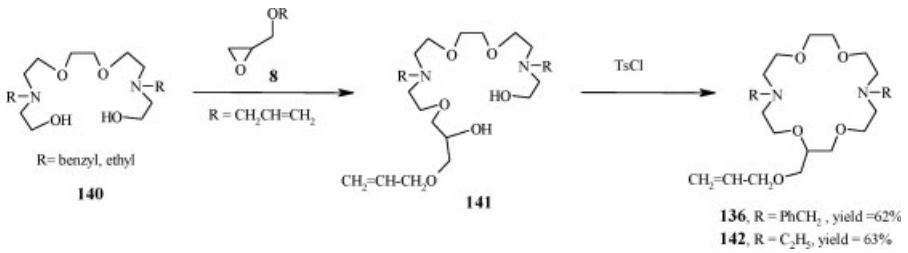
Scheme 22



Scheme 23



Scheme 24



dioxaoctane **135** in refluxing CH_3CN in the presence of anhydrous Na_2CO_3 (Scheme 26).

The starting diamines **145** and **147** were obtained from *N*-[2-(2-chloroethoxy)ethyl]acetamide **149** by initial reaction with each of benzylamine and the appropriate diamines **150** in refluxing toluene in the presence of anhydrous Na_2CO_3 followed by $LiAlH_4$ reduction (Scheme 27).

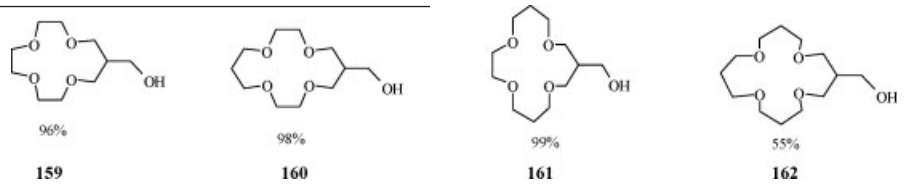
5.2. Synthesis of lariat ethers in which the sidearm is attached to the middle carbon of a trimethylene unit of the macro ring.

5.2.1. Synthesis of C-pivot lariat ethers. There are different methods by which the sidearm can be incorporated into the middle carbon of trimethylene unit of the crown ethers ring.

5.2.1.1. Synthesis of methylenecrown ether followed by hydroboration-oxidation. Tomoi [58] reported the synthesis of 15-crown-5 **155**, 19-crown-6 **156**, and 22-crown-7 **157** with vinylidene group by the reaction of 3-chloro-2-chloromethyl-1-propene **151** with the appropriate oligoethylene glycol **152–154**.

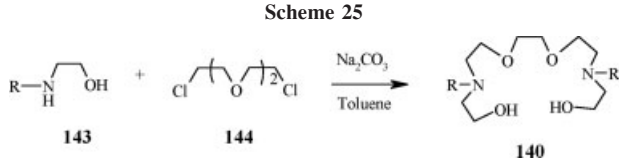
The methylene crown ether **155** was transformed into the corresponding hydroxymethyl crown **158** on treatment with borane-dimethyl sulfide complex followed by oxidation with H_2O_2 (Scheme 28).

Yoshihisa *et al*. [59] and Bartsch *et al*. [33] used a similar approach for the synthesis of hydroxymethyl-substituted crown ethers **159–162** with four ring oxygens and 13-, 14-, 15-, and 16-membered polyether rings.

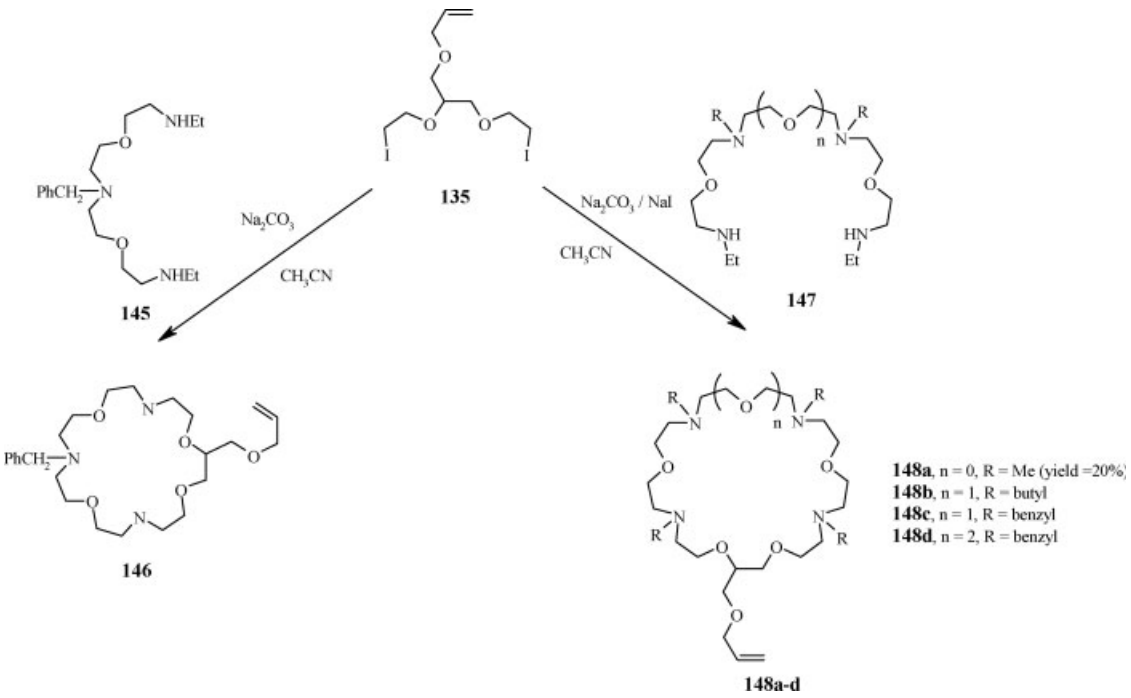


5.2.1.2. Photochemical addition of thioacetic acid to a methylene crown ether followed by reduction. Rasteller *et al*. [39] synthesized mercaptomethyl crown ether **164** by photochemical addition of thioacetic acid to **156** to give thioester **163** followed by cleavage of the thioester with $LiAlH_4$ (Scheme 29).

Scheme 25



Scheme 26



5.2.1.3. Reaction of diols containing sidearm with the corresponding ditosylate compounds. Yoshihisa *et al*. [59] reported the synthesis of lariat ethers **166–169** having a sidearm attached to the 2-position of propane subunit to which was also attached a methyl group by reaction of the appropriate 1,3-propanediol **165** with the corresponding oligoethylene glycol ditosylates **36** and **48** in the presence of NaH as a base in THF (Scheme 30). The introduction of methyl group to the *C*-pivot remarkable improves the complexation ability toward alkali metal cations. As the methyl group is considered to work in restricting the movement of another substituent, this strategy should be also useful for chiral recognition of ammonium salts [25,60,61].

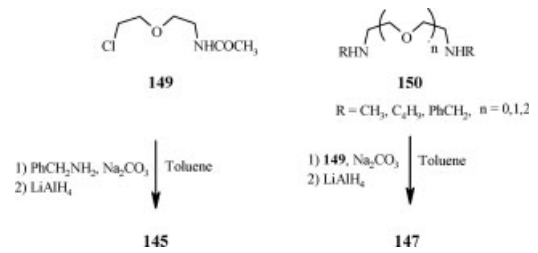
Lariat ethers **166** and **169** (R = —CH_2—O—CH_2Ph) underwent debenzylation upon treatment with Pd/C in EtOH to give the corresponding hydroxymethyl derivatives **170** and **171** [59].

Rasteller *et al*. [39] reported the synthesis of mercaptomethyl crown ether **174** by coupling of the diol **172** with triethylene glycol ditosylate followed by reduction and subsequent reaction with methylsulfonyl chloride to give **173**. Reaction of the latter with potassium thioacetate and subsequent reductive cleavage gave **174** (Scheme 31).

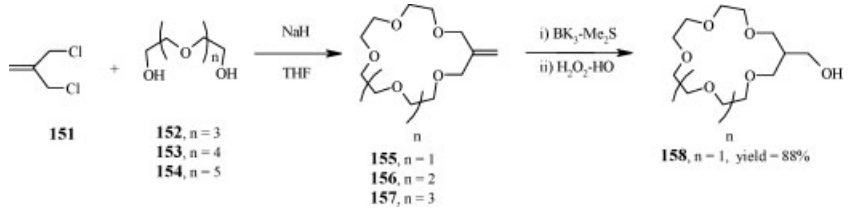
The diol **172** was obtained from multistep reactions starting from diethyl malonate [39].

Weber [62] and Hakushi *et al*. [63] reported the synthesis of lariat ethers with symmetrical double side arms attached through a carbon pivot. They prepared bis(hydroxymethyl) crown ethers **179–183** by reaction of monobenzalpentaerythritol [64] (**175**) with the appropriate oligoethylene glycol ditosylates **15**, **49**, **59**, **176**, and

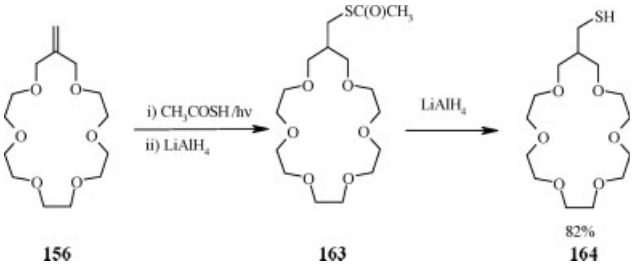
Scheme 27



Scheme 28

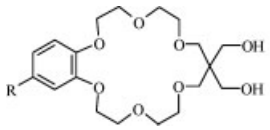


Scheme 29



177 in the presence of NaH, NaOH, or KOH as a base in dioxane or THF, to give the corresponding spirocrown ethers **178** followed by acid hydrolysis (HCl/EtOH) or hydrogenolysis on treatment with H_2, Pd/C (Scheme 32).

Similarly were prepared the bis(hydroxymethyl)benzocrown ethers **184** and **185** from **175** and the appropriate ditosylate followed by acid hydrolysis [62].

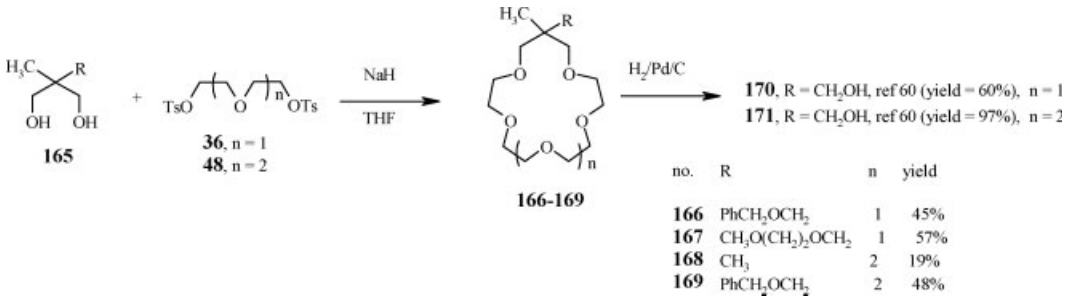


184, R = H, yield = 96%
185, R = CH_3, yield = 92%

Reaction of crown ether diols **180** and **181** with the corresponding oligoethylene glycol monoethyl ether tosylate or oligoethylene glycol tetrahydropyranyl ether in the presence of NaH in THF afforded the corresponding crown ether derivatives with double symmetrical oxyethylene side arms of various chain length (cf. Table 16) [59,62,63,65].

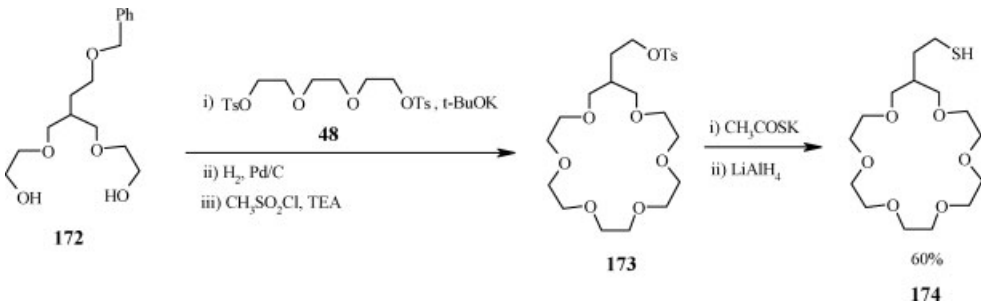
Lariat ethers **190–192** with nonsymmetrical double side arms were prepared from the spiro crown ethers **178** by initial reduction with $LiAlH_4/AlCl_3$ in diethyl ether to afford the hydroxymethyl derivatives **186** in 90 and 92% yields. The latter compounds were then reacted with the appropriate chloride **187** in the presence of NaH in THF to give the crown ether derivatives **188**

Scheme 30

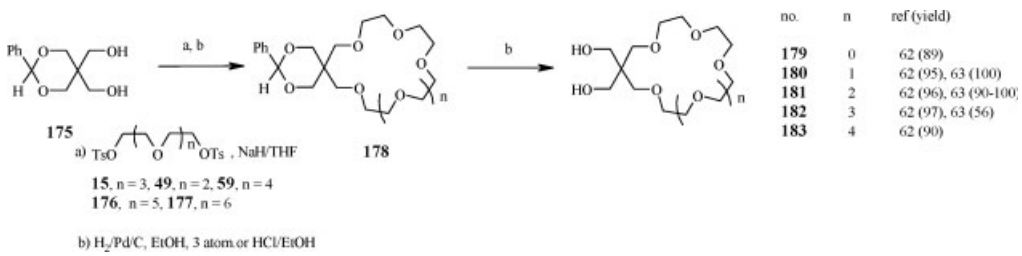


no.	R	n	yield
166	$PhCH_2OCH_2$	1	45%
167	$CH_3O(CH_2)_2OCH_2$	1	57%
168	CH_3	2	19%
169	$PhCH_2OCH_2$	2	48%

Scheme 31

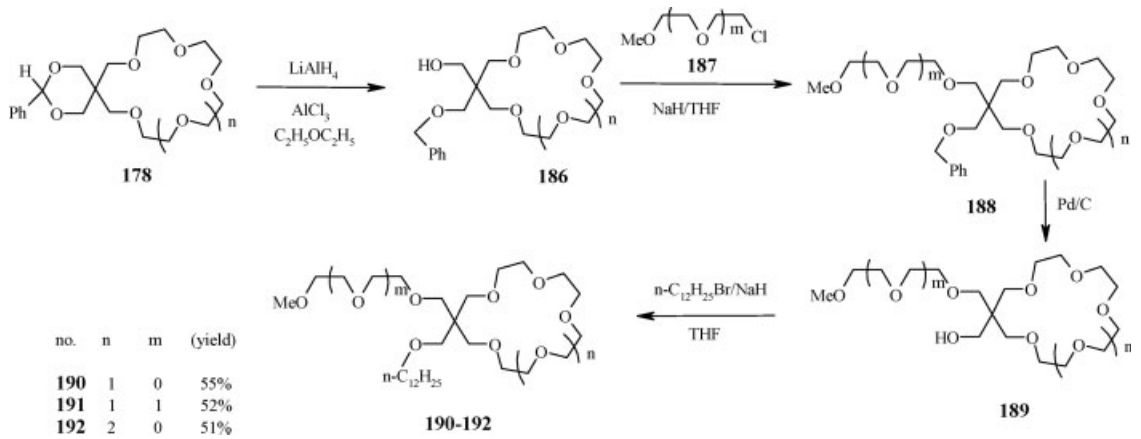


Scheme 32



no.	n	ref (yield)
179	0	62 (89)
180	1	62 (95), 63 (100)
181	2	62 (96), 63 (90-100)
182	3	62 (97), 63 (56)
183	4	62 (90)

Scheme 33



with an oxyethylene chain and a benzyloxymethyl group in 39–47% yields. Hydrogenolysis yielded the corresponding hydroxymethyl crown ethers **189** in 89–95% yields. The latter compounds were then reacted with 1-bromodecane to give **190–192** in 51–55% yield (Scheme 33) [59].

5.2.1.4. Bromoalkoxylation of oligoethylene glycol mono-2-methylallyl ether with NBS and the appropriate alcohol followed by cyclization. Okahara and coworkers [48] prepared lariat crown ethers **195** and **196** having a sidearm in the 2-position to which was also attached a methyl group. Tetraethylene glycol is monosubstituted as its 2-methylpropenyl ether to give **193** and allowed to react with *N*-bromosuccinimide and $Me(CH_2CH_2O)_nH$ to give the crown precursor **194** in which $Me(CH_2CH_2O)_nH$ was incorporated as the incipient sidearm. The cyclization of **194** to **195** and **196** was accomplished on treatment with sodium *t*-butoxide in *t*-butanol (Scheme 34).

A 13-crown-4 version of these compounds was obtained by using triethylene glycol and lithium *t*-butoxide in *t*-butanol [66]. Other variants in ring size and pivot group were also reported by this group [47].

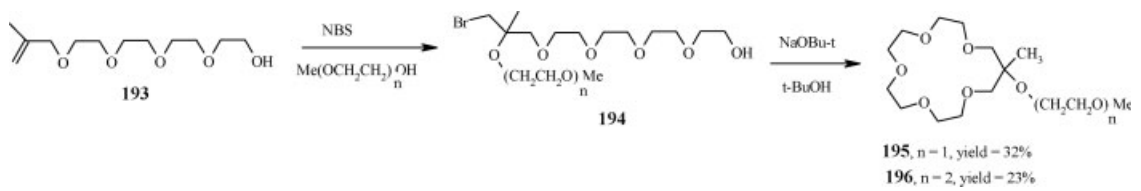
Considerable work has also been done by Inoue and coworkers with $(3n + 1)$-crown systems that incorporate the propene residue [67].

5.2.1.5. Bromoalkoxylation of methylenecrown ethers with NBS and the appropriate alcohol or glycol followed by nucleophilic displacement of the bromide. Ikeda *et al.* [68,69] reported the synthesis of two types of lariat ethers **202–210** and **215** derived from $3n$-methylene-$(3n + 1)$-crown ($n = 5, 6, 7$) with different lengths of oxyethylene sidearm. These two types of *C*-pivot lariat ethers are different in basic skeleton around the pivot carbon, one type such as **202–210** directly connect the oxygen atom to the pivot carbon. The other type such as **215** contains one carbon atom between the pivot carbon and the oxygen atom.

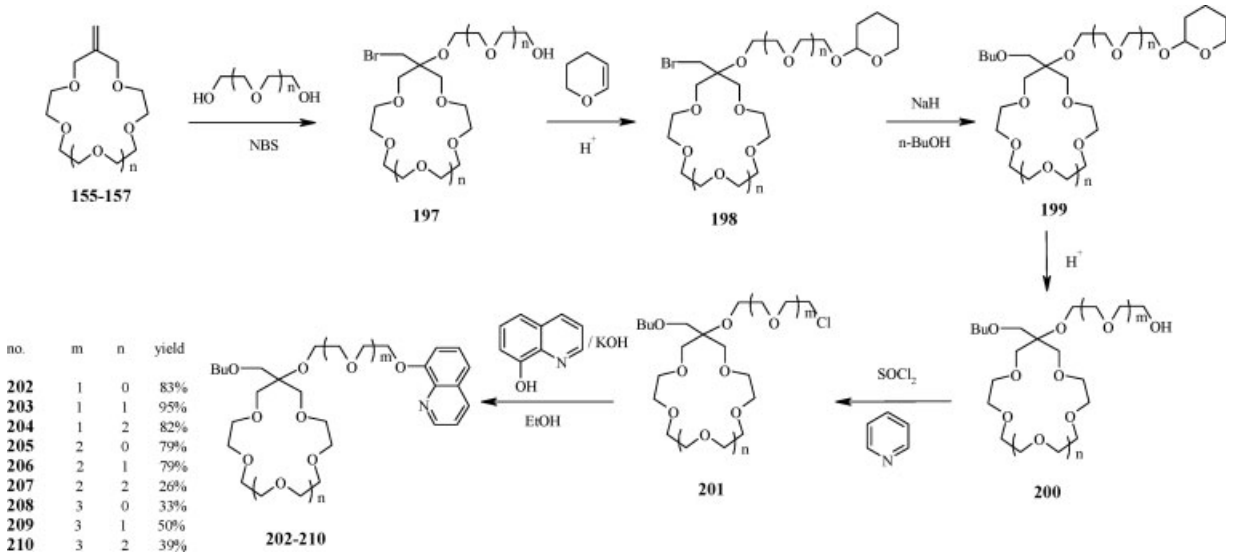
Ligands **202–210** and **215** are structurally regarded to be derived from glycerol and trimethanol-methane, respectively. The difference in skeletal structure of the pivot position of these lariat ethers was found to remarkably affect their complexation properties. The lariat having a 2-methylglycerol structure around the pivot carbon showed much higher complexing ability than did the trimethylolmethane structure.

A series of lariat ethers containing a glycerol unit (compounds **202–210**) were designed to afford systematic structural variations of the crown ring size and the length of the oxyethylene sidearm. The 8-oxyquinoline moiety was introduced at the end of the sidearm of these lariat ethers because of its excellent coordination ability toward alkali metal cations [48]. The presence of the methyl group at the pivot position is expected to play an important role in increasing the complexation ability toward alkali metal cations [48,60,70]. The general synthetic procedures for compounds **202–210** are summarized in Scheme 35. Compounds **197** were obtained from the bromoalkoxylation of $3n$-methylene-$(3n + 1)$-crown-

Scheme 34



Scheme 35

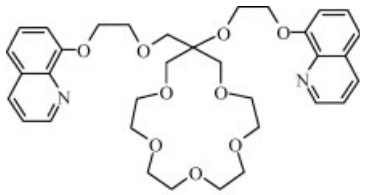


no.	m	n	yield
202	1	0	83%
203	1	1	95%
204	1	2	82%
205	2	0	79%
206	2	1	79%
207	2	2	26%
208	3	0	33%
209	3	1	50%
210	3	2	39%

n (*n* = 5, 6, 7) **155–157** [58] using *N*-bromosuccinimide (NBS) and oligoethylene glycols. The hydroxyl group of compounds **197** was protected by treatment with 3,4-dihydro-2*H*-pyran, according to the conventional method, to give the corresponding tetrahydropyranyl ethers **198**, which were then treated with sodium hydride and *n*-butyl alcohol to give the butoxymethyl derivatives **199**, followed by deprotection under acidic conditions to give butoxymethyl alcohols **200**. The chlorides **201** obtained from the chlorination of alcohols **200** by use of thionyl chloride were further treated with 8-hydroxyquinoline in ethanol in the presence of KOH at reflux temperature for 2 days [71] to give the corresponding lariat ethers **202–210** (Scheme 35).

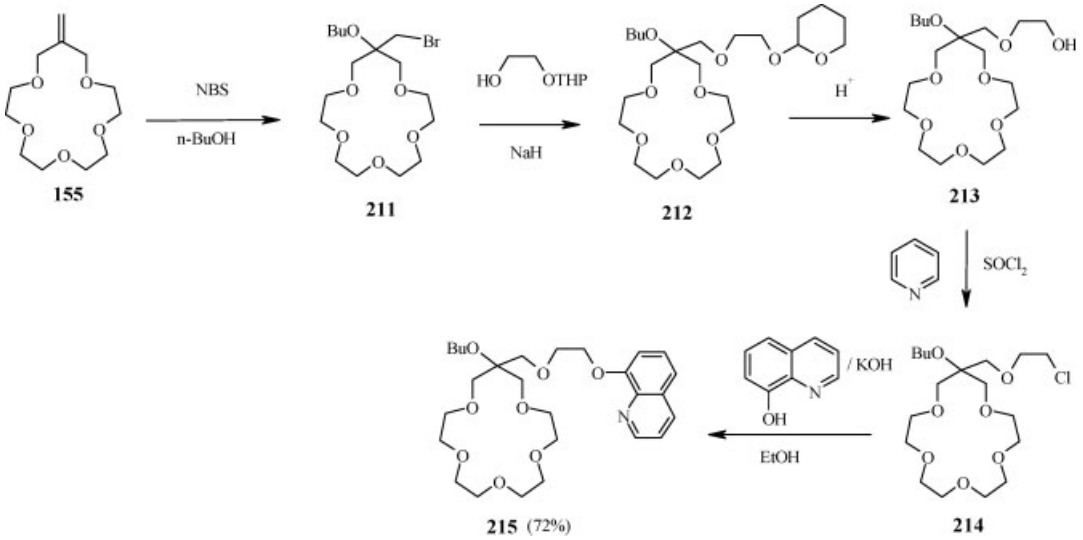
On the other hand, ligand **215** was prepared by changing the reaction sequence used in the case of lariat ethers **202–210**; that is, the bromoalkoxylation of 15-methylene-16-crown-5 (**155**) with NBS and *n*-butyl alcohol was performed as the first step as shown in Scheme 36.

The lariat ether **216**, with two oxyquinoline moieties, was also obtained from substrate **155** in a similar way.

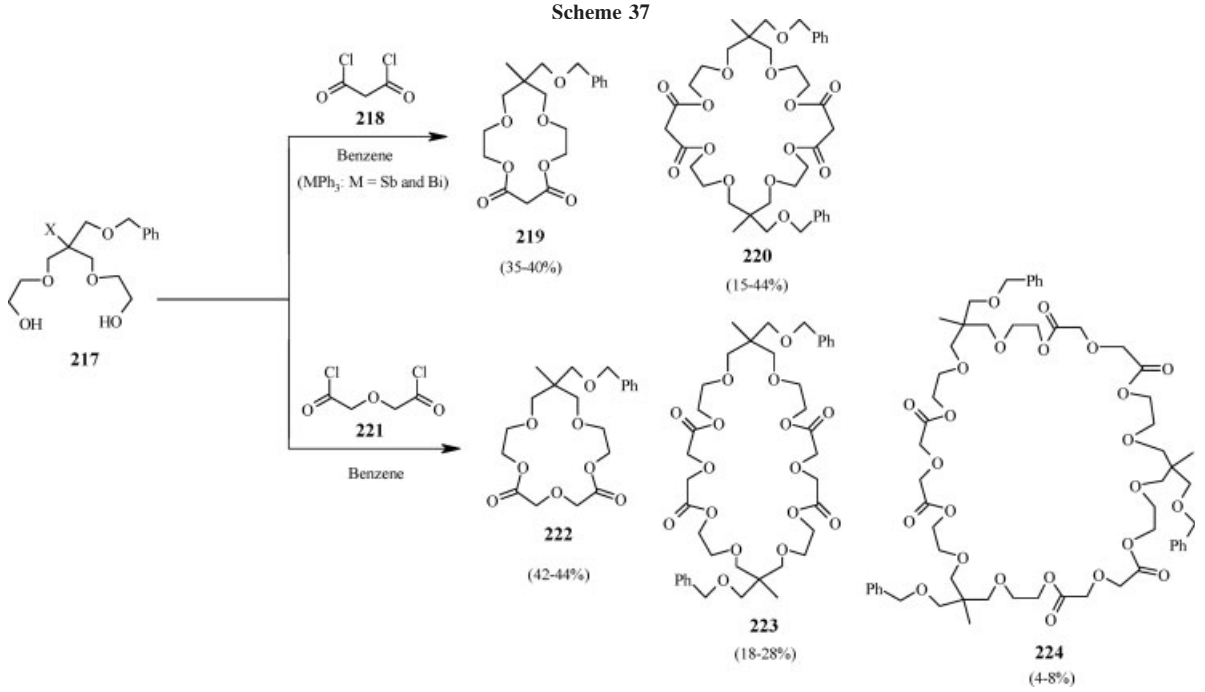


216 (74%)

Scheme 36



Scheme 37



5.2.1.6. Reaction of the appropriate diols with the corresponding diacid dichlorides. Habata *et al.* [72] reported the synthesis of benzyloxymethyl-substituted 14- and 16-membered crown ether ester **219** and **222** by treatment of diols **217** with the corresponding acid chlorides **218** and **221**, respectively, under high dilution condition using $SbPh_3$ and $BiPh_3$ as templates (Scheme 37). It was found that $SbPh_3$ and $BiPh_3$ are effective templates for the synthesis of 14-crown-4 ether ester. When **217** was treated with malonyl chloride, the dimer **220** was obtained together with the monomer **219**.

On the other hand, when diglycolyl chloride **221** was used the dimer **223** and the trimer **224** were obtained as cyclization products together with **222**.

5.2.1.7. Intramolecular cyclization of oligotrimethylene glycol monotosylates. Fredriksen *et al.* [73] reported the synthesis of 12-crown-3 ligands carrying methoxymethyl substituents in either one, two or all three of ring positions 3, 7, and 11.

They prepared 12-crown-3 ether **228** carrying methoxymethyl substituents in position 3 from diol **225** by initial reaction with one equivalent of tosyl chloride in pyridine to give the corresponding monotosylate **226**. Subsequent intramolecular cyclization of **226** in the presence of butyllithium and diisopropylamine **227** in DMF afforded **228** in 48% yield (Scheme 38).

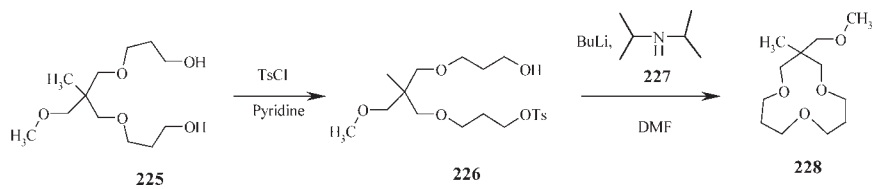
Diol **225** was prepared from the appropriate substituted 1,3-propanediol by double chain extension with acrylonitrile followed by ester formation and $LiAlH_4$ reduction.

The same authors reported the synthesis of **228** from diol **229** by initial reaction with tosyl chloride in pyridine to give the monotosylate **230** followed by intramolecular cyclization using *n*-BuLi in dry DMSO to give the spiro macrocycle **231**. Reduction of **231** with $LiAlH_4$ in dry monoglyme afforded 3-hydroxymethyl derivative **232** which then underwent alkylation with MeI/BuLi to give **228** (Scheme 39).

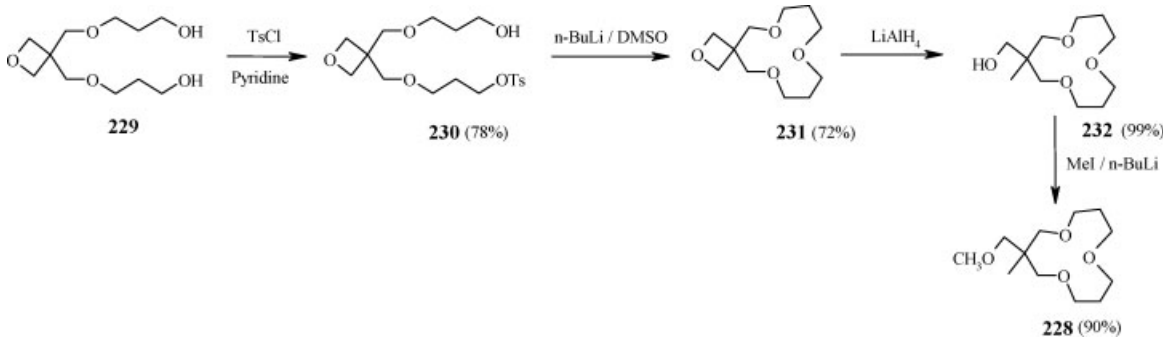
The diol **229** was obtained by the reaction of 3,3-bis(iodomethyl)oxetane with a monobenzyl derivative of 1,3-propanediol followed by removal of the protected-benzyl group using Pd/C in EtOH.

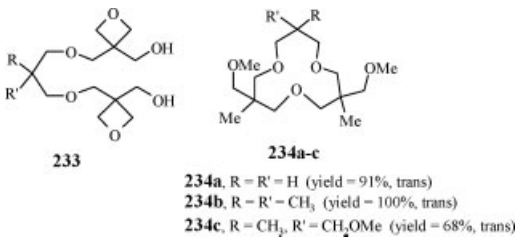
Using the same approach 12-crown-3 ethers carrying methoxymethyl substituent at positions 3, 7 **234a,b** and at positions 3, 7, 11 **234c** were prepared starting from diol **233**.

Scheme 38



Scheme 39

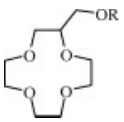




5.2.1.8. Alkylation of hydroxymethylcrown ethers with the appropriate electrophiles. Crown ethers with hydroxymethyl sidearms are versatile intermediates in the synthesis of *C*-pivot lariat ethers. They may be used as nucleophiles and alkylated to form alkoxymethyl or phenoxymethylcrown compounds. The alkylation reactions were carried out using suitable basic solutions. The most common bases used are NaH in THF or K_2CO_3 in DMF [74–76].

Alkoxymethyl-substituted crown ethers have attracted considerable attention as synthons for more complex macrocycles and polymer-supported crown ethers. The more tedious problems in syntheses of these lariat ethers

Table 2



12-Crown-4

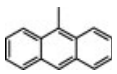
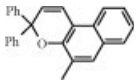
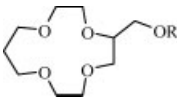
Comp. no.	R	Ref. (yield)
235		77 (73)
236		78 (70)

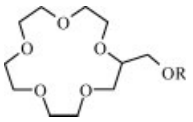
Table 3



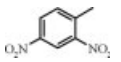
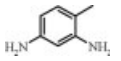
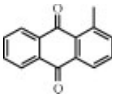
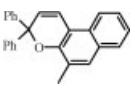
13-Crown-4

Comp. no.	R	Ref. (yield)
237	n-$C_{21}H_{25}$—CH(CO_2H)—	45 (27)

Table 4

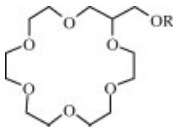


15-Crown-5

Comp. no.	R	Ref. (yield)
238	2-O_2N—C_6H_4-*o*—	79 (55), 80 (55)
239	2-H_2N—C_6H_4-*o*—	80 (90)
240		80 (29)
241[a]		80 (98)
242[b]	$CH_3(CH_2)_2C(O)$—	20 (62)
243[b]	$CH_3(CH_2)_{14}CO$—	20 (32)
244[b]	PhC(O)—	20 (80)
245[b]	4-CH_3O—C_6H_4—C(O)—	20 (74)
246[b]	4-O_2N—C_6H_4—C(O)—	20 (78)
247	$CH_3(CH_2)_3$—	20 (64)
248	$CH_3(CH_2)_{15}$—	20 (84)
249		81 (40)
250	$PhCH_2(OCH_2CH_2)_3$—	82 (68)
251[c]	$CH_3(OCH_2CH_2)_3$—	82 (70)
252		78 (69)
253	n-C_8H_{17}—	25 (64)
254	4-O_2N—C_6H_4—	79 (74)

[a] Compound **241** was obtained by reduction of **240** using H_2/Pd.
[b] Compounds **242–246** were prepared by acylation of the corresponding alcohol in CH_2Cl_2-pyridine.
[c] Compound **251** was obtained by debenzylation of **250** upon treatment with H_2/Pd and subsequent treatment with Me_2SO_4 in the presence of NaH in THF.

Table 5



18-Crown-6 (One side arm)

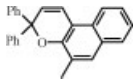
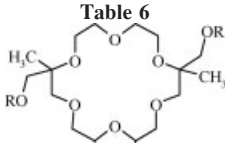
Comp. no.	R	Ref. (yield)
255		78 (83)
256	*n*-$C_{16}H_{33}$—	44 (92)

Table 6



18-Crown-6 (two side arms)

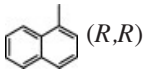
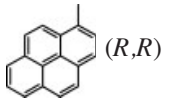
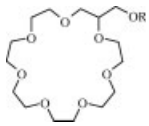
Comp. no.	R	Ref. (yield)
257	$CH_3C(O)$— (*S*,*S*)	61 (30)
258	 (*R*,*R*)	83 (–)
259	 (*R*,*R*)	83 (–)

Table 7

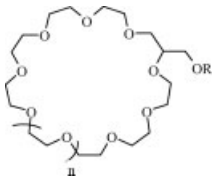


21-Crown-7

Comp. no.	R	Ref. (yield)
260	2-O_2N—C_6H_4-*o*—	80 (40)
261[a]	2-H_2N—C_6H_4-*o*—	80 (98)

[a] Compound **261** was obtained by reduction of **260** using H_2/Pd.

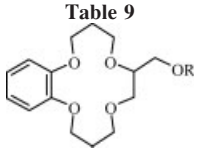
Table 8



27-Crown-9 and 30-Crown-10

Comp. no.	R	*n*	Ref. (yield)
262	*n*-$C_{21}H_{25}$—	1	42 (–)
263	*n*-$C_{21}H_{25}$—	2	42 (–)
264	*n*-$C_{21}H_{25}$—$CH(CO_2H)$—	1	29 (41)

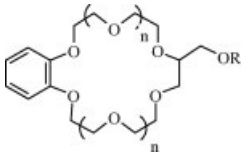
Table 9



Benzo-14-Crown-4

Comp. no.	R	Ref. (yield)
265	*n*-$C_{18}H_{17}$—$CH(CO_2H)$—	45 (47)

Table 10

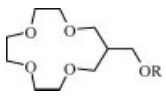


Benzo-12-Crown-4, Benzo-18-Crown-6, and Benzo-30-Crown-10

Comp. no.	R	*n*	Ref. (yield)
266	*n*-C_8H_{17}—$CH(CO_2H)$—	0	45 (63)
267[a]	$HO(O)CC(CH_2)_4$—	1	42 (–), 84 (60)
268[a]	$HO(O)CC(CH_2)_7$—	1	42 (–), 84 (46)
269[a]	$HO(O)CC(CH_2)_{10}$—	1	29 (41), 84 (47)
270	*n*-$C_{18}H_{17}$—$CH(CO_2H)$—	3	29 (56)

[a] Compounds **267–269** were prepared from the corresponding lariat ether alcohol by initial alkylation with the appropriate ester following by basic hydrolysis.

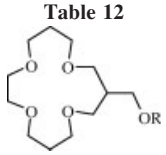
Table 11



13-Crown-4

Comp. no.	R	Ref. (yield)
271	$PhCH_2$—	33 (80)

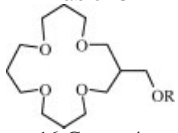
Table 12



15-Crown-4

Comp. no.	R	Ref. (yield)
272	$PhCH_2$—	33 (90)

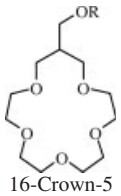
Table 13



16-Crown-4

Comp. no.	R	Ref. (yield)
273	$PhCH_2$—	33 (69)

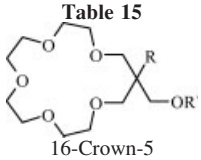
Table 14



16-Crown-5

Comp. no.	R	Ref. (yield)
274	$CH_3OCH_2CH_2$—	59 (85)

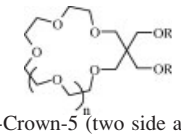
Table 15



16-Crown-5

Comp. no.	R	R′	Ref. (yield)
275	CH_3—	$CH_3(OCH_2CH_2)_2$—	59 (60)
276	CH_3—	*n*-$C_{21}H_{25}$—	59 (61)
277	$PhCH_2$—OCH_2—	$CH_3OCH_2CH_2$—	59 (44)
278	$PhCH_2$—OCH_2—	$CH_3(OCH_2CH_2)_2$—	59 (39)
279	*n*-$C_{21}H_{25}$—OCH_2—	$CH_3OCH_2CH_2$—	59 (55)
280	*n*-$C_{21}H_{25}$—OCH_2—	$CH_3(OCH_2CH_2)_2$—	59 (52)

Table 16

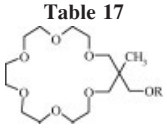


16-Crown-5 (two side arms)

Comp. no.	R	n	Ref. (yield)
281	CH_3—	1	63 (65)
282	*n*-C_8H_{17}—	1	63 (70)
283	$CH_3OCH_2CH_2$—	1	59 (75), 65 ([a])
284	$CH_3(OCH_2CH_2)_2$—	1	65 ([a]), 59 (75)
285	$CH_3(OCH_2CH_2)_4$—	1	65 ([a]), 59 (78)
286	$CH_3(OCH_2CH_2)_5$—	1	65 ([a]), 59 (75)
287	*n*-C_4H_9—OCH_2CH_2—	1	59 (72)
288	*t*-C_4H_9—OCH_2CH_2—	1	59 (60)
289	$HOCH_2CH_2$—	1	62 (87)
290	$H(OCH_2CH_2)_2$—	1	62 (79)
291	$H(OCH_2CH_2)_2$—	2	62 (79)

[a] Yields from 73–78% ref [65].

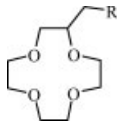
Table 17



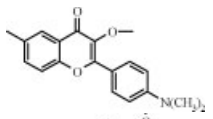
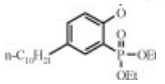
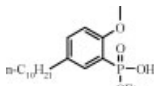
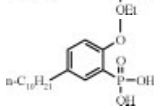
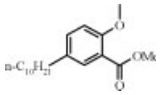
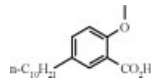
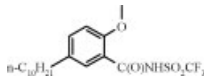
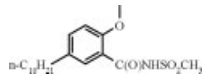
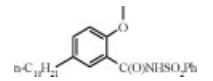
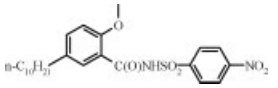
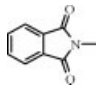
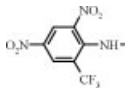
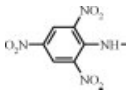
18-Crown-6

Comp. no.	R	Ref. (yield)
292	CH_3O—$(CH_2)_2$—	59 (64)
293	*n*-$C_{12}H_{25}$—	59 (74)
294	CH_3—$(OCH_2CH_2)_2$—	59 (–)

Table 18

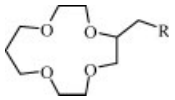


12-Crown-4

Comp. no.	R	Ref. (yield)
295		85 (0.12)
296		86 (61)
297		86 (93)
298		86 (54)
299		74 (58)
300		74 (83)
301[a]		20 (94)
302[a]		20 (44)
303[a]		20 (95)
304[a]		20 (90)
305		87 (88)
306[b]	H_2N—	87 (60)
307[c]		87 (60)
308[c]		87 (60)

[a] Compounds **301–304** were obtained from **300** by initial treatment with oxalyl chloride followed by reaction with the appropriate sulfonamide.
[b] Compound **306** was obtained from **305** by hydrazinolysis and subsequent acidification.
[c] Compounds **307** and **308** were obtained by the reaction of **306** with the appropriate chlorobenzene.

Table 19



13-Crown-4

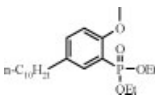
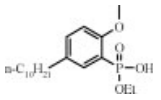
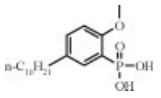
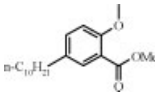
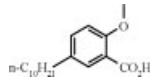
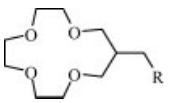
Comp. no.	R	Ref. (yield)
309		86 (40)
310		86 (91)
311		86 (66)
312		45 (–)
313		45 (92)

Table 20



13-Crown-4

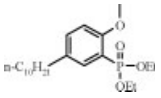
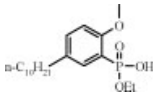
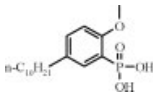
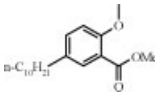
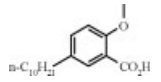
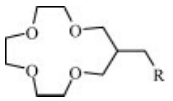
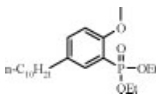
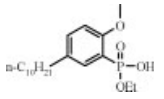
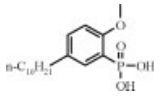
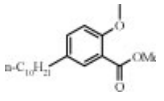
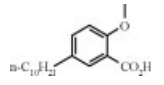
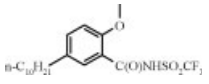
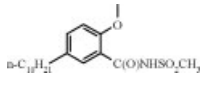
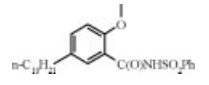
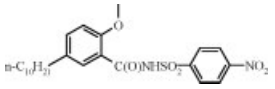
Comp. no.	R	Ref. (yield)
314		86 (40)
315		86 (91)
316		86 (66)
317		45 (–)
318		45 (54)

Table 21



14-Crown-4

Comp. no.	R	Ref. (yield)
319		86 (61)
320		86 (96)
321		86 (71)
322		45 (–)
323		45 (94)
324[a]		35 (84)
325[a]		35 (64)
326[a]		35 (72)
327[a]		35 (89)

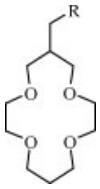
[a] Compounds **324–327** were obtained from **323** by initial treatment with oxalyl chloride followed by reaction with the appropriate sulfonamide.

by cyclization methods are preparation and isolation of the diol precursors [28].

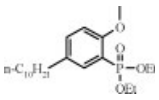
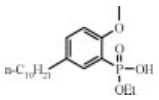
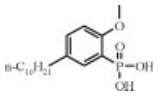
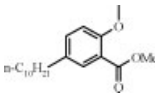
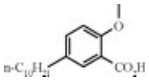
The following *C*-pivot lariat ethers are classified into 16 tables (Tables 2–17) according to the ring size of the macro ring as well as the attachment point of the side-arm. Some lariat ethers were obtained from their precursors by some other reactions as mentioned under the tables.

Compounds **18** and **22** mentioned in Scheme 5 were alternatively obtained in 68% [20] and 58% [59] yields, respectively, from the corresponding lariat ether alcohol on treatment with the appropriate halo compound.

Table 22



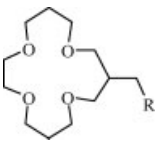
14-Crown-4

Comp. no.	R	Ref. (yield)
328		86 (43)
329		86 (90)
330		86 (49)
331		45 (–)
332		45 (90)

5.2.1.9. Nucleophilic displacement of tosyl groups from tosyloxymethylcrown ethers. Lariat ethers with hydroxymethyl sidearms may be tosylated to afford electrophilic precursors which can be converted into various lariat ethers by nucleophilic displacement of the tosyl group.

The following *C*-pivot lariat ethers are classified into 15 tables (Tables 18–32) according to the ring size of the macro ring as well as the attachment point of the sidearm. Some lariat ethers **297, 300, 310, 313, 315, 318, 320, 323,**

Table 23



15-Crown-4

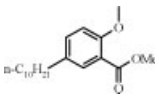
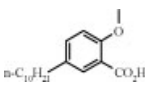
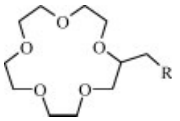
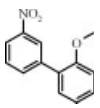
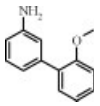
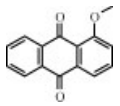
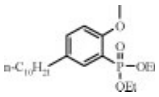
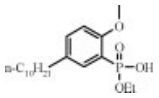
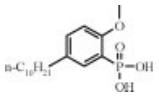
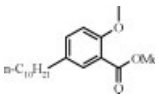
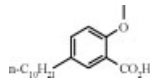
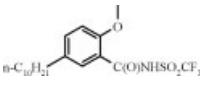
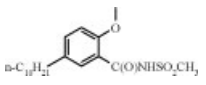
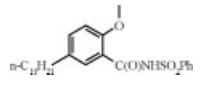
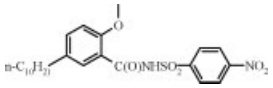
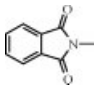
Comp. no.	R	Ref. (yield)
333		45 (–)
334		45 (86)

Table 24

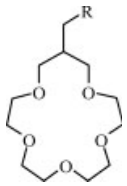


15-Crown-5

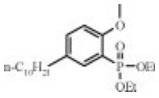
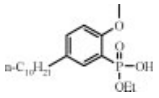
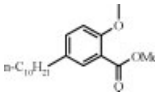
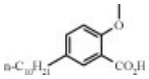
Comp. no.	R	Ref. (yield)
335		80 (61)
336[a]		80 (98)
337		81 (39)
338		86 (59)
339		86 (92)
340		86 (97)
341		74 (61)
342		74 (84)
343[b]		35 (65)
344[b]		35 (61)
345[b]		35 (84)
346[b]		35 (85)
347		87 (90)
348[c]	H_2N—	87 (87)

[a] Compound **336** was obtained by reduction of **335** using H_2/Pd.
[b] Compounds **343–346** were obtained from **342** by initial treatment with oxalyl chloride followed by reaction with the appropriate sulfonamide.
[c] Compound **348** was obtained from **347** by hydrazinolysis and subsequent acidification.

Table 25



16-Crown-5

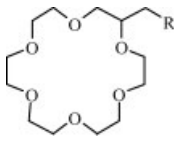
Comp. no.	R	Ref. (yield)
349		86 (35)
350		86 (61)
351		45 (–)
352		45 (91)

334, 339, 342, 350, 352, 354, 358, 366, 375, 377, 379, 381, 383, 386, 388, 390, and **393** in the following tables were obtained from their ester precursors by basic hydrolysis followed by acidification. Some other lariat derivatives **298**, **311**, **316, 321**, **330, 340**, **355**, **384,** and **391** were obtained from their ester precursors on treatment with Me_3SiBr at 100°C. Various lariat ethers in the following tables were obtained from their precursors by some other reactions as mentioned under the tables.

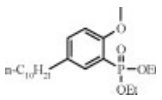
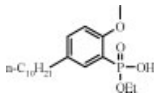
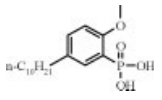
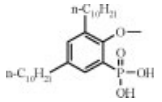
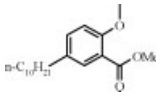
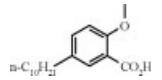
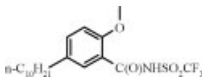
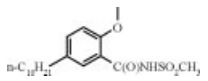
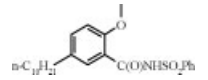
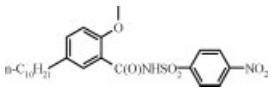
5.2.1.10. Nucleophilic displacement of bromide from bromomethylcrown ethers. Lariat ethers with bromomethyl sidearms can also be converted into various lariats by nucleophilic displacement of the bromide. The following *C*-pivot lariat ethers are classified into nine tables (Tables 33–41) according to the ring size of the macro ring as well as the attachment point of the sidearm.

5.2.2. Synthesis of lariat dibenzocrown ethers. Bartsch *et al*. [89] developed an approach to dibenzo lariat ethers in which the sidearm is attached to the C2 position of a propane subunit. They studied some structure variations within these series of lariat ethers with the goal of enhancing their selectivity for alkali metal cations as well as their extraction efficiency. These structure variations include crown ether cavity size, basicity of the oxygen atoms, substituents on the benzene rings, nature of the alkyl group (linear or branched) attached to the central carbon or to the sidearm, and the linkage, which joins the functional group

Table 26

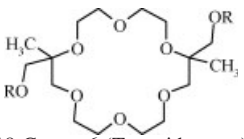


18-Crown-6 (One side arm)

Comp. no.	R	Ref. (yield)
353		86 (71)
354		86 (69)
355		86 (96)
356		86 (90)
357		74 (68)
358		74 (81)
359[a]		74 (29)
360[a]		35 (86)
361[a]		35 (89)
362[a]		35 (92)

[a] Compounds **359–362** were obtained from **358** by initial treatment with oxalyl chloride followed by reaction with the appropriate sulfonamide.

Table 27



18-Crown-6 (Two side arms)

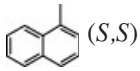
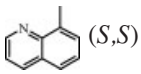
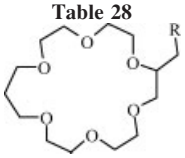
Comp. no.	R	Ref. (yield)
363	 (*S*,*S*)	61 (–)
364	 (*S*,*S*)	83 (–)

Table 28



19-Crown-6

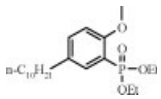
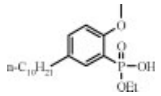
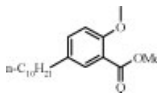
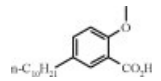
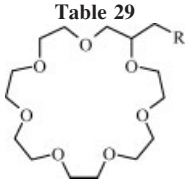
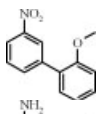
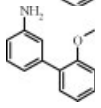
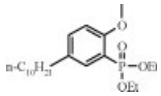
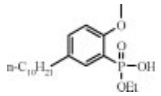
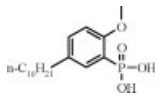
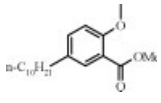
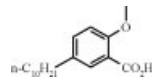
Comp. no.	R	Ref. (yield)
365		86 (73)
366		86 (93)
367		45 (–)
368		45 (94)

Table 29

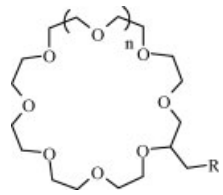


21-Crown-7

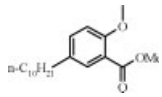
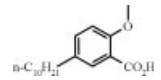
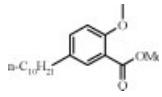
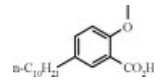
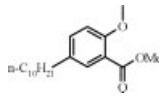
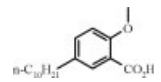
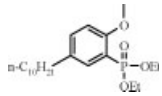
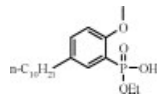
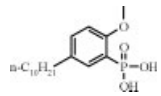
Comp. no.	R	Ref. (yield)
369		80 (53)
370[a]		80 (95)
371		80 (76)
372		86 (91)
373		86 (95)
374		74 (78)
375		74 (79)

[a] Compound **370** was obtained by reduction of **369** using H_2/Pd.

Table 30



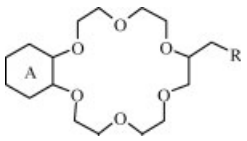
24-Crown-8, 27-Crown-9, and 30-Crown-10

Comp. no.	R	n	Ref. (yield)
376		1	45 (–)
377		1	45 (90)
378		2	45 (–)
379		2	45 (quant.)
380		3	45 (–)
381		3	45 (71)
382		1	86 (69)
383		1	86 (89)
384		1	86 (64)

of the sidearm to a common polyether ring. These series of lariat crown ethers are designed to provide systematic variations of some structural features while keeping the others unvaried. For example, in some cases, the crown ether cavity size is varied while holding the pendant arm constant. In others cases, the attachment site of the lipophilic group is varied while keeping the polyether ring and the linkage which join functional group on the sidearm and polyether portions invariant.

5.2.2.1. Synthesis of dibenzocrown ether alcohols. Bartsch *et al*. [89] reported the synthesis of dibenzocrown ether alcohols and studied their synthetic

Table 31



Cyclohexano-18-Crown-6 and Benzo-18-Crown-6

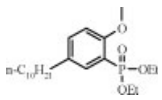
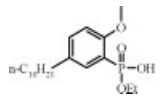
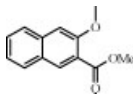
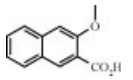
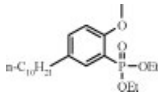
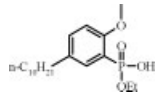
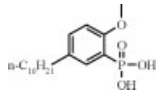
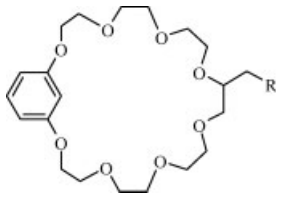
Comp. no.	A	R	Ref. (yield)
385	benzo		86 (50)
386	benzo		86 (98)
387	benzo		53 (–)
388	benzo		53 (58)
389	cyclohexano		86 (45)
390	cyclohexano		86 (96)
391	cyclohexano		86 (90)

Table 32



25-Crown-8

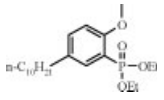
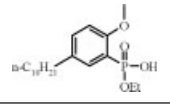
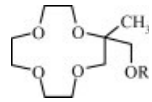
Comp. no.	R	Ref. (yield)
392		54 (74)
393		54 (96)

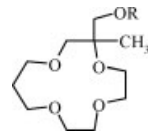
Table 33



14-Crown-4

Comp. no.	R	Ref. (yield)
394		47 (56)
395	$CH_3OCH_2CH_2$—	47 (32)
396	$C_{10}H_{21}$—	47 (32)

Table 34



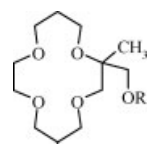
13-Crown-4

Comp. no.	R	Ref. (yield)
397		47 (35)
398	$CH_3OCH_2CH_2$—	47 (68)
399	$C_{10}H_{21}$—	47 (43)

utilities as key intermediates for the preparation of lariat ethers with pendant ether, carboxylic acid, ester, amide, amine, *etc*. groups.

5.2.2.1.1. Dibenzocrown ethers with a hydroxy group on the central carbon of the three carbon bridge. The approach developed by Bartsch *et al*. [89] involves reaction between epichlorohydrin **7** and a diol **456**. In the presence of base the diol presumably opens the epoxide, which recloses in the opposite sense. The remaining hydroxy group then attacks the newly formed epoxide to

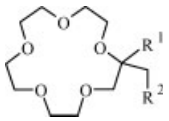
Table 35



14-Crown-4

Comp. no.	R	Ref. (yield)
400		47 (31)

Table 36



15-Crown-5

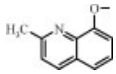
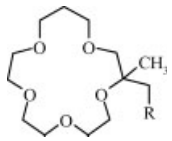
Comp. no.	R^1	R^2	Ref. (yield)
401	CH_3—	*n*-$C_6H_{13}O$—	60 (–), 25 (68)
402	CH_3—	*n*-$C_6H_{13}S$—	60 (–), 25 (82)
403	CH_3—	*n*-$C_6H_{13}NH$—	60 (–), 25 (94)
404	CH_3—	$CH_3OCH_2CH_2O$—	60 (–), 25 (82), 48 (–)
405	CH_3—	$CH_3(OCH_2CH_2)_2O$—	60 (–), 25 (88), 48 (60)
406	CH_3—	$CH_3(OCH_2CH_2)_3O$—	60 (–), 25 (80), 48 (64)
407	CH_3—		48 (74)
408	CH_3—		48 (81)
409	CH_3—		48 (71)
410	CH_3—		48 (63)
411	CH_3—		48 (76)
412	CH_3—	$CH_3OCH_2CH_2CH_2O$—	48 (57)
413	CH_3—	$HOCH_2CH_2O$—	48 (60)
414	CH_3—	$C_8H_{17}O$—	48 (71)
415	CH_3—	$C_8H_{17}OCH_2CH_2O$—	48 (86)
416	CH_3—	$C_8H_{17}O(CH_2CH_2O)_2$—	48 (70)
417	CH_3—	$C_{12}H_{25}O$—	48 (67)
418	CH_3—	$C_{12}H_{25}O(CH_2CH_2O)_2$—	48 (75)
419	C_6H_{13}—	$C_6H_{13}O$—	48 (72)
420	C_6H_{13}—	$CH_3OCH_2CH_2O$—	48 (87)
421	C_6H_{13}—	$CH_3O(CH_2CH_2O)_2$—	48 (78)
422	C_6H_{13}—	$CH_3O(CH_2CH_2O)_3$—	48 (70)
423	C_6H_{13}—	$C_8H_{17}O$—	48 (80)
424	C_6H_{13}—	$C_8H_{17}OCH_2CH_2O$—	48 (71)
425	C_6H_{13}—	$C_8H_{17}O(CH_2CH_2O)_2$—	48 (74)
426	C_6H_{13}—		48 (70)
427	C_8H_{17}—	$CH_3OCH_2CH_2O$—	48 (80)
428	C_8H_{17}—	$CH_3O(CH_2CH_2O)_2$—	48 (64)
429	C_8H_{17}—	$CH_3O(CH_2CH_2O)_3$—	48 (75)

Table 37



16-Crown-5 (3-Substituted isomer)

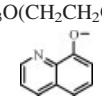
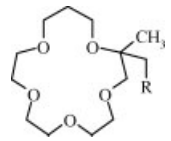
Comp. no.	R	Ref. (yield)
430	$CH_3OCH_2CH_2O$—	48 (68)
431	$CH_3O(CH_2CH_2O)_2$—	48 (83)
432		48 (56)

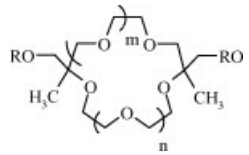
Table 38



16-Crown-5 (2-Substituted isomer)

Comp. no.	R	Ref. (yield)
433	$CH_3OCH_2CH_2O$—	48 (70)
434	$CH_3O(CH_2CH_2O)_2$—	48 (83)
435		48 (65)

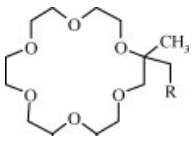
Table 39



15-Crown-5 (Two sidearms)

Comp. no.	R	m	n	Ref. (yield)
436	$CH_3OCH_2CH_2$—	0	2	52 (quantitavely)
437	$CH_3OCH_2CH_2$—	1	1	52 (quantitavely)
438		0	2	88 (–) cis
439		0	2	88 (–) trans
440		0	2	51 (43) cis
441		0	2	51 (55) trans
442		1	1	88 (–) cis
443		1	1	88 (–) trans
444		1	1	51 (81) cis
445		1	1	51 (29) trans
446		2	0	51 (38) cis
447		2	0	51 (49) trans
448		1	1	51 (58) cis

Table 40



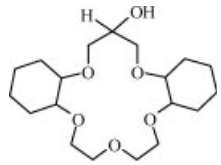
18-Crown-6

Comp. no.	R	Ref. (yield)
449	$C_6H_{13}O$—	48 (60)
450	$C_6H_{13}S$—	48 (61)
451	$C_6H_{13}NH$—	48 (84)
452	$CH_3OCH_2CH_2O$—	48 (88)
453	$CH_3O(CH_2CH_2O)_2$—	48 (78)
454	$CH_3O(CH_2CH_2O)_3$—	48 (72)
455		48 (62)

afford 1,3-disubstituted glycerol derivative **457** in which the 2-hydroxy group is free. An example of this cyclization is shown in Scheme 40.

In this reaction, the alkali hydroxide metal cation was varied to take advantage of the template effect [30,75]. Using this approach, lariat ether alcohols with different cavity sizes and different ring substituents **458–467** (Table 42) have been prepared [75,90–92]. Lariat ether alcohol (R = $C(CH_3)_3$) with *t*-butyl groups attached to the aromatic rings of dibenzocrown ethers was synthesized by reaction of lariat ether alcohol **457** with *tert*-butyl alcohol and 85% phosphoric acid at 100–110°C [92]. Lariat ether alcohol with nitro groups on its benzene rings **466** was obtained by reaction of **457** with nitric acid in acetic acid-chloroform-water. Reduction of **466** to the corresponding diamino derivative **467** was achieved by treatment with hydrazine hydrate over Pd/C as the hydrogen source in ethanol [92].

High-pressure catalytic hydrogenation of *sym*-hydroxydibenzo-16-crown-5 **457** produced the corresponding saturated crown ether alcohol **468** in good yield [75].

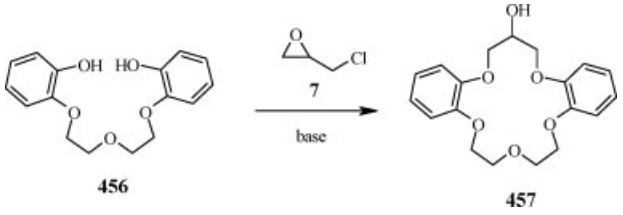


468 (50%)

Fuji *et al*. [93] reported the synthesis of binaphthyl crown receptors **470** with pendant hydroxyl group in 30% yield by the reaction of (S)-binaphthol **469** with 2-(2-chloroethoxy)ethanol in the presence of K_2CO_3 and KI, followed by cyclization with epichlorohydrin in the presence of tetrafluoroborate as a template (Scheme 41).

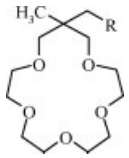
Bartsch *et al*. [92] reported the synthesis of lariat ether **472** with geminal methyl group on the central carbon of the propane subunit by reaction of the

Scheme 40



456 **457**

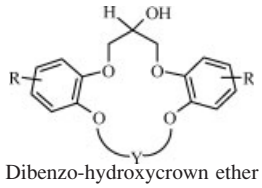
Table 41



16-Crown-5

Comp. no.	R′	Ref. (yield)
167	$CH_3OCH_2CH_2O$—	48 (32)
275	$CH_3O(CH_2CH_2O)_2$—	48 (23)

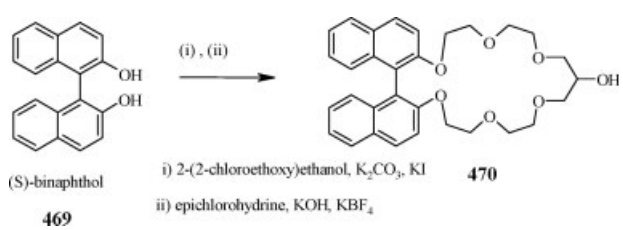
Table 42



Dibenzo-hydroxycrown ether

Comp. no.	R	Y	Ref. (yield)
458	H	$-(CH_2)_2-$	90 (50)
459	H	$-(CH_2)_3-$	75 (51)
460	H	$-CH_2(CH_2OCH_2)_2CH_2-$	75 (39)
461	H	$-CH_2(CH_2OCH_2)_3CH_2-$	75 (35)
462	H	$-CH_2CH(OH)CH_2-$	90 (55)
463	H	$-CH_2C(O)NH(CH_2)_2NHC(O)CH_2-$	90 (–)
464	F	$-(CH_2)_2O(CH_2)_2-$	91 (33)
465	$C(CH_3)_3$	$-(CH_2)_2O(CH_2)_2-$	92 (93)
466	NO_2	$-(CH_2)_2O(CH_2)_2-$	92 (100)
467	NH_2	$-(CH_2)_2O(CH_2)_2-$	92 (50)

Scheme 41



(S)-binaphthol

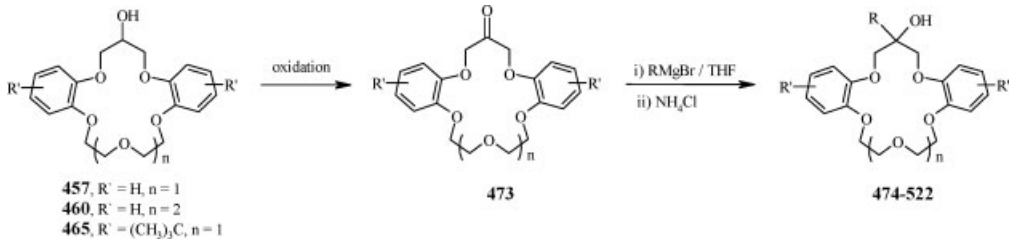
469

i) 2-(2-chloroethoxy)ethanol, K_2CO_3, KI

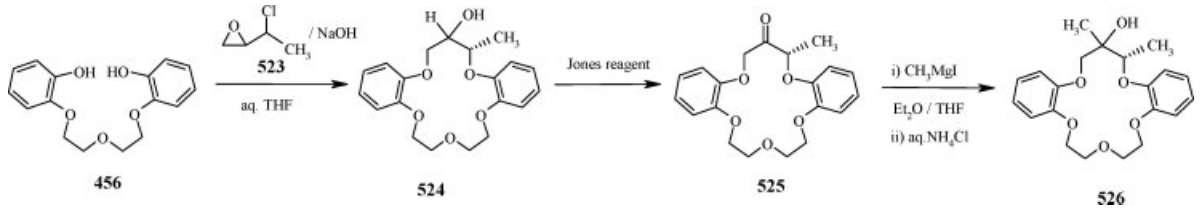
ii) epichlorohydrine, KOH, KBF_4

470

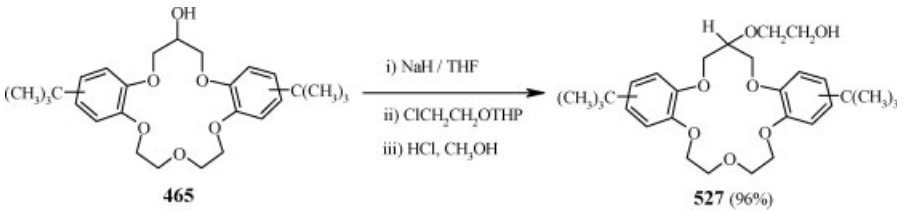
Scheme 42



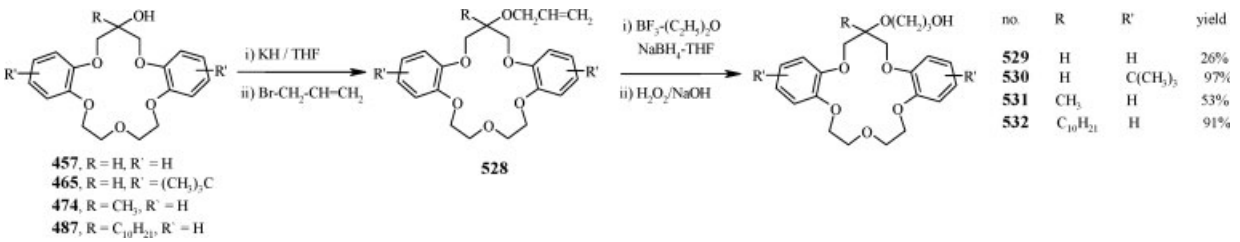
Scheme 43



Scheme 44



Scheme 45



Scheme 46

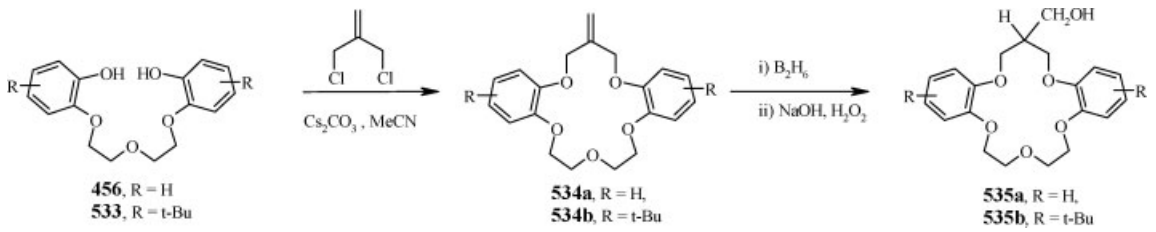
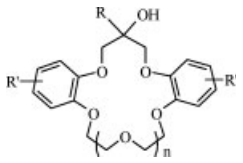


Table 43

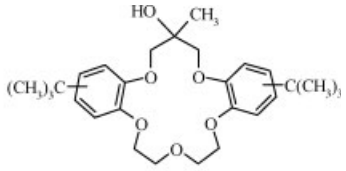


15-Crown-5,18-crown-6

Comp. no.	R′	R	*n*	Ref. (yield)
474	H	CH_3—	1	92 (92)
475	H	C_2H_5—	1	92 (89)
476	H	C_3H_7—	1	92 (84)
477	H	$(CH_3)_2CH$—	1	92 (88)
478	H	C_4H_9—	1	75 (90)
479	H	C_5H_{11}—	1	92 (84)
480	H	$(CH_3)_3CCH_2$—	1	92 (29)
481	H	C_6H_{13}—	1	92 (88)
482	H	c-C_6H_{11}—	1	94 (74)
483	H	C_7H_{15}—	1	92 (89)
484	H	C_8H_{17}—	1	75 (91)
485	H	$C_4H_9CH(C_2H_5)CH_2$—	1	92 (71)
486	H	C_9H_{19}—	1	92 (92)
487	H	$C_{10}H_{21}$—	1	94 (90)
488	H	$C_{11}H_{23}$—	1	92 (97)
489	H	$C_{12}H_{25}$—	1	92 (77)
790	H	$C_{13}H_{27}$—	1	92 (96)
491	H	$C_{14}H_{29}$—	1	75 (79)
492	H	$C_{15}H_{31}$—	1	92 (95)
493	H	$C_{16}H_{33}$—	1	92 (75)
494	H	$C_{18}H_{37}$—	1	94 (89)
495	H	$C_{20}H_{41}$—	1	92 (70)
496	H	Ph—	1	94 (90), 91 (48)
497	H	2-$(CH_3)C_6H_4$—	1	92 (87)
498	H	3-$(CH_3)C_6H_4$—	1	92 (78)
499	H	4-$(CH_3)C_6H_4$—	1	92 (80)
500	H	3,5-$(CH_3)_2C_6H_3$—	1	92 (89)
501	H	4-$(CH_2{=}CH)C_6H_4$—	1	92 (90)
502	H	4-$(CH_2{=}C(CH_3)C_6H_4$—	1	92 (73)
503	H	$PhCH_2CH_2$—	1	92 (92)
504	H	$Ph(CH_2)_3$—	1	92 (95)
505	H	$Ph(CH_2)_4$—	1	92 (81)
506	H	$Ph(CH_2)_5$—	1	92 (97)
507	H	$CH{=}C(CH_3)_2$—	1	92 (86)
508	H	$CH_2{=}CH(CH_2)_8$—	1	92 (56)
509	H	$CH_3(CH_2)_3C{\equiv}C$—	1	92 (96)
510	H	$CH_3(CH_2)_5C{\equiv}C$—	1	92 (94)
511	H	$CH_3(CH_2)_7C{\equiv}C$—	1	92 (94)
512	H	$CH_3(CH_2)_9C{\equiv}C$—	1	92 (96)
513	H	$CH_3(CH_2)_{11}C{\equiv}C$—	1	92 (95)
514	H	C_3F_7—	1	92 (60)
515	H	C_6F_{13}—	1	92 (28)
516	H	C_8F_{17}—	1	92 (33)
517	H	C_6F_5—	1	91 (48)
518	H	2-$(CF_3)C_6H_4$—	1	92 (90)
519	H	3-$(CF_3)C_6H_4$—	1	91 (75)
520	H	3,5-$(CF_3)_2C_6H_3$—	1	91 (68)
521	$(CH_3)_3C$—	C_3H_7—	1	92 (53)
522	H	*n*-C_8H_{17}—	2	75 (74)

appropriate bisphenol with 2-methyl-2-chloromethyloxirane **471** in THF in the presence of NaH.

471



472 (64%)

The preparation of lariat ether tertiary alcohols **474–522** (Table 43) with (R = alkyl, alkenyl, alkynyl, aryl, aralkyl) was alternatively obtained using another strategy as depicted in Scheme 42 [75,91,92,94]. Thus, Jones oxidation or Swern oxidation of the appropriate lariat ether alcohol **457, 460,** and **465** gave the corresponding ketone **473**. Subsequent reaction of **473** with the appropriate Grignard reagent produced the corresponding lariat ether tertiary alcohols.

Kim *et al*. [95] reported the synthesis of lariat ether alcohol **526** with a second methyl group attached to a terminal carbon of the three-carbon bridge by initial cyclization of the bisphenol **456** with epoxide **523** and NaOH in THF-water to give the asymmetric crown ether alcohol **524** in an 31% yield. Oxidation of the latter compound with Jones reagent provided crown ether ketone **525** in 74% yield. Grignard reaction of **525** with methylmagnesium iodide gave the target **526** in an 87% yield (Scheme 43).

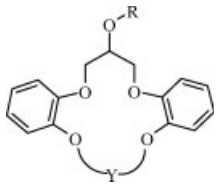
5.2.2.1.2. Dibenzocrown ethers with $O(CH_2)_nOH$ groups on the central carbon of the three carbon bridge. Lariat ether alcohol **527** with a —$O(CH_2)_2$—OH sidearm and a *tert*-butyl group on each benzene ring was prepared by addition of tetrahydropyranyl-protected ethylene chlorohydrin to the sodium alkoxide of lariat ether alcohol **465** followed by removal of the THP group with 10% HCl-methanol (Scheme 44) [92,96].

The synthesis of lariat ether alcohols **529–532** which have a —$O(CH_2)_3$—OH sidearm was accomplished by the addition of allyl bromide to the alkoxide of the appropriate lariat ether alcohol to give the corresponding allyloxycrown ethers **528** followed by hydroboration-oxidation (Scheme 45).

5.2.2.1.3. Dibenzocrown ethers in which one carbon atom mediates between the pivot carbon and the hydroxy group. Hydroxymethyl lariat ethers **535a,b** were synthesized as outlined in Scheme 46 [58,97]. Vinylidene dibenzo-crown ethers **534a,b** were prepared in 72–74% yield by cyclization of bisphenols **456** and **533** with methallyl dichloride and cesium carbonate in acetonitrile. Subsequent hydroboration with borane-THF complex, followed by oxidation with H_2O_2 and basic hydrolysis gave **535a,b** in 60 and 45% yields, respectively.

5.2.2.2. Synthesis of dibenzocrown ethers with a pendant ether groups from the corresponding lariat ethers alcohols. Reaction of lariat ethers alcohols with NaH

Table 44



15-Crown-5

Comp. no.	R	Y	Ref. (yield)
536	$CH_3OCH_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	99 (85), 98 (85)
537	CH_2=$CHCH_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	99 (35)
538	4-$CH_3OC_6H_4CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (81)
539	3-$CH_3OC_6H_4CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (80)
540	2-$CH_3OC_6H_4CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (80)
541	$PhOCH_2CH_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (50)
542	3-$CH_3C_6H_4SO_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (80)
543	3,5-$(CH_3O)_2C_6H_3CH_2$—	—$CH_2CH_2OCH_2CH_2$—	100 (80)
544	$HOC(O)CH_2$—	—CH_2CH_2—	89 (76)
545	$HOC(O)CH_2$—	—$CH_2CH_2CH_2$—	89 (80)
546	$HOC(O)CH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (82)
547	$HOC(O)CH_2$—	—$CH_2(CH_2OCH_2)_2CH_2$—	89 (66)
548	HOC(O)CH(Et)—	—$CH_2CH_2OCH_2CH_2$—	89 (40)
549	$HOC(O)CH((CH_2)_3CH_3)$—	—$CH_2CH_2OCH_2CH_2$—	89 (40)
550	$HOC(O)CH((CH_2)_5CH_3)$—	—$CH_2CH_2OCH_2CH_2$—	89 (23)
551	$EtOC(O)(CH_2)_3CH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (76)
552[a]	$HOC(O)(CH_2)_3CH_2$—	-$CH_2CH_2OCH_2CH_2$—	89 (91)
553	CH_2=$CHCH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (95)
554	$HO(CH_2)_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (81)
555[b]	$HOC(O)CH_2CH_2$—	—$CH_2CH_2OCH_2CH_2$—	89 (6)

[a] Compound **552** was prepared from **551** by hydrolysis using NaOH/EtOH.
[b] Compound **555** was prepared from **554** by oxidation.

and the appropriate haloalkane in THF gave the corresponding dibenzocrown ethers with pendant ether groups **536–555** (Table 44) [89,98–100].

Lariat ethers **557** was prepared in 18% yield from compound **470** on treatment with the mesylate **556** in the presence of NaH followed by deprotection of the methoxymethyl group under acidic conditions (Scheme 47) [93].

5.2.2.3. Synthesis of dibenzocrown ethers with a pendant carboxylic acid group from the corresponding ethers alcohols. 5.2.2.3.1. Synthesis of dibenzocrown ether oxyacetic acid. Two approaches have been reported for the synthesis of this class of compounds (cf. compounds **558–620**, Table 45). The first approach involves initial formation of methyl ester from the corresponding lariat ether alcohol upon treatment with NaH and methyl bromoacetate in THF followed by basic hydrolysis and subsequent acidification [75,89,101].

In the second approach, the crown ether carboxylic acid were prepared in one step by reaction of the corresponding alcohol with NaH and bromoacetic acid in THF [89].

Using both approaches, Bartsch *et al*. [75,89,94,97,101–104] reported the synthesis of

Scheme 47

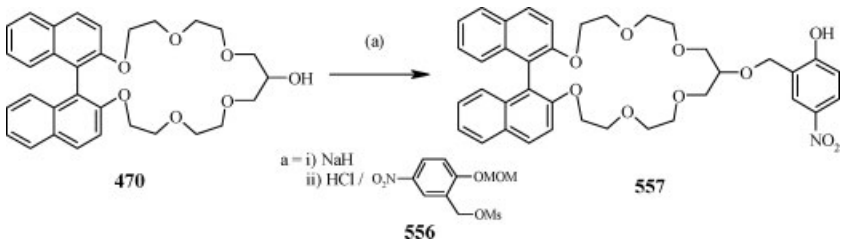
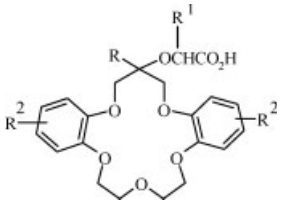


Table 45



Dibenzo-15-crown-5 with pendant oxyacetic acid derivatives

Comp. no.	R	R^1	R^2	Ref. (yield)
558	H	$C_{10}H_{21}$—	H	97 (80)
559	H	$C_{12}H_{25}$—	H	97 (66)
560	H	$C_{14}H_{29}$—	H	97 (70)
561	H	$C_{16}H_{33}$—	H	97 (64)
562	CH_3-	C_8H_{17}—	H	97 (48)
563	Ph—	Ph—	H	97 (97)
564	$C_{10}H_{21}$—	Ph—	H	97 (86)
565	CH_3—	H	H	97 (84)
566	C_2H_5—	H	H	97 (69)
567	C_3H_7—	H	H	97 (62)
568	$(CH_3)_2CH$—	H	H	97 (88)
569	C_3F_7—	H	H	97 (71)
570	C_4H_9——	H	H	97 (55)
571	C_5H_{11}—	H	H	97 (79)
572	$(CH_3)_2CCH_2$—	H	H	97 (76)
573	c-C_6H_{11}—	H	H	97 (26)
574	C_6H_{13}—	H	H	97 (88)
575	C_6F_{13}—	H	H	97 (93)
576	C_7H_{15}—	H	H	97 (79)
577	C_8H_{17}—	H	H	97 (90)
578	C_8H_{17}—	H	H	97 (87)
579	$CH_3(CH_2)_3CH(C_2H_5)CH_2$—	H	H	97 (58)
580	C_9H_{19}—	H	H	97 (98)
581	$C_{10}H_{21}$—	H	H	97 (57)
582	$C_{11}H_{23}$—	H	H	97 (78)
583	$C_{12}H_{25}$—	H	H	97 (92)
584	$C_{13}H_{27}$—	H	H	97 (55)
585	$C_{14}H_{29}$—	H	H	97 (72)
586	$C_{15}H_{31}$—	H	H	97 (81)
587	$C_{16}H_{33}$—	H	H	97 (85)
588	$C_{18}H_{37}$—	H	H	97 (84)
589	$C_{20}H_{41}$—	H	H	97 (92)
590	$PhCH_2CH_2$—	H	H	97 (75)
591	$Ph(CH_2)_3$—	H	H	97 (68)
592	$Ph(CH_2)_4$—	H	H	97 (53)
593	$Ph(CH_2)_5$—	H	H	97 (63)
594	Ph—	H	H	97 (76)
595	2-CH_3—C_6H_4—	H	H	97 (67)
596	3-CH_3—C_6H_4—	H	H	97 (87)
597	4-CH_3—C_6H_4—	H	H	97 (82)
598	3-CF_3—C_6H_4—	H	H	97 (89)
599	4-$(CH_2{=}CH)C_6H_4$—	H	H	97 (90)
600	4-$(CH_2{=}C(CH_3)C_6H_4$—	H	H	97 (80)
601	3,5-$(CH_3)_2C_6H_3$—	H	H	97 (72)
602	3,5-$(CF_3)_2C_6H_3$—	H	H	97 (96)
603	$(CH_3)_2C{=}CH$—	H	H	97 (92)
604	$CH_2{=}CH(CH_2)_6$—	H	H	97 (92)
605	$CH_2{=}CH(CH_2)_8$—	H	H	97 (97)
606	$CH_3(CH_2)_3C{\equiv}C$—	H	H	97 (94)
607	$CH_3(CH_2)_5C{\equiv}C$—	H	H	97 (85)
608	$CH_3(CH_2)_7C{\equiv}C$—	H	H	97 (84)

Table 45
(*Continued*)

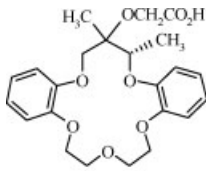
Comp. no.	R	R^1	R^2	Ref. (yield)
609	$CH_3(CH_2)_9C{\equiv}C$—	H	H	97 (88)
610	$CH_3(CH_2)_{11}C{\equiv}C$—	H	H	97 (86)
611	H	H	F	91 (49)
612	H	H	$(CH_3)_3C$—	97 (86)
613	H	H	NO_2—	97 (99)
614	H	H	NH_2—	97 (89)
615	H	H	HO_3S—	97 (93)
616	CH_3—	H	$(CH_3)_3C$—	97 (74)
617	C_3H_7—	H	NO_2—	97 (99)
618	CH_3—	H	HO_3S—	97 (86)
619	C_4H_9—	H	HO_3S—	97 (82)
620	H	H	F	97 (49)

lipophilic lariat ether carboxylic acids in which the lipophilic group is incorporated either into the sidearm or on the geminal carbon.

Similarly, were prepared lariat carboxylic acids with lipophilic groups at both the geminal position and on the sidearm [97].

Dibenzo lariat ether carboxylic acids with substituents on both benzene rings were prepared by two methods. In the first method, the appropriate lariat ether alcohol containing the ring substituents were reacted with NaH and then bromoacetic acid to give the target lariat ethers [91,97]. In the second method, nitro- and sulfonic acid groups were introduced into the benzene rings of the preformed lariat ether carboxylic acid by nitration and sulfonation, respectively. Reduction of dinitro-derivatives to the corresponding diamines was accomplished with 85% hydrazine hydrate in ethanol in the presence of Pd/C [91,97].

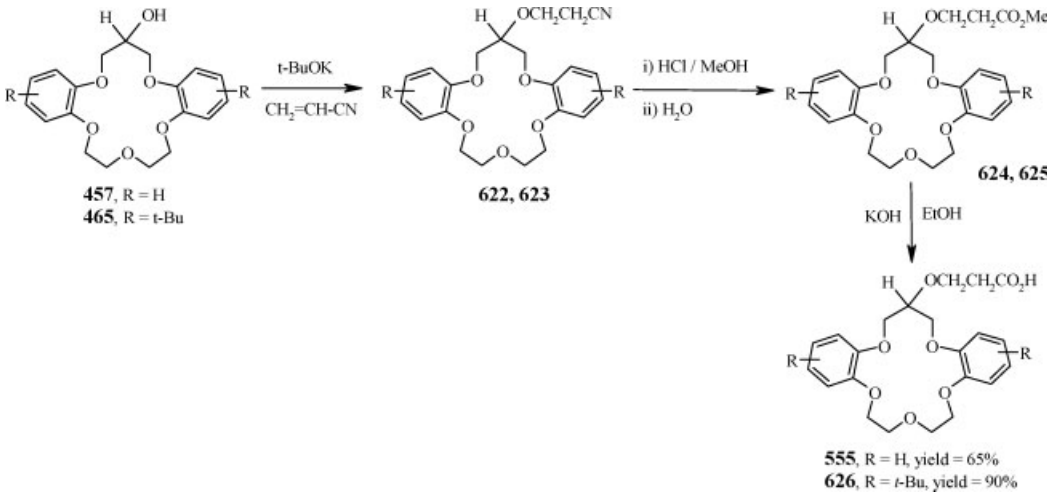
Kim *et al*. [95] used a similar approach for the synthesis of lariat ether carboxylic acid **621** with a second methyl group attached to a terminal carbon of the propane subunit from the corresponding crown ether alcohol.



621 (87%)

5.2.2.3.2. Synthesis of dibenzocrown ether oxypropanoic aicd, oxybutanoic acid and oxypentanoic acid. The length of the spacer that connects the acidic function to the polyether ring is an important structural parameter for proton-ionizable lariat ethers.

Scheme 48



Three synthetic routes were employed for the synthesis of this class of compounds. In the first route, potassium *tert*-butoxide catalyzed cyanoethylation of the corresponding lariat ether alcohol in neat acrylonitrile or acrylonitrile in THF to give the corresponding lariat ether nitriles **622** and **623**. Hydrolysis of the latter compounds with methanolic solution containing HCl gas afforded the corresponding methyl esters **624** and **625**. Saponification with ethanolic KOH gave **555** and **626**, respectively (Scheme 48) [97].

In the second synthetic route, lariat ether oxypropanoic acid **555** was obtained in 6% yield by Jones oxidation of the corresponding alcohol [89].

In the third synthetic route [97], lariat ether alcohols **529, 531,** and **627** ($n = 2, 3$) were reacted with methanesulfonyl chloride in dichloromethane in the presence of TEA to give lariat ether mesylate **628–630**. Subsequent reaction with NaCN in DMSO gave lariat ether nitriles **631–633**. The latter compounds underwent reaction with anhydrous HCl gas in anhydrous methanol to give the corresponding lariat ether methyl esters **634–636**. Hydrolysis with KOH in 95% ethanol afforded the target molecules **637–639** in 88–97% yields (Scheme 49).

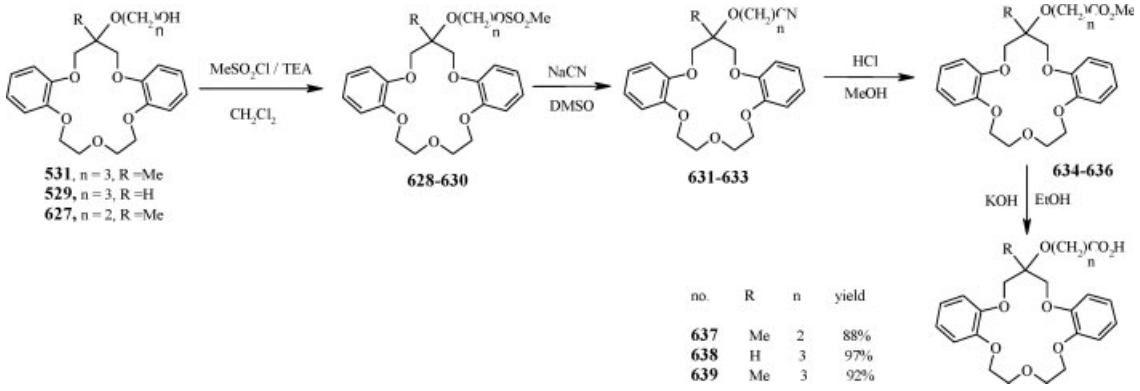
Lariat ether alcohol **627** ($n = 2$, R = Me) was obtained from the corresponding lariat ether acetic acid on estrification with ethanol and *p*-toluenesulfonic acid and subsequent reduction with $LiAlH_4$ [92].

Lariat ether oxypentanoic acid **641** was obtained from lariat ether alcohol **457** by initial reaction with ethyl 5-bromopentanoate in the presence of NaH in THF to give the corresponding ester **640** followed by basic hydrolysis with ethanolic NaOH (Scheme 50) [89].

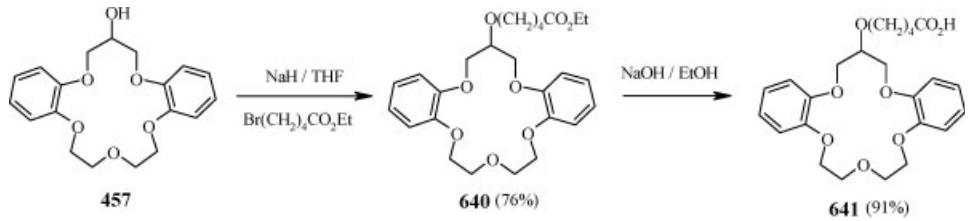
5.2.2.3.3. Synthesis of dibenzocrown ether acetic acid. This type of lariat ether contain one or more carbon atom between the pivot carbon and the carboxylic group on the sidearm.

(*sym*-Dibenzo-16-crown-5)acetic acid **645** was synthesized as shown in Scheme 51. Thus, reaction of lariat ether alcohol **535a** with methanesulfonyl chloride in dichloromethane in the presence of triethylamine gave lariat ether mesylate **642** which was treated with sodium

Scheme 49

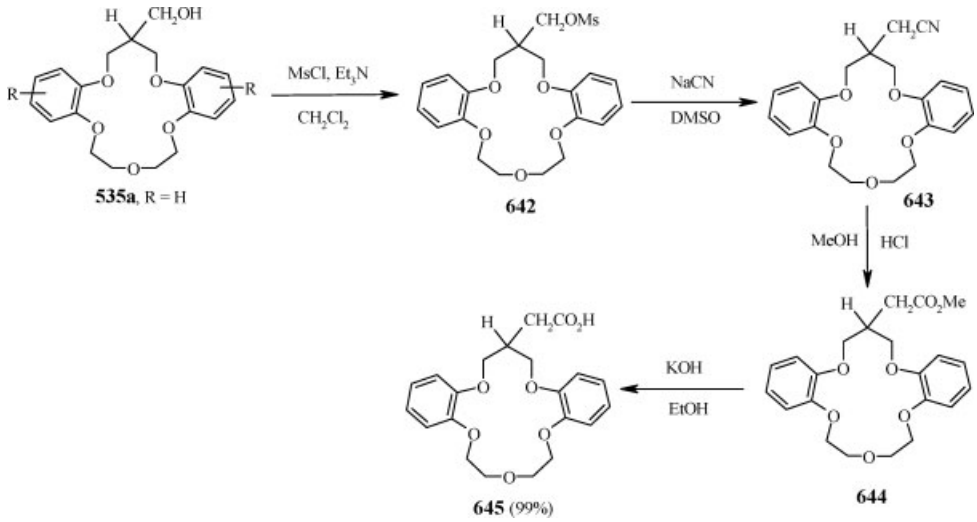


Scheme 50



457 **640** (76%) **641** (91%)

Scheme 51

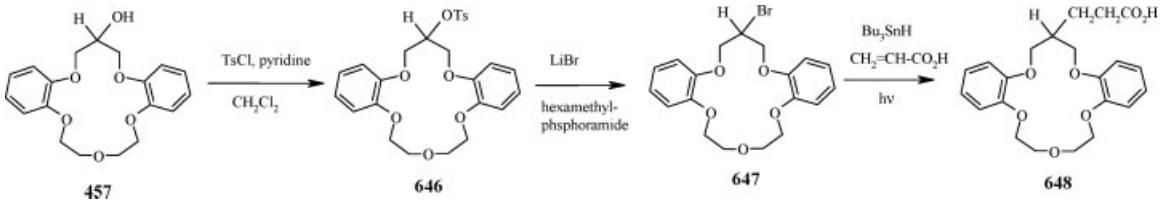


535a, R = H **642** **643** **644** **645** (99%)

cyanide in dimethyl sulfoxide at 60°C to provide an 98% yield of lariat ether nitrile **643**. Passing hydrogen chloride gas through a refluxing methanolic solution of the latter compound gave a quantitative yield of lariat ether methyl ester **644**. Hydrolysis with potassium hydroxide in 95% ethanol at room temperature gave a quantitative yield of the target **645** [97].

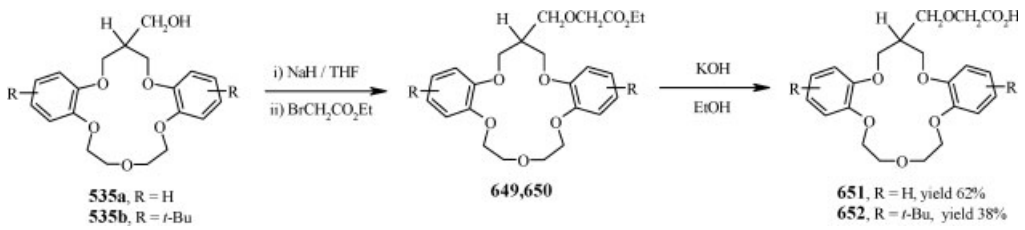
5.2.2.3.4. Synthesis of dibenzocrown ether propanoic acid. The synthetic route to 3-(sym-dibenzo-16-crown-5)propanoic acid **648** is shown in Scheme 52. Lariat

Scheme 52



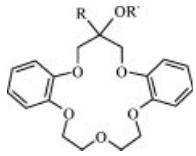
457 **646** **647** **648**

Scheme 53

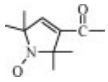


535a, R = H
535b, R = *t*-Bu
649,650
651, R = H, yield 62%
652, R = *t*-Bu, yield 38%

Table 46



Dibenzo-16-crown-5 with a pendant ester group (OCOR')

Comp. no.	R	R′	Method	Ref. (yield)
653	H	$CH_3C(O)$—	d	105 (77)
654	H	$C_5H1_{11}C(O)$—	d	105 (87)
655	H	$(CH_3)_3CC(O)$—	d	105 (66)
656	H	PhC(O)—	d	105 (77)
657	H	4-CH_3O—$C_6H_4C(O)$—	d	105 (59)
658	H	4-O_2N—$C_6H_4C(O)$—	d	105 (70)
659	C_3H_7—	$CH_3C(O)$—	d	105 (46)
660	C_3H_7—	$C_5H1_{11}C(O)$—	d	105 (50)
661	C_3H_7—	$(CH_3)_3CC(O)$—	d	105 (81)
662	C_3H_7—	PhC(O)—	d	105 (99)
663	C_3H_7—	4-CH_3O—$C_6H_4C(O)$—	d	105 (72)
664	C_3H_7—	4-O_2N—$C_6H_4C(O)$—	d	105 (86)
665	C_3H_7—	$(CH_3)_3COC(O)CH_2$—	a	105 (56)
666	4-CH_2=CH—C_6H_4—	$C_2H_5OC(O)CH_2$—	a	105 (72)
667	4-CH_2=$C(CH_3)$—C_6H_4—	$C_2H_5OC(O)CH_2$—	a	105 (80)
668	H	$C_2H_5OC(O)CH_2$—	b	105 (98)
669	C_3H_7—	$C_2H_5OC(O)CH_2$—	b	105 (94)
670	H		c	105 (5)
671	H	$C_2H_5OC(O)CH_2CH_2$—	e	105 (28)

ether alcohol **457** was converted into tosylate **646** in 97% yield. This tosylate was reacted with 10 equivalents of lithium bromide in hexamethylphosphoramide to give an 85% yield of lariat ether bromide **647,** which was photolyzed in the presence of acrylic acid and tributyltin hydride to produce an 30% yield of the desired lariat ether carboxylic acid **648** [97].

5.2.2.3.5. Synthesis of dibenzocrown ether 4-(2-oxabutanoic acid). The preparation of dibenzo-16-crown-5 compounds with 4-(2-oxabutanoic acid) side arms **651** and **652** is summarized in Scheme 53. Reaction of hydroxymethyl lariat ethers **535a,b** with ethyl bromoacetate and sodium hydride in tetrahydrofuran at room temperature gave lariat ether esters **649** and **650** in 36 and 40% yields, respectively. Hydrolysis with potassium hydroxide in 95% ethanol provided lariat ether carboxylic acids **651** and **652** in 94% yields [97].

5.2.2.4. Synthesis of dibenzocrown ethers with a pendant ester group. Bartsch *et al*. [105] reported the synthesis of dibenzo-16-crown-5 with pendant ester groups **653–671** (Table 46) from the corresponding lariat ether alcohols using the following synthetic routes:

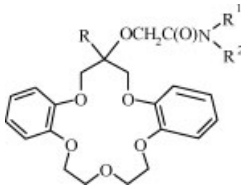
(a) Reaction of the corresponding lariat ether alcohol with NaH and the appropriate alkyl bromoacetate in THF.
(b) Reaction of a lariatether alcohol with ethyl diazoacetate and boron trifluoride in benzene.
(c) Reaction of *sym*-(hydroxy)dibenzo-16-crown-5 and carboxylic acid nitroxide in the presence of *N*,*N*′-dicyclohexylcarbodiimide in THF.
(d) Treatment of a lariat ether alcohol with KH followed by addition of the appropriate acid chloride.
(e) Heating the appropriate lariat ether nitrile under reflux in ethanol-benzene (1:2) through which gaseous HCl was passed.

5.2.2.5. Synthesis of dibenzocrown ethers with a pendant acetamide group. Bartsch *et al*. [106,107] reported the synthesis of *sym*-dibenzo-16-crown-5 oxyacetamides **672–704** (Table 47) by the reaction of *sym*-hydroxydibenzo-16-crown-5 with KH in THF followed by addition of the appropriate 2-chloroacetamide.

5.2.2.6. Synthesis of dibenzocrown ethers with a pendant amine group. Bartsch *et al*. [109] reported a synthetic method for attachment of an amino group to the central carbon atom of a variety of dibenzocrown ethers with subsequent conversion of these lariat ether primary amines into proton-ionizable lariat ether containing picrylamino type side arms.

The synthetic route to *sym*-(amino)dibenzocrown ethers **707** starting from the appropriate lariat ether

Table 47



Dibenzo-16-crown-5 with a pendant oxyacetamide group

Comp. no.	R	R^1	R^2	Ref. (yield)
672	H	C_8H_{17}—	C_8H_{17}—	107 (75)
673	H	$C_{10}H_{21}$—	$C_{10}H_{21}$—	107 (76)
674	C_3H_7—	C_8H_{17}—	C_8H_{17}—	107 (85)
675	C_3H_7—	$C_{10}H_{21}$—	$C_{10}H_{21}$—	107 (70)
676	$(CH_3)_2CH$—	C_5H_{11}—	C_5H_{11}—	107 (76)
677	$(CH_3)_2CH$—	C_6H_{13}—	C_6H_{13}—	107 (76)
678	$(CH_3)_2CH$—	C_8H_{17}—	C_8H_{17}—	107 (77)
679	$(CH_3)_2CH$—	$C_{10}H_{21}$—	$C_{10}H_{21}$—	107 (72)
680	$(CH_3)_3CCH_2$—	C_8H_{17}—	C_8H_{17}—	107 (73)
681	$(CH_3)_3CCH_2$—	$C_{10}H_{21}$—	$C_{10}H_{21}$—	107 (76)
682	H	H	H	106 (93), 108 (65)
683	H	CH_3—	CH_3—	106 (68)
684	H	C_2H_5—	C_2H_5—	106 (96)
685	H	H	C_3H_7—	106 (89)
686	H	C_3H_7—	C_3H_7—	106 (92)
687	H	C_4H_9—	C_4H_9—	106 (98)
688	H	H	C_5H_{11}—	106 (97)
689	H	C_5H_{11}—	C_5H_{11}—	106 (96)
690	H	C_6H_{13}—	C_6H_{13}—	106 (96)
691	H	$CH_3O(CH_2)_2$—	$CH_3O(CH_2)_2$—	106 (100)
692	H	$CH_3O(CH_2)_2O(CH_2)_2$—	$CH_3O(CH_2)_2O(CH_2)_2$—	106 (91)
693	H	—$(CH_2)_5$—		106 (100)
694	H	—$(CH_2)_2O(CH_2)_2$—		106 (100)
695	C_3H_7—	CH_3—	CH_3—	106 (66)
696	C_3H_7—	C_2H_5—	C_2H_5—	106 (100)
697	C_3H_7—	C_3H_7—	C_3H_7—	106 (100)
698	C_3H_7—	C_4H_9—	C_4H_9—	106 (100)
699	C_3H_7—	C_5H_{11}—	C_5H_{11}—	106 (98)
700	C_3H_7—	C_6H_{13}—	C_6H_{13}—	106 (100)
701	C_3H_7—	$CH_3O(CH_2)_2$—	$CH_3O(CH_2)_2$—	106 (97)
702	C_3H_7—	$CH_3O(CH_2)_2O(CH_2)_2$—	$CH_3O(CH_2)_2O(CH_2)_2$—	106 (63)
703	C_3H_7—	—$(CH_2)_5$—		106 (93)
704	C_3H_7—	—$(CH_2)_2O(CH_2)_2$—		106 (95)

Scheme 54

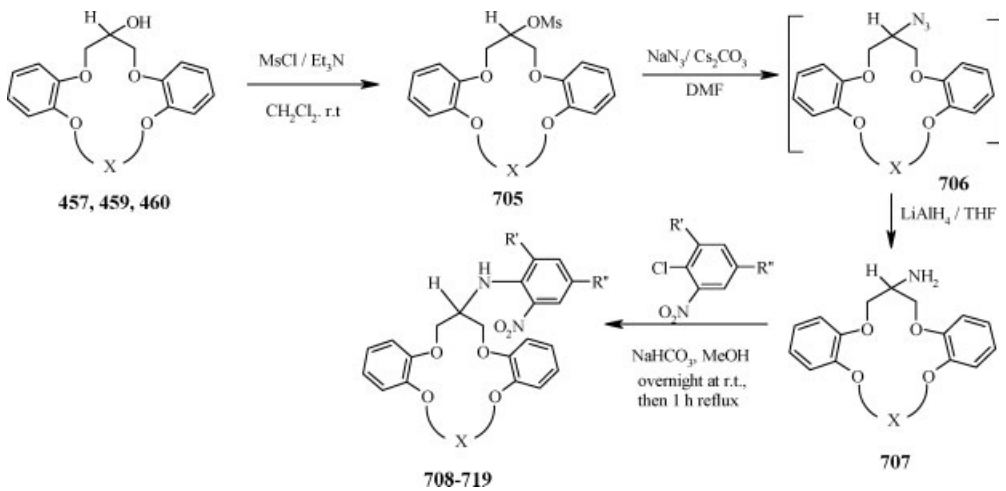
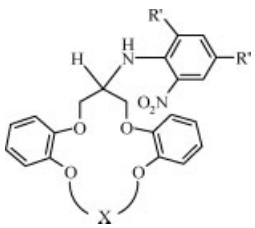


Table 48



Dibenzo-14-crown-4, Dibenzo-16-crown-5, Dibenzo-19-crown-6 with a pendant amine group

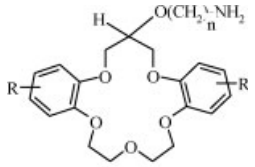
Comp. no.	X	R′	R″	Yield%
708	—$CH_2CH_2CH_2$—	NO_2	NO_2	95
709	—$CH_2CH_2CH_2$—	NO_2	CN	93
710	—$CH_2CH_2CH_2$—	NO_2	CF_3	90
711	—$CH_2CH_2CH_2$—	CF_3	NO_2	68
712	—$CH_2CH_2OCH_2CH_2$—	NO_2	NO_2	91
713	—$CH_2CH_2OCH_2CH_2$—	NO_2	CN	88
714	—$CH_2CH_2OCH_2CH_2$—	NO_2	CF_3	96
715	—$CH_2CH_2OCH_2CH_2$—	CF_3	NO_2	88
716	—$CH_2(CH_2OCH_2)_2CH_2$—	NO_2	NO_2	91
717	—$CH_2(CH_2OCH_2)_2CH_2$—	NO_2	CN	93
718	—$CH_2(CH_2OCH_2)_2CH_2$—	NO_2	CF_3	90
719	—$CH_2(CH_2OCH_2)_2CH_2$—	CF_3	NO_2	88

alcohols is shown in Scheme 54. The latter compounds were converted to lariat ether mesylate **705** in 91–93% yields upon treatment with methylsulfonyl chloride in THF. Reaction of the mesylates **705** with NaN_3 and Na_2CO_3 in DMF produced lariat ether azides **706** which were reduced to the desired lariat ether amines **707** in 75–81% yields. Reaction of the latter with the appropriate chlorobenzenes in methanol containing $NaHCO_3$ afforded the corresponding lariat ethers with picrylamino sidearms **708–719** (Table 48).

Similarly, binaphthyl crown receptor with a pendant amine **722** was prepared from the corresponding alcohol **470** by reaction with tosyl chloride in pyridine to give tosylate **720**. The latter was subjected to azidation of tosyl group to give **721** in 94% yield and then reduced to form the amine **722** in 98% yield. Amine **722** was reacted with a large excess of activated carbamate (which was generated in situ by the reaction of 2,4-dinitroaniline and phenyl chloroforamte) to yield host **723** in 75% yield and an overall yield of 53% (Scheme 55) [110].

Bartsch *et al*. [111] reported also the synthesis of lariat ethers with a pendant amines **724** starting from ketone **473** by initial treatment with the appropriate primary amines and 5*N* HCl-methanol in methanol in the presence of 4 A° molecular sieves as the drying agent followed by reduction with sodium cyanoborohydride. Subsequent reaction of lariat ether amines with *N*,*N*-dipentylchloroacetamide in acetonitrile in the presence of sodium bicarbonate and a catalytic amount of NaI afforded amides **725** and **726**, respectively (Scheme 56).

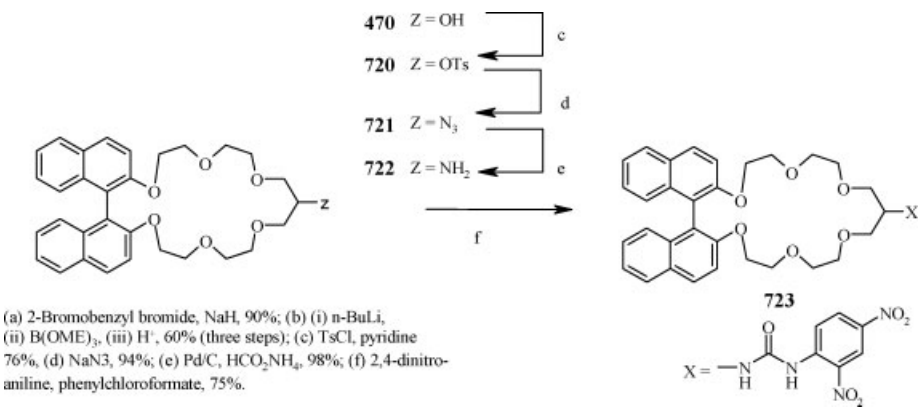
Lariat ether amines **727–729** in which the nitrogen atom is not directly attached to the pivot carbon can be obtained by reduction of the corresponding lariat ether amide [97] or lariat ether nitriles [108] with borane-dimethylsulfide in THF in 68%, 54%, and 40% yields, respectively.



727, R = H, n = 2
728, R = H, n = 3
729, R = *t*-Bu, n = 3

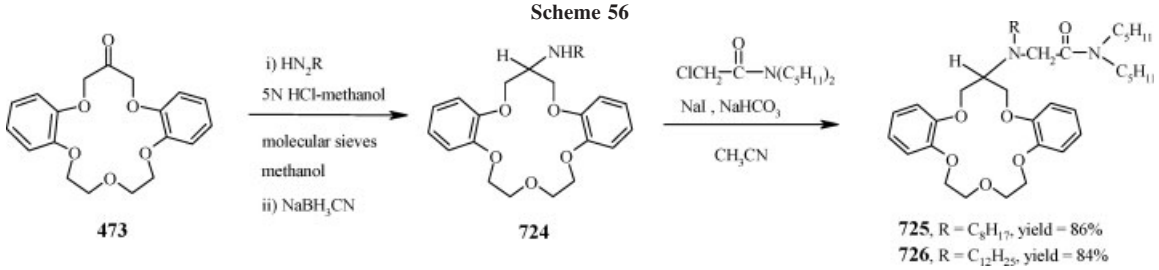
5.2.2.7. Synthesis of dibenzocrown ethers with pendant phosphinic acid and phosphonic acid monoalkyl ester groups. Burns *et al*. [112] reported the synthesis of lariat ether **730** having a phosphinic acid group by condensation of *sym*-hydroxydibenzo-14-crown-4 with

Scheme 55

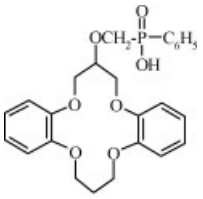


(a) 2-Bromobenzyl bromide, NaH, 90%; (b) (i) n-BuLi, (ii) $B(OME)_3$, (iii) H^+, 60% (three steps); (c) TsCl, pyridine 76%, (d) NaN3, 94%; (e) Pd/C, HCO_2NH_4, 98%; (f) 2,4-dinitroaniline, phenylchloroformate, 75%.

Scheme 56

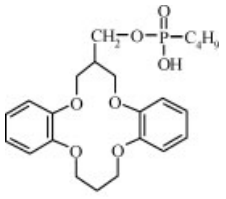


(chloromethyl)phenyl-phosphinic acid in presence of NaH in THF.



730

Habata *et al*. [113–116] reported the synthesis of alkylphosphoric acid armed dibenzo-14-crown-4 **731** by the reaction of hydroxymethyldibenzo-14-crown-4 with dichloroalkylphosphate in benzene or THF followed by hydrolysis.



731

Bartsch *et al*. [96] reported the synthesis of crown ether phosphonic acid monoethyl ester **735** ($n = 1$) by the reaction of the alkoxide from the appropriate lariat ether alcohol with monoethyl iodomethylphosphonic acid. Lariat ether phosphonic acid monoethyl esters **736–738** ($n = 2, 3, 4$) were obtained by the reaction of appropriate lariat ether substituted alkyl bromides **732–734** with triethyl phosphite followed by basic hydrolysis (Scheme 57).

Bromo derivatives **732** and **733** ($n = 2, 3$) were obtained from the corresponding alcohols on treatment with PBr_3 in DMF. Compound **734** ($n = 4$) was obtained from the corresponding alcohol upon treatment with 1,4-dibromobutane in aqueous NaOH in the presence of tetrabutylammonium hydrogen sulfate (Scheme 57).

5.2.2.8. Synthesis of various lariat ethers from dibenzocrown ethers carboxylic acids. Lariat ether carboxylic acids are important starting materials for the synthesis of lariat ethers with pendant ester, amide, hydroxamate, and *N*-(X)-sulfonylcarboxamide groups [97]. The functional groups may provide additional ligating atoms for cation complexation and serve as sites for further structure elaboration or function as attachment points for binding crown ethers to polymers [90].

Scheme 57

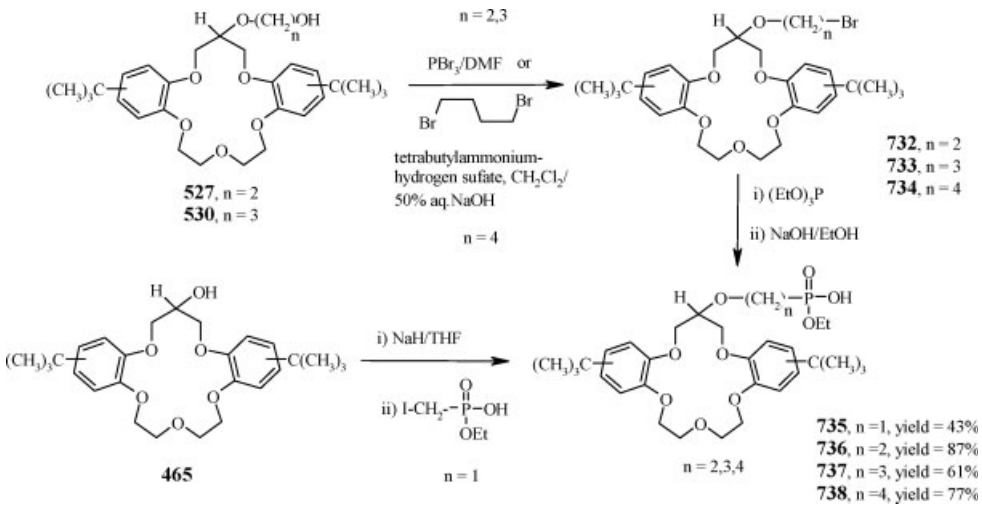
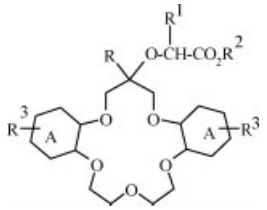


Table 49



Dibenzo(dicyclohexano)-16-crown-5 with a pendant ester group ($OCHR^1CO_2R^2$)

Comp. no.	A	R	R^1	R^2	R^3	Ref. (yield)
739	benzo	CH_3—	H	C_2H_5—	H	92 (94)
740	benzo	$C_{10}H_{21}$—	H	C_2H_5—	H	92 (97)
741	benzo	CH_3—	H	C_2H_5—	H	117 (–)
742	benzo	C_2H_5—	H	C_2H_5—	H	117 (–)
743	benzo	C_4H_9—	H	C_2H_5—	H	117 (–)
744	benzo	C_8H_{17}—	H	C_2H_5—	H	117 (–)
745	benzo	$C_{10}H_{21}$—	H	C_2H_5—	H	117 (–)
746	benzo	$(CH_3)_2CH$—	H	C_2H_5—	H	117 (–)
747	benzo	$(CH_3)_3C$—CH_2—	H	C_2H_5—	H	117 (–)
748	benzo	C_6F_{13}—	H	C_2H_5—	H	117 (–)
749	benzo	$(CH_3)_2C$=CH—	H	C_2H_5—	H	117 (–)
750	benzo	Ph—	H	C_2H_5—	H	117 (–)
751	benzo	$C_6H_{13}C{\equiv}C$—	H	C_2H_5—	H	117 (–)
752	benzo	H	H	C_6H_{13}—	H	117 (–)
753	benzo	H	H	$C_{10}H_{21}$—	H	117 (–)
754	benzo	H	H	$(CH_3)_2CH$—	H	117 (–)
755	benzo	H	H	$(CH_3)_3C$—	H	117 (–)
756	benzo	C_3H_7—	H	C_6H_{13}—	H	117 (–)
757	benzo	C_3H_7—	H	$C_{10}H_{21}$—	H	117 (–)
758	benzo	C_3H_7—	H	$(CH_3)_2CH$—	H	117 (–)
759	benzo	H	H	CH_3—	H	105 (82)
760	benzo	H	H	C_2H_5—	H	105 (98)
761	benzo	H	H	C_6H_{13}—	H	105 (62)
762	benzo	H	H	C_8H_{17}—	H	105 (86)
763	benzo	H	H	$C_{10}H_{21}$—	H	105 (84)
764	benzo	H	H	$C_{12}H_{25}$—	H	105 (78)
765	benzo	H	H	$(CH_3)_2CH$—	H	105 (94)
766	benzo	H	H	$(CH_3)_3C$—	H	105 (62)
767	benzo	H	Ph—	CH_3—	H	105 (100)
768	benzo	CH_3—	H	C_2H_5—	H	105 (91)
769	benzo	C_2H_5—	H	C_2H_5—	H	105 (93)
770	benzo	C_3H_7—	H	CH_3—	H	105 (94)
771	benzo	C_3H_7—	H	C_2H_5—	H	105 (94)
772	benzo	C_3H_7—	H	C_6H_{13}—	H	105 (85)
773	benzo	$(CH_3)_2C$=CH—	H	C_2H_5—	H	105 (53)
774	benzo	CH_2=$CH(CH_2)_8$—	H	C_2H_5—	H	105 (90)
775	benzo	$C_6H_{13}C{\equiv}C$—	H	C_2H_5—	H	105 (80)
776	benzo	Ph—	H	C_2H_5—	H	105 (97)
777	benzo	Ph—	H	C_2H_5—	H	105 (84)
778	benzo	Ph—	Ph—	C_2H_5—	H	105 (96)
779	benzo	C_3H_7—	H	C_8H_{17}—	H	105 (80)
780	benzo	C_3H_7—	H	$C_{10}H_{21}$—	H	105 (77)
781	benzo	C_3H_7—	H	$(CH_3)_2CH$—	H	105 (90)
782	benzo	C_3H_7—	H	$(CH_3)_3C$—	H	105 (56)
783	benzo	$(CH_3)_2CH$—	H	C_2H_5—	H	105 (89)
784	benzo	C_3F_7—	H	C_2H_5—	H	105 (90)
785	benzo	C_4H_9—	H	C_2H_5—	H	105 (92)
786	benzo	C_6H_{13}—	H	C_2H_5—	H	105 (94)
787	benzo	C_6F_{13}—	H	C_2H_5—	H	105 (90)
788	benzo	C_8H_{17}—	H	C_2H_5—	H	105 (93)
789	benzo	$C_{10}H_{21}$—	H	CH_3—	H	105 (79)
790	benzo	$C_{10}H_{21}$—	H	C_2H_5—	H	105 (91)

Table 49
(*Continued*)

Comp. no.	A	R	R^1	R^2	R^3	Ref. (yield)
791	benzo	$C_{10}H_{21}$—	Ph—	C_2H_5—	H	105 (99)
792	benzo	$HO(CH_2)_{10}$—	H	C_2H_5—	H	105 (86)
793	benzo	$C_{12}H_{25}$—	H	C_2H_5—	H	105 (95)
794	benzo	$C_{14}H_{29}$—	H	C_2H_5—	H	105 (96)
795	benzo	$C_{16}H_{33}$—	H	C_2H_5—	H	105 (94)
796	benzo	$C_{18}H_{37}$—	H	C_2H_5—	H	105 (97)
797	benzo	$C_{20}H_{41}$—	H	C_2H_5—	H	105 (95)
798	benzo	H	H	C_2H_5—	O_2N—	105 (95)
799	benzo	H	H	CH_3—	H_2N—	105 (92)
800	benzo	H	H	C_2H_5—	H_2N—	105 (93)
801	benzo	C_3H_7—	H	CH_3—	H_2N—	105 (93)
802	benzo	C_3H_7—	H	C_2H_5—	H_2N—	105 (89)
803	cyclohexano	C_3H_7—	H	C_2H_5—	H	105 (93)
804	cyclohexano	C_3H_7—	H	C_2H_5—	H	105 (96)

Compounds no. **665–669** mentioned in Table 46 were prepared in 72—80% yield [117,105] using the above methods.

5.2.2.8.1. Synthesis of dibenzocrown ethers with a pendant ester group. Bartsch *et al*. [105] used two synthetic approaches for the preparation of dibenzo-16-crown-5 with pendant ester group **739–816** (Tables 49 and 50) from the corresponding crown ether carboxylic acid. These synthetic approaches include:

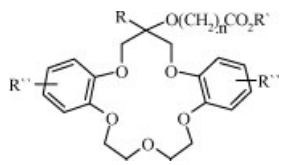
(a) Esterification of a carboxylic acid function in a lariat ether carboxylic acid with ethanol or methanol in the presence of H_2SO_4 or *p*-toluenesulfonic acid as catalyst [92,97,105,117].
(b) Conversion of a lariat ether carboxylic acid into the corresponding lariat ether acid chloride by treatment with oxalyl chloride in benzene and subsequent reaction with the appropriate alcohol in pyridine [95,117].

5.2.2.8.2. Synthesis of dibenzocrown ethers with pendant amide, hydroxamate, hydroxamic acid, and N-(X)sulfonyl carboxamide groups. Lariat ethers with oxyacetamide group were prepared from the corresponding lariat ether carboxylic acids by initial reaction with oxalyl chloride in benzene to give the corresponding acid chloride followed by reaction with ammonia gas or the appropriate alkyl amine [20,106,107,111,118].

Lariat ethers hydroxamates were obtained from the corresponding lariat ether acid chloride upon treatment with *o*-benzylhydroxylamine hydrochloride and pyridine in acetonitrile. Subsequent catalytic hydrogenation of the *o*-benzyl group afforded the lariat ether hydroxamic acid [91,94,111,119]. *N*-(X)sulfonyl carboxamide lariat ethers were prepared by coupling of the corresponding lariat ether acid chloride with the K-salt of the commercially available sulfonamides [18,120]. The following lariat ethers **739–816** (Tables 51 and 52) are prepared using the above strategies.

5.2.3. Synthesis of di-/tetrabenzo lariat azacrown ethers. *5.2.3.1. Synthesis of lariat ether formazan*. Katritzky [122] reported the synthesis of crown formazan **881** with a pendant hydroxyl group by coupling of tetrazotized 1,3-bis(2-aminophenoxy)propan-2-ol **879** with the sodium salt of β-phenylpyruvic acid **880** under phase transfer conditions. Acylation of the hydroxyl group of **881** with 2-chloroacetyl chloride

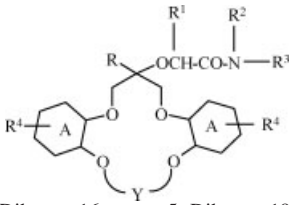
Table 50



Dibenzo-16-crown-5 with a pendant ester group ($O(CH_2)_nCO_2R'$)

Comp. no.	R	R″	R′	n	Ref. (yield)
805	H	C_2H_5—	H	2	105 (28)
806	H	CH_3—	$(CH_3)_3C$—	2	105 (74)
807	H	CH_3—	H	3	105 (79)
808	CH_3—	CH_3—	H	2	105 (65)
809	CH_3—	C_2H_5—	H	2	105 (92)
810	CH_3—	CH_3—	H	3	105 (94)
811	CH_3—	C_2H_5—	H	3	105 (94)
812	CH_3—	H	CH_3—	2	97 (65)
813	H	H	CH_3—	3	97 (79)
814	CH_3—	H	CH_3—	3	97 (94)
815	H	H	CH_3—	2	97 (94)
816	H	*t*-Bu—	CH_3—	2	97 (74)

Table 51

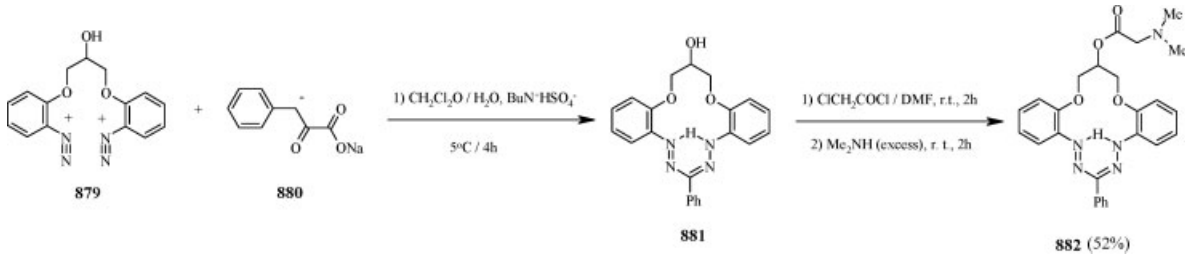


Dibenzo-13-crown-4, Dibenzo-14-crown-4, Dibenzo-16-crown-5, Dibenzo-19-crown-6 with pendant amide, hydroxamate, and hydroxamic acid groups

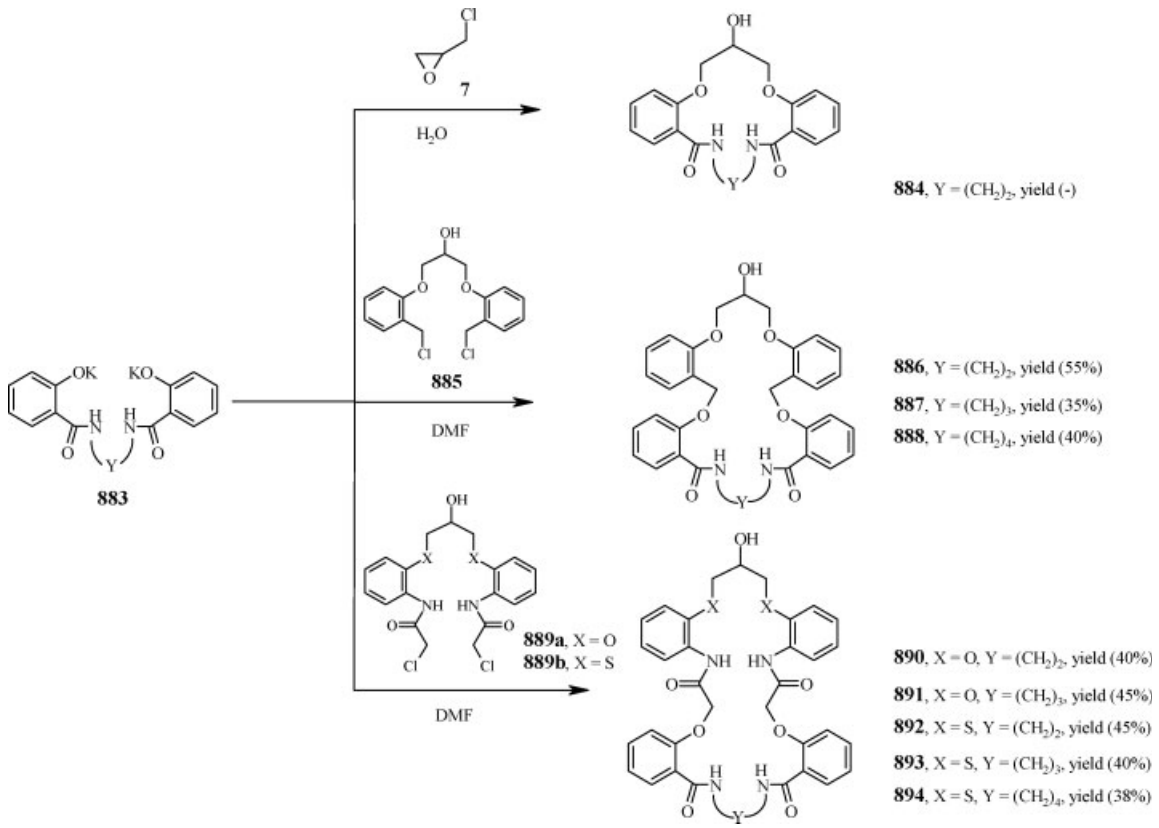
Comp. no.	Y	R	R^1	R^2	R^3	Ref. (yield)
817	$(CH_2)_2O(CH_2)_2$	$CH_3(CH_2)_2$—	H	H		118 (67)
818	$(CH_2)_2O(CH_2)_2$	$CH_3(CH_2)_2$—	H	H		118 (61)
819	$(CH_2)_2O(CH_2)_2$	CH_3—	H	C_5H_{11}—	C_5H_{11}—	107 (90)
820	$(CH_2)_2O(CH_2)_2$	C_2H_5—	H	C_5H_{11}—	C_5H_{11}—	107 (98)
821	$(CH_2)_2O(CH_2)_2$	C_4H_9—	H	C_5H_{11}—	C_5H_{11}—	107 (97)
822	$(CH_2)_2O(CH_2)_2$	C_6H_{13}—	H	C_5H_{11}—	C_5H_{11}—	107 (99)
823	$(CH_2)_2O(CH_2)_2$	C_8H_{17}—	H	C_5H_{11}—	C_5H_{11}—	107 (89)
824	$(CH_2)_2O(CH_2)_2$	$C_{10}H_{21}$—	H	C_5H_{11}—	C_5H_{11}—	107 (94)
825	$(CH_2)_2O(CH_2)_2$	$C_{12}H_{25}$—	H	C_5H_{11}—	C_5H_{11}—	107 (82)
826	$(CH_2)_2O(CH_2)_2$	$C_{14}H_{29}$—	H	C_5H_{11}—	C_5H_{11}—	107 (97)
827	$(CH_2)_2O(CH_2)_2$	$C_{16}H_{33}$—	H	C_5H_{11}—	C_5H_{11}—	107 (92)
828	$(CH_2)_2O(CH_2)_2$	$C_{18}H_{37}$—	H	C_5H_{11}—	C_5H_{11}—	107 (99)
829	$(CH_2)_2O(CH_2)_2$	$C_{20}H_{41}$—	H	C_5H_{11}—	C_5H_{11}—	107 (88)
830	$(CH_2)_2$	H	H	C_5H_{11}—	C_5H_{11}—	107 (91)
831	$(CH_2)_2$	C_3H_7—	H	C_5H_{11}—	C_5H_{11}—	107 (95)
832	$(CH_2)_3$	H	H	C_5H_{11}—	C_5H_{11}—	107 (93)
833	$(CH_2)_3$	C_3H_7—	H	C_5H_{11}—	C_5H_{11}—	107 (82)
834	$(CH_2)_3$	$(CH_3)_2CH$—	H	C_5H_{11}—	C_5H_{11}—	107 (75)
835	$(CH_2)_3$	$C_{10}H_{21}$—	H	C_5H_{11}—	C_5H_{11}—	107 (88)
836	$(CH_2)_3$	Ph—	H	C_5H_{11}—	C_5H_{11}—	107 (93)
837	$(CH_2)_2O(CH_2)_2$	C_3H_7—	H	H	H	106 (95)
838	$(CH_2)_2O(CH_2)_2$	C_3H_7—	H	H	C_3H_7—	106 (97)
839	$(CH_2)_2O(CH_2)_2$	C_3H_7—	H	H	C_5H_{11}—	106 (97)
840	$(CH_2)_2$	H	H	H	$PhCH_2O$—	94 (80)
841	$(CH_2)_2O(CH_2)_2$	H	H	H	$PhCH_2O$—	94 (83)
842	$CH_2(CH_2OCH_2)_2CH_2$	H	H	H	$PhCH_2O$—	94 (84)
843	$(CH_2)_2O(CH_2)_2$	H	Ph	H	$PhCH_2O$—	94 (74)
844	$(CH_2)_2O(CH_2)_2$	H	$C_{10}H_{21}$—	H	$PhCH_2O$—	94 (69)
845	$(CH_2)_2O(CH_2)_2$	H	$C_{12}H_{25}$—	H	$PhCH_2O$—	94 (73)
846	$(CH_2)_2O(CH_2)_2$	H	$C_{14}H_{29}$—	H	$PhCH_2O$—	94 (79)
847	$(CH_2)_2O(CH_2)_2$	H	$C_{16}H_{33}$—	H	$PhCH_2O$—	94 (76)
848	$(CH_2)_2O(CH_2)_2$	C_3H_7—	H	H	$PhCH_2O$—	94 (66)
849	$(CH_2)_2O(CH_2)_2$	Ph—	H	H	$PhCH_2O$—	94 (79)
850	$(CH_2)_2O(CH_2)_2$	$C_{10}H_{21}$—	H	H	$PhCH_2O$—	94 (92)
851	$(CH_2)_2O(CH_2)_2$	$C_{18}H_{37}$—	H	H	$PhCH_2O$—	94 (88)
852	$(CH_2)_2O(CH_2)_2$	Ph—	$C_{10}H_{21}$—	H	$PhCH_2O$—	94 (93)
853	$(CH_2)_2O(CH_2)_2$	Ph—	Ph	H	$PhCH_2O$—	94 (92)
854	$(CH_2)_2O(CH_2)_2$	3-F_3C—C_6H_4—	H	H	$PhCH_2O$—	91 (46)
855	$(CH_2)_2O(CH_2)_2$	3,5-F_3C—C_6H_3—	H	H	$PhCH_2O$—	91 (46)
856	$(CH_2)_2O(CH_2)_2$	H	C_8H_{17}—	H	$PhCH_2O$—	111 (76)
857[a]	$(CH_2)_2O(CH_2)_2$	H	H	H	$PhCH_2O$—	111 (75)
858	$(CH_2)_2O(CH_2)_2$	2-H_3C—C_6H_4—	H	H	$PhCH_2O$—	111 (68)
859	$(CH_2)_2O(CH_2)_2$	3-H_3C—C_6H_4—	H	H	$PhCH_2O$—	111 (52)
860	$(CH_2)_2O(CH_2)_2$	4-H_3C—C_6H_4—	H	H	$PhCH_2O$—	111 (64)
861	$(CH_2)_2O(CH_2)_2$	c-C_6H_{11}—	H	H	$PhCH_2O$—	111 (62)
862	$(CH_2)_2O(CH_2)_2$	H	H	H	C_6H_{13}—	111 (81)
863	$(CH_2)_2O(CH_2)_2$	H	H	CH_3—	C_6H_{13}—	111 (46)
864	$(CH_2)_2O(CH_2)_2$	H	H	H	$C_{12}H_{25}$—	111 (79)
865	$(CH_2)_2O(CH_2)_2$	H	H	H	Ph—	111 (93)
866	$(CH_2)_2O(CH_2)_2$	$C_{10}H_{21}$—	H	H	H	111 (96)
867	$(CH_2)_2O(CH_2)_2$	$C_{10}H_{21}$—	Ph—	C_5H_{11}—	C_5H_{11}—	111 (96)
868	$(CH_2)_2O(CH_2)_2$	$(CH_3)_3CCH_2$—	H	C_5H_{11}—	C_5H_{11}—	111 (83)
869	$(CH_2)_2O(CH_2)_2$	Ph—	H	H	$PhCH_2$—	111 (70)
870	$(CH_2)_2O(CH_2)_2$	Ph—	Ph—	C_5H_{11}—	Ph—	111 (87)
871[b]	$(CH_2)_2O(CH_2)_2$	H	H	H	C_6H_{13}—	111 (56)
872[b]	$(CH_2)_2O(CH_2)_2$	H	H	H	H	18 (86)

[a] $R^4 = (CH_3)_3C$— but in all other compounds R^4 = H.
[b] A = Cyclohexano but in all other compounds A = benzo.

Scheme 58



Scheme 59



Scheme 60

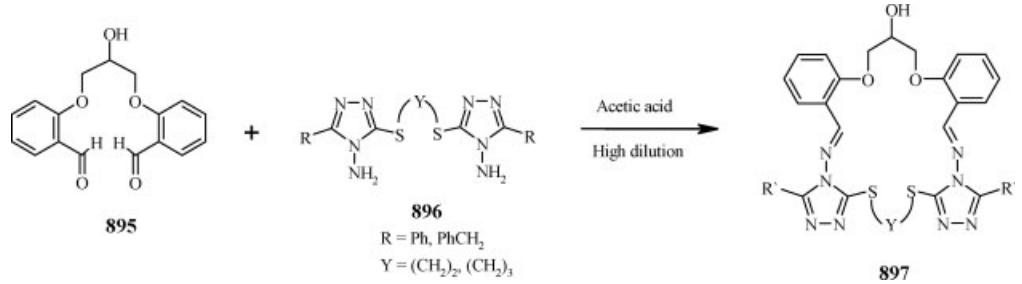
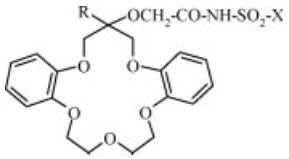


Table 52



Dibenzo-16-crown-5 with a pendant *N*-(X)sulfonyl carboxamide group

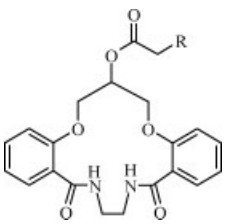
Comp. no.	R	X	Ref. (yield)
873	$C_{10}H_{21}$—	CF_3—	120, 18 (–)
874	$C_{10}H_{21}$—	CH_3—	120, 18 (–)
875	$C_{10}H_{21}$—	Ph	120, 18 (–)
876	$C_{10}H_{21}$—	4-O_2N—C_6H_4—	120, 18 (–)
877	H		121 (76)
878	C_3H_7—		121 (55)

followed by reaction with dimethylamine afforded lariat ether formazans **882** with a pendant aminoacetyloxy group (Scheme 58).

5.2.3.2. Synthesis of lariat azacrown ethers. Abbas *et al*. [123–126] used an approach similar to that described by Katritzky [122] for the synthesis of azacrown ethers with pendant alkylaminoacetyloxy or phenoxy groups **898–917** (Tables 53–56) from the corresponding hydroxyl azacrown ethers **884, 886–888, 890–894,** and **897** by initial acylation of the hydroxyl group in these compounds with 2-choloroacetyl chloride followed by reaction with the appropriate alkyl amine or phenol.

The hydroxyazacrown ethers **884, 886–888,** and **890–894** were obtained by reaction of the appropriate

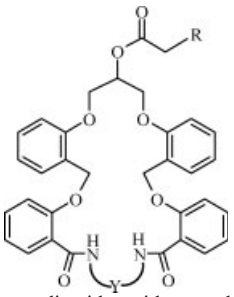
Table 53



Macrocyclic dibenzodiamides with a pendant ($OCOCH_2NR_2$) group

Comp. no.	R	Ref. (yield)
898	$(CH_3CH_2)_2N$—	125 (60)
899		125 (61)
900		125 (65)

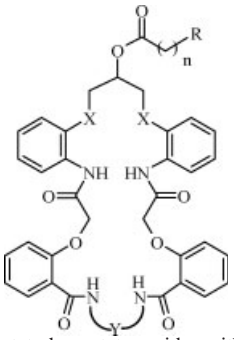
Table 54



Macrocyclic tetrabenzodiamides with a pendant $OCOCH_2NR_2$ or $OCOCH_2OAr$ group

Comp. no.	Y	R	Ref. (yield)
901	$(CH_2)_2$		125 (60)
902	$(CH_2)_4$		125 (63)
903	$(CH_2)_4$		125(60)
904	$(CH_2)_2$	4—H(O)C—C_6H_4—O—	125 (50)
905	$(CH_2)_4$	2-H(O)C—C_6H_4—O—	125 (55)
906	$(CH_2)_2$	2-O_2N—C_6H_4—O—	125 (50)

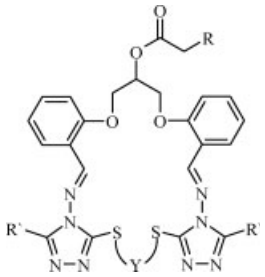
Table 55



Macrocyclic tetrabenzotetraamides with a pendant $OC(O)CH_2NR_2$ group

Comp. no.	Y	n	X	R	Ref. (yield)
907	$(CH_2)_2$	1	O	$(CH_3CH_2)_2N$—	124 (60)
908	$(CH_2)_2$	1	O		124 (65)
909	$(CH_2)_3$	1	O		124 (60)
910	$(CH_2)_3$	1	O		124 (65)
911	$(CH_2)_2$	1	S		124 (61)
912	$(CH_2)_3$	2	S		124 (85)
913	$(CH_2)_3$	2	S		124 (92)
914	$(CH_2)_4$	2	S		126 (60)

Table 56



Macrocyclic Schiff bases with a pendant $OC(O)CH_2NR$ group

Comp. no.	X	R′	R	Ref. (yield)
915	$(CH_2)_3$	Ph—		123 (70)
916	$(CH_2)_4$	$PhCH_2$—		123 (65)
917	$(CH_2)_4$	$PhCH_2$—	$(CH_3CH_2)_2N$—	123 (60)

dipotassium salts **883** with epichlorohydrin (**7**) for **884**, 1,3-bis(2-chloromethylphenoxy)propan-2-ol (**885**) for **886–888**, 1,3-bis(2-chloroacetyloxy-aminophenoxy)propan-2-ol (**889a**) and 1,3-bis(2-chloroacetyloxy-aminothiophenoxy)propan-2-ol (**889b**) for **890–894**, respectively [124,125] (Scheme 59).

The hydroxyazacrown ethers **897** were obtained by cyclocondensation of the aldehyde **895** with the corresponding bis(amine)s [123] **896** in refluxing acetic acid under high dilution conditions (Scheme 60).

Acknowledgments. Prof. Dr. Ahmed H. M. Elwahy thanks the Alexander von Humboldt Foundation for a research fellowship. He is also greatly indebted to Prof. K. Hafner, University of Darmstadt, for his continuous help and generous support.

REFERENCES AND NOTES

[1] Pedersen, C. J. J Am Chem Soc 1967, 89, 7017.

[2] Gokel, G. W.; Korzenionowski, S. H. Macrocyclic Polyethers Synthesis; Springer-Verlag: Berlin, 1982.

[3] Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. Chem Rev 1989, 89, 929.

[4] Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. Tetrahedron 1992, 48, 4475.

[5] Bradshaw; J. S.; Krakowiak, K. E.; Izatt, R. M. In "Azacrown Macrocycles" The Chemistry of Heterocyclic Compounds Series; Taylor, E. C. Ed.; Wiley: New York, NY, 1993; Vol. 51, p 885.

[6] Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. Chem Rev 1991, 91, 1721.

[7] Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. Chem Rev 1995, 95, 2529.

[8] Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L.; Tarbet, B. J Chem Rev 1992, 92, 1261.

[9] Dietrich, B. In Comprehensive Supramolecular Chemistry, Gokel, G. W. Ed.; Perganon: New York, 1996; Vol. 1, pp 153–212.

[10] Gokel, G. W.; Schall, O. F. In Comprehensive Supramolecular Chemistry, Gokel, G. W. Ed.; Elsevier: Oxford, 1996; Vol. 1, pp 97–152.

[11] Elwahy, A. H. M. J Heterocycl Chem 2003, 40, 1.

[12] Ibrahim, Y. A.; Abbas, A. A.; Elwahy, A. H. M. J Heterocycl Chem 2004, 12, 135.

[13] Gokel, G. W.; Dishong, D. M.; Diamond, C. J. J Chem Soc Chem Commun 1980, 1053.

[14] (a) Gatto, V. J.; Gokel, G. W. J Am Chem Soc 1984, 106, 8240; (b) Gatto, V. J., Arnold, K. A.; Viscariello, A. M.; Miller, S. R.; Morgan, C. R.; Gokel, G. W. J Org Chem 1986, 51, 5373; (c) Tsukube, H.; Yamashita, K.; Iwashido, T.; Zenki, M. Tetrahedron Lett 1989, 30, 3983; (d) Tsukube, H.; Adachi, H.; Morosawa, S. J Chem Soc Perkin Trans 1 1989, 89; (e) Matsumoto, K.; Minatogawa, H.; Munakata, M.; Toda, M.; Tsukube, H. Tetrahedron Lett 1990, 31, 3923.

[15] Gokel, G. W. Chem Soc Rev 1992, 21, 39.

[16] (a) Hriciga, A.; Lehn, J.-M., Proc Natl Acad Sci USA 1983, 80, 37; (b) Izatt, R. M.; Lindh, G. C.; Clark, G. A.; Bradshaw, J. S.; Nakatsuji, Y.; Lamb, J. D.; Christensen, J. J. J Chem Soc Chem Commun 1985, 1676; (c) Bradshaw, J. S.; Colter, M. L.; Nakatsuji, Y.; Spencer, N. O.; Brown, M. F.; Izatt, R. M.; Arena, G.; Tse, P.-K.; Wilson, B. E.; Lamb, J. D.; Dalley, N. K.; Morin, F. G.; Grant, D. M. J Org Chem 1985, 50, 4865.

[17] (a) Takagi, M.; Nakamura, H.; Ueno, K. Anal Lett 1977, 10, 1115; (b) Nakamura, H.; Takagi, M.; Ueno, K. Talanta 1979, 26, 921; (c) Takagi, M.; Ueno, K. Top Curr Chem 1984, 121, 39; (d) Eyring, E. M.; Petrucci, S. In Cation Binding by Macrocycles, Inoue, Y.; Gokel, G. W. Eds.; Marcel Dekker: New York, 1990; Chapter 4; (e) Sakai, Y.; Kawano, N.; Nakamura, H.; Takagi, M. Talanta 1986, 33, 407; (f) Katayama, Y.; Fukuda, R.; Iwasaki, T.; Nita, K.; Takagi, M. Anal Chim Acta 1988, 204, 113; (g) Katayama, Y.; Fukuda, R.; Takagi, M. Anal Chim Acta 1986, 185, 295.

[18] Elshani, S.; Hwang, H. S.; Wai, C. M.; Shreeve, J. M.; Bartsch, R. A. J Heterocycl Chem 2003, 40, 451.

[19] Elwahy, A. H. M.; Abbas, A. A. J Heterocycl Chem 2008, 45, 1.

[20] Dishong, D. M.; Diamond, G. J.; Cinoman, M. I.; Gokel, G. W. J Am Chem Soc 1983, 105, 586.

[21] Schultz, R. A.; White, B. D.; Dishong, D. M.; Arnold, K. A.; Gokel, G. W. J Am Chem Soc 1985, 107, 6659.

[22] Tsukube, H.; Uenishi, J.; Higaki, H.; Kikkawa, K.; Tanaka, T.; Wakabayashi, S.; Oae, S. J Org Chem 1993, 58, 4389.

[23] Galaup, C.; Carrie, M. C.; Tisnes, P.; Picard, C. Eur J Org Chem 2001, 2165.

[24] Bartsch, R. A.; Ivy, S. N.; Lu, J.; Huber, V. J.; Talanov, V. S.; Walkowiak, W.; Park, C.; Amiri-Eliasi, B. Pure Appl Chem 1998, 70, 2393.

[25] Nakatsuji, Y.; Nakamura, T.; Okahara, M. J Org Chem 1983, 48, 1237.

[26] Gokel, G. W.; Hernandez, J. C.; Viscariello, A. M.; Arnold, K. A.; Campana, C. F.; Echegoyen, L.; Fronczek, F. R.; Gandour, R. D.; Morgan, C. R.; Trafton, J. E.; Miller, S. R.; Minganti, C.; Eiband, D.; Schultz, R. A.; Tamminen, M. J Org Chem 1987, 52, 2963.

[27] Fukunishi, K.; Czech, B. P.; Regen, S. L. J Org Chem 1981, 46, 1218.

[28] Jungk, S. J.; Moore, J. A.; Gandour, R. D. J Org Chem 1983, 48, 1116.

[29] Aarts, V. M. L. J.; Grutenhuis, P. D. J.; Reinhoudt, D. N. Recl Trav Chim Poys-Bas 1988, 107, 94.

[30] Greene, R. N. Tetrahedron Lett 1972, 1793.

[31] Mandolini, L.; Masci, B. J Am Chem Soc 1977, 99, 7709.

[32] De-Sousa, M.; Rest, E. J. J Chem Soc Chem Commun 1981, 149.

[33] Czech, B. P.; Babb, D. A.; Son, B.; Bartsch, R. A. J Org Chem 1984, 49, 4805.
[34] Czech, B. Tetrahedron Lett 1980, 21, 4197.
[35] Hu, H.; Bartsch, R. A. J Heterocycl Chem 2004, 41, 557.
[36] Jarvis, B. B.; Vrudhula, V. M.; Dishong, D. M.; Gokel, G. W. J Org Chem 1984, 94, 2423.
[37] Krakowiak, K. E.; Bradshaw, J. S.; Izatt, R. M. J Heterocycl Chem 1990, 27, 1011.
[38] Nabeshima, T.; Tsukada, N.; Haruyama, T.; Yano, Y. Bull Chem Soc Jpn 1995, 68, 227.
[39] Phillion, D. P.; Rastetter, W. J Org Chem 1981, 46, 3208.
[40] Maeda, H.; Kikui, T.; Nakatsuji, Y.; Okahara, M. J Org Chem 1982, 47, 5167.
[41] Czech, B.; Czech, A.; Bartsch, R. A. Tetrahedron Lett 1983, 24, 1327.
[42] Son, B.; Czech, B. P.; Babb, D. A.; Bartsch, R. A. Tetrahedron Lett 1984, 25, 1647.
[43] Czech, B. P.; Son, B.; Babb, D. A.; Bartsch, R. A. Synthesis 1985, 315.
[44] Montanari, F.; Tundo, P. Tetrahedron Lett 1979, 5055.
[45] Czech, B. P.; Czech, A.; Son, B.; Lee, H. K.; Bartsch, R. A. J Heterocycl Chem 1986, 23, 465.
[46] Maeda, H.; Kikui, T.; Nakatsuji, Y.; Okahara, M. Synthesis Commun 1983, 185.
[47] Wakita, R.; Yonetani, M.; Nakatsuji, Y.; Okahara, M. J Org Chem 1990, 55, 2752.
[48] Nakatsuji, Y.; Nakamura, T.; Yonetani, M.; Yuva, H.; Okahara, M. J Am Chem Soc 1988, 110, 531.
[49] Nakamura, T.; Nakatsuji, Y.; Okahara, M. J Chem Soc Chem Commun 1981, 219.
[50] Masuyama, A.; Nakatsuji, Y.; Ikeda, I.; Okahara, M. Tetrahedron Lett 1982, 22, 4665.
[51] Nakatsuji, Y.; Muraoka, M.; Kajiya, H.; Zhang, W.; Kida, T.; Ikeda, I. Bull Chem Soc Jpn 2002, 75, 1765.
[52] Nakatsuji, Y.; Mori, T.; Okahara, M. Tetrahedron 1984, 25, 2171.
[53] Czech, B.; Kang, S. I.; Bartsch, R. A. Tetrahedron Lett 1983, 24, 457.
[54] Czech, B. P.; Huh, H.; Bartsch, R. A. J Org Chem 1992, 57, 725.
[55] Babb, D. A.; Czech, B. P.; Bartsch, R. A. J Heterocycl Chem 1986, 23, 609.
[56] Bradshaw, J. S.; Krakowiak, K. E.; Bruening, R. L.; Tarbet, B. J.; Savage, P. B.; Izatt, R. M. J Org Chem 1988, 53, 3190.
[57] Krakowiak, K. E.; Bradshaw, J. S.; Izatt, R. M. Tetrahedron Lett 1988, 29, 3521.
[58] Tomoi, M.; Abe, O.; Ikeda, M.; Kihara, K.; Kakiuchi, H. Tetrahedron Lett 1987, 28, 3031.
[59] Ouchi, M.; Inoue, Y.; Wada, K.; Iketani, S.; Hakushi, T.; Weber, E. J Org Chem 1987, 52, 2420.
[60] Nakatsuji, Y.; Nakamura, T.; Okahara, M.; Dishong, D. M.; Gokel, G. W. Tetrahedron Lett 1982, 23, 1351.
[61] Muraoka, M.; Ueda, A.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I.; Kanehisa, N.; Kai, Y. Tetrahedron 1998, 39, 9493.
[62] Weber, E. J Org Chem 1982, 47, 3478.
[63] Ouchi, M.; Inoue, Y.; Sakamoto, H.; Yamahira, A.; Yoshinaga, M.; Hakushi, T. J Org Chem 1983, 48, 3168.
[64] Issidorides, C. H.; Gulen, R. Org Synthesis 1958, 38, 65.
[65] Ouchi, M.; Inoue, Y.; Wada, K.; Hakushi, B. Chem Lett 1984, 1137.
[66] Wakita, R.; Yonetani, M.; Nakatsuji, Y.; Okahara, M. J Heterocycl Chem 1990, 27, 1377.
[67] Ouchi, M.; Hakushi, T.; Inoue, Y. In "Cation Binding by Macrocycles" Gokel, G. W., Inoue, Y., Eds.; Dekker, New York, 1990; p 549.
[68] Kita, K.; Kida, T.; Nakatsuji, Y.; Ikeda, I. Chem Lett 1997, 405.
[69] Kita, K.; Kida, T.; Nakatsuji, Y.; Ikeda, I. J Chem Soc Perkin Trans 1 1998, 3857.
[70] Bartsch, R. A.; Kim, J. S.; Olsher, U.; Purkiss, D. W.; Ramesh, V.; Dalley, N. K.; Hayashita, T. Pure Appl Chem 1993, 65, 399.
[71] Wakita, R.; Miyakoshi, M.; Nakatsuji, Y.; Okahara, M. J Inclusion Phenom Mol Recognit Chem 1991, 10, 127.
[72] Habata, Y.; Fujishiro, F.; Akabori, S. J Chem Soc, Perkin Trans 1 1996, 953.
[73] Fredriksen, S. B.; Dale, J. Acta Chem Scand 1992, 46, 574.
[74] Czech, B.; Son, B.; Bartsch, R. A. Tetrahedron Lett 1983, 24, 2923.
[75] Bartsch, R. A.; Liu, Y.; Kang, S. I.; Son, B.; Heo, G. S.; Suk, G.; Hipes, P. G.; Bills, L. J. J Org Chem 1983, 48, 4864.
[76] Bartsch, R. A.; Czech, B. P.; Kang, S. I.; Stewart, L. E.; Walkowiak, W. J Am Chem Soc 1985, 107, 4997.
[77] Iwata, S.; Matsuoka, H.; Tanaka, K.; J Chem Soc, Perkin Trans 1 1997, 1357.
[78] Ahmed, S. A.; Tanaka, M.; Ando, H.; Iwamoto, H.; Kimura, K. Tetrahedron 2004, 60, 3211.
[79] Kaifer, A.; Echegoyen, L.; Gustowski, D. A.; Goli, D. M.; Gokel, G. W. J Am Chem Soc 1983, 105, 7168.
[80] Beadle, J. R.; Dishong, D. M.; Khanna, R. K.; Gokel, G. W. Tetrahedron 1984, 40, 3935.
[81] Gustowski, D. A.; Delgado, M.; Gatto, V. J.; Echegoyen, L.; Gokel, G. W. J Am Chem Soc 1986, 108, 7553.
[82] Goli, D. M.; Dishong, D. M.; Diamond, C. J.; Gokel, G. W. Tetrahedron Lett 1982, 23, 5243.
[83] Nakatsuji, Y.; Nakahara, Y.; Muramatsu, A.; Kida, T.; Akashi, M. Tetrahedron Lett 2005, 46, 4331.
[84] Haberle, I. B.; Spasojevic, I.; Jang, Y.; Bartsch, R. A.; Crumbliss, A. L. Inorg Chem 1998, 37, 1438.
[85] L., H.; Xie, H.; Wang, P.; Wu, S. New J Chem 2000, 24, 105.
[86] Czech, B. P.; Desai, D. H.; Koszuk, J.; Czech, A.; Babb, D. A.; Robison, T. W.; Bartsch, R. A. J Heterocycl Chem 1992, 29, 867.
[87] Bubnis, B. P.; Pacey, G. E. Tetrahedron Lett 1984, 25, 1107.
[88] Muraoka, M.; Kajiya, H.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. Chem Lett 1999, 283.
[89] Bartsch, R. A.; Heo, G. S.; Kang, S. I.; Liu, Y.; Strzelbicki, J. J Org Chem 1982, 47, 457.
[90] Geo, G. S.; Bartsch, R. A.; Schlobohm, L. L.; Lee, J. G. J Org Chem 1981, 46, 3574.
[91] Elshani, S.; Du, H.; Laintz, K. E.; Natale, N. R.; Wai, C. M.; Elkarim, N. S. A.; Bartsch, R. A. Tetrahedron 2000, 56, 4651.
[92] Bartsch, R. A.; Bitalac, L. P.; Cowey, C. L.; Elshani, R. J.; Kim, J. S.; Luboch, E.; McDonough, J. A.; Pugia, M. J.; Son, B.; Zhao, Q. J Heterocycl Chem 2000, 37, 1337, and references cited therein.
[93] Tsubaki, K.; Tanaka, H.; Kinoshita, T.; Fuji, K. Tetrahedron 2002, 58, 1679.
[94] Elshani, S.; Noriyuki, R.; Wai, C. M.; Natale, N. R.; Bartsch, R. A. J Heterocycl Chem 1998, 35, 875.
[95] Seungkim, J.; Bartsch, R. A.; Ramesh, V. J Inclusion Phenom Mol Recognit Chem 2000, 36, 287.
[96] Pugia, M. J.; Nolip, G.; Lee, H. K. Yang, I. W.; Bartsch, R. A. Anal Chem 1986, 58, 2723.
[97] Bartsch, R. A.; Cowey, C. L.; Elshani, S.; Goo, M.; Huber, V. J.; Ivy, S. N.; Johnson, R. J.; Kim, J. S.; Luboch, E.; Mc Donough, J. A.; Pugia, M. J.; Son, B.; Zhao, Q. J Heterocycl Chem 2001, 38, 311, and references cited therein.

[98] Liu, L. K.; Lin, C. S; Young, D. S.; Shyu, W. J.; Heng, C. H. Chem Commun 1996, 1255.

[99] Su, C. C.; Chang, M. C.; Liu, L.K. Anal Chim Acta 2001, 432, 261.

[100] Su, C. C.; Liu, L. K.; Lu, L. H. J Luminescence 2006, 121, 159.

[101] Walkowiak, W.; Charewicz, W. A.; Kang, S. I.; Yang, I. W.; Pugia, M. J.; Bartsch, R. A. Anal Chem 1990, 62, 2018.

[102] Charewicz, W. A.; Heo, G. S.; Bartsch, R. A. Anal Chem 1982, 54, 2094.

[103] Strzelbick, J.; Bartsch, R. A. Anal Chem 1981, 53, 2247.

[104] Strzelbick, J.; Bartsch, R. A. Anal Chem 1981, 53, 1894.

[105] Babb, D. A.; Bartsch, R. A.; Collier, J. J.; Desai, D. H.; Elshani, S.; Goo, M.; Hallman, J. L.; Heo, G. S.; Huang, X.; Huber, V. J.; Hwang, H. S.; Johnson, R. J.; Liu, Y.; Pugia, M. J.; Zhao, Q. J Heterocycl Chem 2004, 41, 659, and references cited therein.

[106] Kasprzyk, S. P.; Bartsch, R. A. J Heterocycl Chem 1993, 30, 119.

[107] Huang, X.; Jang, Y.; Collier, J. J.; Hwang, H. S.; Bartsch, R. A. J Heterocycl Chem 1996, 33, 223.

[108] Elshani, S.; Xia, M. X. B.; Wai, C. M.; Natale, N. R..; Widener, R. W.; Bartsch, R. A. J Heterocycl Chem 1998, 35, 1381.

[109] Bartsch, R. A.; Hwang, H. S.; Talanov, V. S.; Talanova, G. G.; Purkiss, D. W.; Rogers, R. D. J Org Chem 1999, 64, 5341.

[110] Tsubaki, K.; Tanaka, H.; Morikawa, H.; Fuji, K. Tetrahedron 2003, 59, 3195.

[111] Elshani, S.; Hwang, H. S.; Pugia, M. J.; Krzykawski, J.; Bartsch, R. A. J Heterocycl Chem 2003, 40, 443.

[112] Sachleben, R. A.; Burns, J. H.; Brown, G. M. Inorg Chem 1988, 27, 1787.

[113] Habata, Y.; Ikeda, M.; Akabori, S. Tetrahedron Lett 1992, 33, 3157.

[114] Habata, Y.; Ikeda, M.; Akabori, S. J Chem Soc Perkin Trans 1 1992, 2651.

[115] Habata, Y.; Akabori, S. Tetrahedron Lett 1992, 33, 5818.

[116] Habata, Y.; Akabori, S. Coord Chem Rev 1996, 148, 97.

[117] Ohki, A.; Lu, J. P.; Hallman, J. L.; Huang, X.; Bartsch, R. A. Anal Chem 1995, 67, 2405.

[118] Hayashita, T.; Taniguchi, S.; Tanamura, Y.; Uchida, T.; Nishizawa, S.; Teramae, N.; Jin, Y. S.; Lee, J. C.; Bartsch. R. A. J Chem Soc Perkin Trans 2 2000, 1003.

[119] Wood, D. J.; Elshani, S.; Du, H. S.; Natale, N. R.; Wai, C. M. Anal Chem 1993, 65, 1350.

[120] Huber, V. J.; Ivy, S. N.; Lu, J.; Bartsch, R. A. Chem Commun 1997, 1499.

[121] Tong, A. J.; Song, Y. S.; Li, L. D.; Hayashita, T.; Teramae, N.; Park, C.; Bartsch, R. A. Anal Chim Acta 2000, 420, 57.

[122] Katritzky, A. R.; Belyakov, S. A.; Durst, H. D. Tetrahedron Lett 1994, 35, 6465.

[123] Abbas. A. A. Tetrahedron 2004, 60, 1541.

[124] Abbas. A. A. Synthesis 2004, 419.

[125] Abbas. A. A.; Elwahy, A. H. M.; Ahmed, A. A. M. J Heterocycl Chem 2005, 42, 93.

[126] Abbas. A. A. J Heterocycl Chem 2007, 44, 651.