New Diazadi(and tri)thia-21-crown-7 Ethers Containing 8-Hydroxyquinoline Side Arms

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A series of macrocyclic diazadi(and tri)thiacrown ethers containing two 5-substituent-8-hydroxyquinoline side arms have been synthesized from the corresponding macrocyclic diazadi(and tri)thiacrown ethers. The crown ethers were obtained by reduction of the proper macrocyclic di(and tri)thiadiamides by borane-tetrahydrofuran or by sodium borohydride-boron trifluoride ethyl etherate-tetrahydrofuran. The yields for the reduction of diamides by sodium borohydride-boron trifluoride ethyl etherate-tetrahydrofuran were higher than those by borane-tetrahydrofuran. The following four methods were used to prepare macrocycles bearing two 8-hydroxyquinoline side arms: (1) Mannich reaction with 8-hydroxyquinoline; (2) Reductive amination with 8-hydroxyquinoline-2-carboxaldehyde using sodium triacetoxyborohydride as the reducing agent; (3) Cyclization of N,N'-bis(8-hydroxyquinolin-2-ylmethyl)-1,2-bis(2-aminoethoxy)ethane (**38**) with bis(α-chloroamide) **5**; and (4) A step-by-step process wherein macrocyclic trithiadiamide **11** was reduced by lithium aluminum hydride-tetrahydrofuran to the cyclic monoamide **36**, which smoothly reacted with 5-chloro-8-hydroxyquinoline to produce monosubstituted-macrocyclic monoamide **39**.

Introduction.

Contamination of water supplies by toxic metal ions is a major environmental concern [1]. The high toxicity of many transition and post-transition metal ions, especially Hg^{2+} and Pb^{2+}, is well-recognized [2]. There is a great need for monitoring the level of these metal ions in the environment. Currently, the methods to measure metal ion concentrations in waste streams are usually spectroscopic and wet chemical analysis techniques on samples removed from waste streams [3]. It would be an attractive alternative to monitor the concentrations of specific metal ions in a complex matrix continuously and remotely by using ion-selective sensory devices.

Recently, chemical optic sensors based on synthetic fluoroionophores and chromoionophores capable of signaling the complexation of metal ions have been reported [4-6], however, most of them lacked metal ion selectivity. Many macrocyclic crown ethers interact selectively with specific metal ions, and some of them have been used to develop metal ion sensors [7-11]. 5-Chloro-8-hydroxyquinoline(CHQ)-containing azacrown ethers in which CHQ was attached through its 7-position (**1**, Figure 1) or its 2-position (**3**) [12,13] demonstrated a much greater selectivity toward certain metal ions than their parent diaza-18-crown-6. Compound **1** exhibited a stronger complexing ability for Mg^{2+} than for Ba^{2+} (log K value in methanol for Ba^{2+} is 3.60, for Mg^{2+} is 6.82). Ligand **3** has a very strong complexing ability for Ba^{2+} and does not complex with Mg^{2+} (log K value in methanol for Ba^{2+} is 12.2). Indeed, compound **1** is a very effective sensor for Mg^{2+} [14]. It was reported very recently that

diaza-18-crown-6 containing two 5-nitro-8-hydroxyquinoline sidearms connected through the 7-position (**2**) showed a high affinity and selectivity for Hg^{2+} ion and proved to be a chemosensor for Hg^{2+} [15].

1 X = Cl
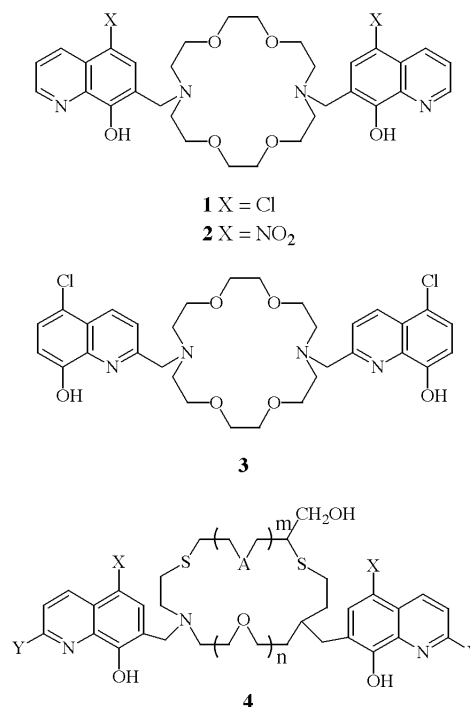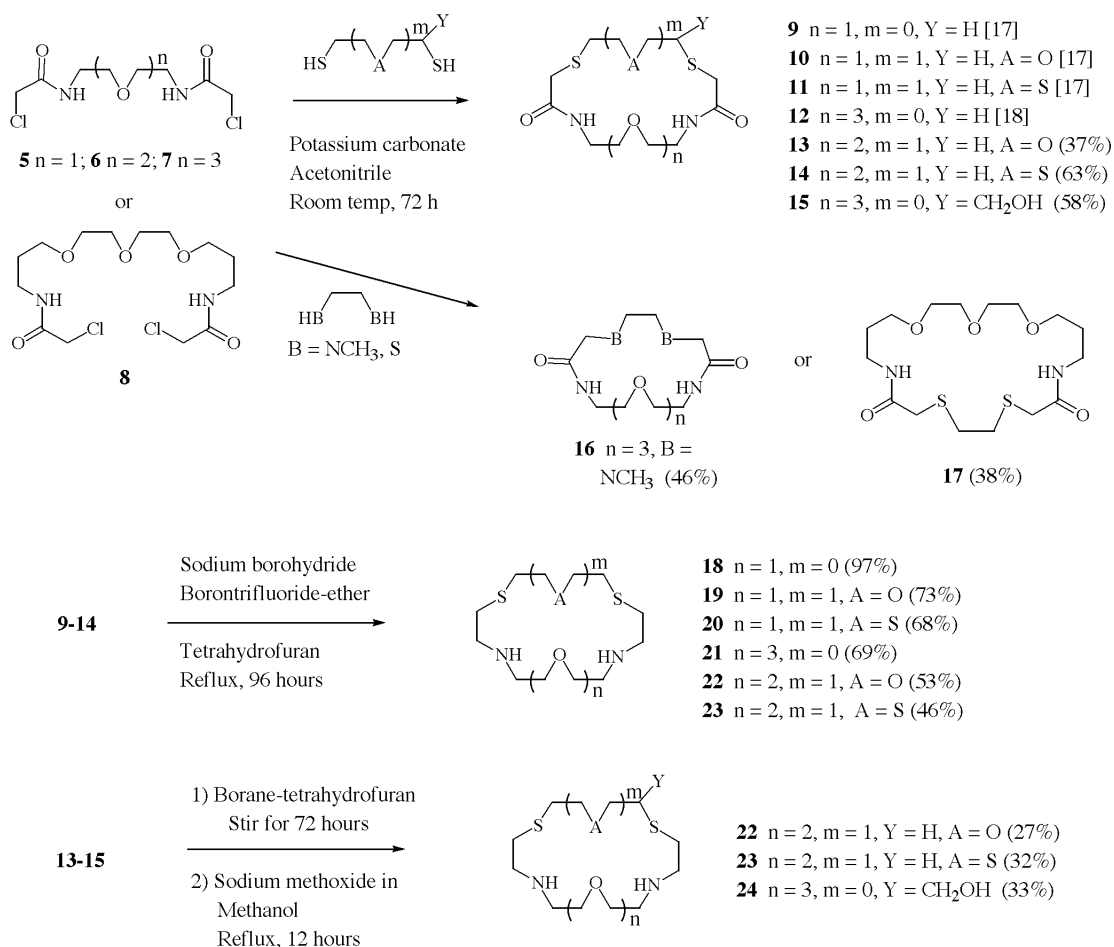**2** X = NO$_2$

3

4

Figure 1. 8-Hydroxyquinoline-substituted ligands mentioned in the introduction.

The complexing ability and selectivity of the lariat ethers for metal ions can be varied by changing certain parameters, such as the size of the crown ether ring and the type, number, and position of the complexing heteroatoms. 8-Hydroxyquinoline-containing diaza-18-crown-6 and analogues [16] showed high selection and complexation with selected metal ions. Sulfur atoms have a high affinity and selectivity for Hg^{2+}, therefore, various macrocyclic diazadi(and tri)thiacrown ethers containing two 5-substituted(or 2-methyl)-8-hydroxyquinoline units (**4**) have been prepared [17-20]. In addition, since the syntheses and complexation properties of crown ethers of 15 and18 ring members containing two 8-hydroxyqinoline sidearms have most often been reported, we now report the preparation of some macrocyclic diazadi(and tri)thiacrown ethers containing 21 ring members and two 8-hydroxyquinoline sidearms. In addition, the preparation of 8-hydroxyquinoline-containing macrocyclic ethers by four different methods are reported.
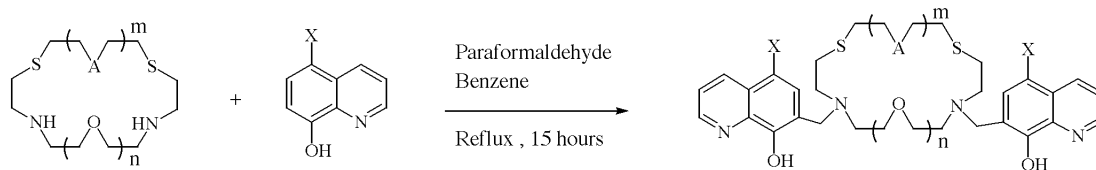
Results and Discussion.

The 8-hydroxyquinoline side arms are best attached to the diazacrown ethers through the macroring secondary amine functions. We have developed a very convenient method to prepare a wide variety of diazacrown ethers containing two secondary N-H functions [17-24]. The oligoazacrown ethers containing two secondary amine functions were prepared by treating bis(α-chloroamide)s with the appropriate diamines or dimercaptans. The two secondary N-H functions of the bis(α-chloroamide)s are unreactive toward alkylating agents, however, the chloride groups of the (α-chloroamide)s are superior leaving groups. In the present case, bis(α-chloroamide)s **5-8** were treated with various dimercaptans to form macrocyclic diazadi(tri)thiadiamides **9-15** and **17** and with *N,N'*-dimethylethylenediamine to form macrocyclic tetraazadiamide **16** (Scheme 1). Macrocyclic diamides

Scheme 1

9 n = 1, m = 0, Y = H [17]
10 n = 1, m = 1, Y = H, A = O [17]
11 n = 1, m = 1, Y = H, A = S [17]
12 n = 3, m = 0, Y = H [18]
13 n = 2, m = 1, Y = H, A = O (37%)
14 n = 2, m = 1, Y = H, A = S (63%)
15 n = 3, m = 0, Y = CH$_2$OH (58%)

5 n = 1; **6** n = 2; **7** n = 3

or

8

Potassium carbonate
Acetonitrile
Room temp, 72 h

B = NCH$_3$, S

16 n = 3, B = NCH$_3$ (46%)

or

17 (38%)

Sodium borohydride
Borontrifluoride-ether

9-14

Tetrahydrofuran
Reflux, 96 hours

18 n = 1, m = 0 (97%)
19 n = 1, m = 1, A = O (73%)
20 n = 1, m = 1, A = S (68%)
21 n = 3, m = 0 (69%)
22 n = 2, m = 1, A = O (53%)
23 n = 2, m = 1, A = S (46%)

1) Borane-tetrahydrofuran
Stir for 72 hours

13-15

2) Sodium methoxide in
Methanol
Reflux, 12 hours

22 n = 2, m = 1, Y = H, A = O (27%)
23 n = 2, m = 1, Y = H, A = S (32%)
24 n = 3, m = 0, Y = CH$_2$OH (33%)

Scheme 2

25 n = 1, m = 1, A = O, X = NO$_2$ (28%)
26 n = 2, m = 1, A = O, X = H (65%)
27 n = 2, m = 1, A = O, X = CH$_3$ (51%)
28 n = 2, m = 1, A = O, X = Cl (64%)
29 n = 2, m = 1, A = S, X = CH$_3$ (66%)
30 n = 2, m = 1, A = S, X = Cl (76%)
31 n = 3, m = 0, X = H (57%)
32 n = 3, m = 0, A = O, X = CH$_3$ (57%)

13-17 are new compounds as are the macrocyclic polyamines and bis(8-hydroxyquinoline)-substituted diazadi(tri)thiacrown ethers prepared from **13-15**.

The macrocyclic diamides usually have been reduced to form the diazacrown ethers using borane in tetrahydrofuran. Macrocyclic diamides **13-15** were reduced using the borane-tetrahydrofuran method in only moderate yields (27%-33%) (Scheme 1). Diamides **9-14** were reduced to form **18-23**, respectively, using sodium borohydride-boron trifluoride ethyl etherate. In this case, the reduction yields were much higher (compare ligands **22** and **23** where the sodium borohydride reduction approach gave higher yields by 26% and 14%, respectively). Ligands **18** and **19** were also prepared in higher yields by the sodium borohydride method (97% and 73%, respectively) than by the borane method (55% and 62%, respectively) [17].

The bis(8-hydroxyquinolin-7-ylmethyl)-substituted diazacrown ethers **25-32** were prepared by treating the diazacrowns with the appropriate 8-hydroxyquinoline and paraformaldehyde (Scheme 2) [20,25-27]. Ligand **33** containing two 8-hydroxyquinolin-2-ylmethyl substituents was prepared by the reductive amination process [19,27,28] as shown in Scheme 3.

Two new 8-hydroxyquinoline-containing macrocyclic amides were prepared as shown in Schemes 4 and 5. Using lithium aluminum hydride, macrocyclic diamide **11** was reduced to macrocyclic monoamide **34** in a 37% yield. This material was treated with 5-chloro-8-hydroxyquinoline and paraformaldehyde to give 5-chloro-8-hydroxyquinolin-7-ylmethyl-substituted macrocyclic monoamide **35**. Ligand **35** could be an intermediate in the formation of the diazacrown ether containing both 8-hydroxyquinolin-7-ylmethyl and 8-hydroxyquinolin-2-ylmethyl substituents by reduction followed by reductive amination with 8-hydroxyquinolin-2-carboxaldehyde. This latter synthesis was not attempted.

Macrocyclic diamide **37** containing two 8-hydroxyquinolin-2-ylmethyl substituents was prepared by first preparing intermediate diamine **36** containing two 8-hydroxyquinolin-2-ylmethyl groups. This diamine was then treated with bis(α-chloroamide) **5** to give **37** in a low yield. The cyclization reaction was carried out in acetonitrile using triethylamine as the base. The low yield in this reaction could be due to the fact that triethylamine is a weak base which may not effectively remove the proton from the formed ammonium ion in reaction intermediate **37a** (Figure 2). That proton could hydrogen bond with the amine function on the other side of the pseudo macroring, thus, reducing its nucleophilicity. It is also possible that the 8-hydroxy group of one 8-hydroxyquinoline could hydrogen bond with the amine close to the other 8-hydroxyquinoline thereby reducing its nucleophilicity (structure **37b**, Figure 2).
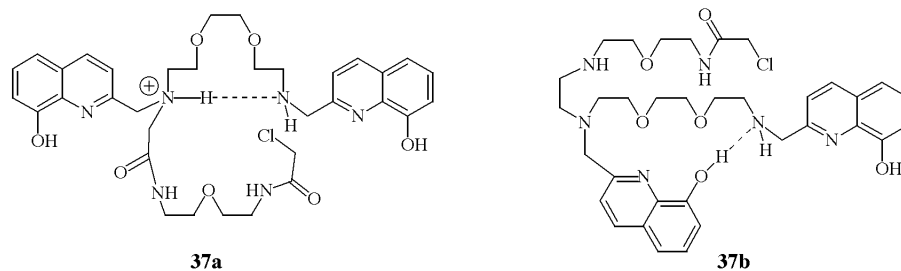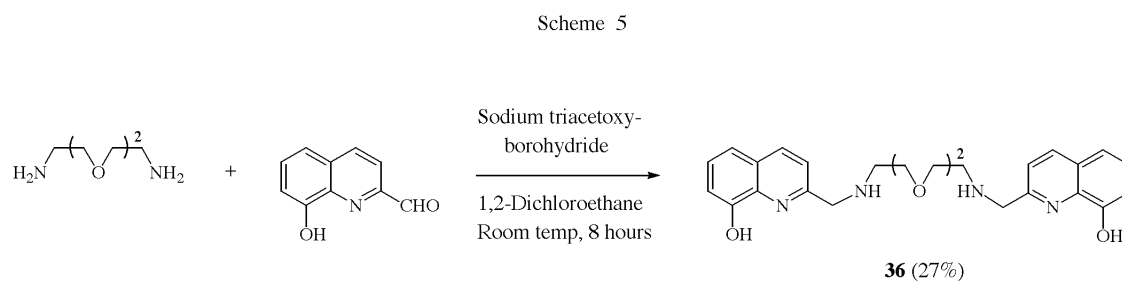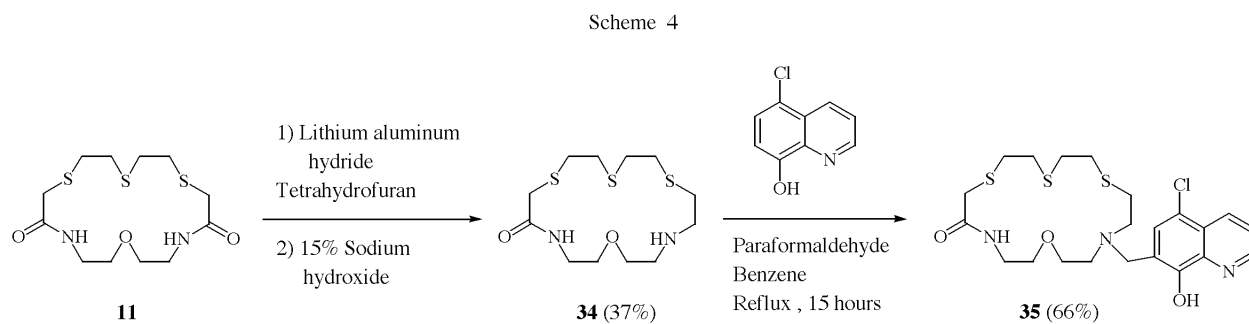
Scheme 3

33 (48%)
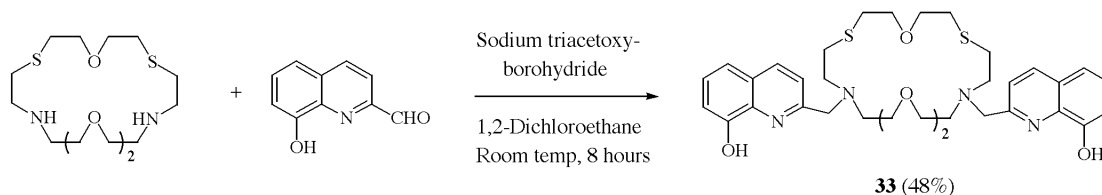
Figure 2. Possible Intermediates in the Cyclization of **36** with
Bis-(α-chloroamide) **5** (Scheme 5).

Scheme 4

Scheme 5

EXPERIMENTAL

The ^{1}H and ^{13}C nmr spectra were recorded in deuteriochloroform on Varian nmr instruments. Solvents and starting materials were used as purchased. Bis(α-chloroamide)s **5-8** were prepared from the appropriate diamines and chloroacetic anhydride as reported [17-19].

General Procedure **A** to Prepare Macrocyclic Diamides **9-17** (Scheme 1) [17-19].

A mixture of the appropriate bis(α-chloroamide), an equimolar amount of dithiol or diamine, a 4 fold excess of anhydrous potassium carbonate and acetonitrile (350 ml/ 0.1 mole of bis(α-chloroamide)) was stirred at room temperature for 72 hours. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was separated by chromatography (silica gel, ethylene chloride:methanol:-ammonium hydroxide = 80:10:1) to give the macrocyclic diamide. The physical and spectral properties of 1,7-diaza-4-oxa-10,13-dithiacyclopentadecan-8,15-dione (**9**) [17], 1,7-diaza-4,13-dioxa-10,16-dithiacyclooctadecan-8,18-dione (**10**) [17], 1,7-diaza-4-oxa-10,13,16-trithiacyclooctadecan-8,18-dione (**11**) [17], and 1,13-diaza-4,7,10-trioxa-16,19-dithiacycloheneicosan-14,21-dione (**12**) [18] were identical to those reported.

1,10-Diaza-4,7,16-trioxa-13,19-dithiacycloheneicosan-11,21-dione (**13**).

According to general procedure A, macrocyclic dithiadiamide **13** (5.39 g, 37%) was obtained from 12.04 g (40 mmole) of bis(α-chloroamide) **6** and 5.53 g (40 mmole) of 2-mercaptoethyl ether; mp 96-97.5°; ^{1}H nmr: δ 2.79 (t, J=5.2 Hz, 4H), 3.33 (s, 4H), 3,49-3.66 (m, 16H); hrms (fab) calcd for $C_{14}H_{26}N_2O_5S_2Na$: 389.1181, found: 389.1156.
Anal. Calcd. for $C_{14}H_{26}N_2O_5S_2$: C, 45.88; H, 7.15; found C, 45.92; H, 7.03.

1,10-Diaza-4,7-dioxa-13,16,19-trithiacycloheneicosan-11,21-dione (**14**).

Macrocyclic dithiadiamide **14** (8.43 g, 63%) was obtained from 10.54 g (35 mmole) of bis(α-chloroamide) **6** and 9.32 g (35 mmole) of bis(2-mercaptoethyl) sulfide according to general procedure A; mp 113-114.5°; ^{1}H nmr: δ 2.80 (t, J=5.0 Hz, 8H), 3.23 (s, 4H), 3.50 (t, J= 5.2 Hz, 4H), 3.61 (m, 8H); hrms (fab) calcd. for $C_{14}H_{26}N_2O_4S_3(M)^+$: 382.1055, found: 382.1039. A satisfactory elemental analysis was obtained for **29**, a derivative of **14**.

17-Hydroxymethyl-1,13-diaza-4,7,10-trioxa-16,19-dithiacyclo-heneicosan-14,21-dione (**15**).

According to general procedure A, compound **15** (9.22 g, 58%) was prepared from 4.96 g (40.0 mmole) of 1,2-dimercapto-3-propanol and 13.80 g (40.0 mmole) of bis(α-chloroamide) **7**; mp 118-119°; ^{1}H nmr : δ 2.87 (m, 3H), 3.36 (m, 4H), 3.59 (m, 16H), 3.88 (m, 2H); ^{13}C nmr: δ 34.6, 35.4, 36.6, 39.6, 39.7, 49.1, 62.8, 69.8, 70.0, 70.1, 70.2, 70.9, 71.0, 168.6, 169.3; hrms (fab) calcd. for $C_{15}H_{29}N_2O_6S_2(M+H)^+$: 397.1467, found: 397.1451.
Anal. Calcd. for $C_{15}H_{28}N_2O_6S_2$: C, 45.43; H, 7.12. Found: C, 45.62; H, 7.04.

13,16-Dimethyl-1,10,13,16-tetraaza-4,7-dioxacyclooctadecan-11,18-dione (**16**).

Macrocyclic diamide **16** (46%) was prepared from 6.02 g (20.0 mmole) of bis(α-chloroamide) **6** and 1.60 g (20.0 mmole) of *N,N'*-dimethylethylenediamine; ^{1}H nmr: δ 2.31 (s, 6H), 2.43 (s, 4H), 3.09 (s, 4H), 3.58 (m, 12H); ^{13}C nmr: δ 39.1, 42.9, 55.6, 62.6, 69.8, 70.3, 170.9; hrms (fab) calcd. for $C_{14}H_{29}N_4O_4(M+H)^+$: 317.2189, found: 317.2178.
Anal. Calcd. for $C_{14}H_{28}N_4O_4$: C, 53.15; H, 8.92. Found: C, 53.62; H, 9.04.

1,15-Diaza-5,8,11-trioxa-18,21-dithiacyclotetracosan-16,23-dione (**17**).

According to general procedure A, macrocyclic diamide **17** (38%) was prepared from 0.94 g (10.0 mmole) of 1,2-ethanedithiol and 3.73 g (10.0 mmole) of bis(α-chloroamide) **8**; ^{1}H nmr: δ 1.81 (t, J=4.6 Hz, 4H), 2.82 (m, 4H), 3.23 (s, 4H), 3.45 (m, 4H), 3.62 (m, 12H); hrms (fab) calcd. for $C_{16}H_{31}N_2O_5S_2(M+H)^+$: 395.1674, found: 395.1688.
Anal. Calcd. for $C_{16}H_{30}N_2O_5S_2$: C, 48.71; H, 7.66. Found: C, 48.53; H, 7.62.

General Procedure B to Reduce Macrocyclic Diamides into Secondary Macrocyclic Diamines **18-23** by Sodium Borohydride-Boron Trifluoride Ethyl Etherate (Scheme 1).

A solution of 10 mmole of macrocyclic diamide and 3.39 g (90 mmole) of sodium borohydride in 120 ml of tetrahydrofuran was stirred and cooled to 0-5° in an ice bath. Boron trifluoride ethyl etherate (15.61 g, 110 mmole) was added into the solution over a period of 3 hours during which the temperature of the solution was kept at 0-5°. The mixture was filtered and some water was added to the stirred filtrate until hydrogen stopped evolving at room temperature. The mixture was neutralized with aqueous sodium hydroxide (20%) until the pH value of the mixture was to 8-9. Tetrahydrofuran was evaporated under reduced pressure and the residue was extracted three times with 20 ml portions of ethylene chloride. The combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to get the crude product. The crude product was purified by chromatography on silica gel.

1,7-Diaza-4-oxa-10,13-dithiacyclopentadecane (**18**) [29];
1,7-Diaza-4,13-dioxa-10,16-dithiacyclooctadecane (**19**) [17];
1,7-Diaza-4-oxa-10,13,16-trithiacyclooctadecane (**20**) [17]; and
1,13-diaza-4,7,10-trioxa-16,19-dithiacycloheneicosanne (**21**) [18].

Macrocycles **18-21** were prepared as shown in Scheme 1 to give **18** (97%), **19** (73%), **20** (68%), and **21** (69%) whose mp, hrms, ^{1}H nmr and ^{13}C nmr spectral data were identical to those reported.

1,10-Diaza-4,7,16-trioxa-13,19-dithiacycloheneicosane (**22**).

Macrocyclic crown ether **22** (0.98 g, 53%) was synthesized from diamide **13** (2.02 g, 5.5 mmole) according to general procedure B; ^{1}H nmr: δ 2.69-2.83 (m, 16H), 3.57-3.66 (m, 12H); hrms (fab) calcd. for $C_{14}H_{31}N_2O_3S_2(M+H)^+$: 339.1776, found: 339.1760. A satisfactory elemental analysis was obtained for **28**, a derivative of **22**.

1,10-Diaza-4,7-dioxa-13,16,19-trithiacycloheneicosane (23).

Macrocyclic crown ether **23** (0.77 g, 46%) was prepared from **14** (1.85 g, 4.8 mmole); ^{1}H nmr: δ 2.70-2.74 (m, 4H), 2.78-2.83 (m, 12H), 2.56-3.68 (m, 12H); hrms (fab) calcd. for $C_{14}H_{31}N_2O_2S_3$ (M+H)$^+$: 355.1548, found: 355.1568. A satisfactory elemental analysis was obtained for **29**, a derivative of **23**.

General Procedure C to Reduce Macrocyclic Diamides to Form Diazacrown Ethers 22-24 by Borane in Tetrahedrofuran (Scheme 1).

To a solution of 10.0 mmoles of macrocyclic diamide in 30 ml of dry tetrahydrofuran was added 80 ml of a solution of borane in tetrahydrofuran (1 mole of borane per liter of tetrahydrofuran). The mixture was stirred for 72 hours at room temperature, and then the solvent was evaporated under reduced pressure. To the residue was added a dilute solution of sodium methoxide in methanol, and the mixture was refluxed overnight. After the methanol was evaporated, some water was added and the mixture was extracted several times by portions of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated to give the crude product. The crude product was purified by chromatography on silica gel (eluent: methylene chloride:methanol:ammonium hydroxide = 50:5:1).

1,10-Diaza-4,7,16-trioxa-13,19-dithiacycloheneicosane (22).

Macrocycle **22** (0.27 g, 27%) was synthesized from diamide **13** (1.08 g, 3.0 mmole) to give the same compound reported above under general procedure B.

1,10-Diaza-4,7-dioxa-13,16,19-trithiacycloheneicosane (23).

Macrocycle **23** (32%) was prepared from diamide **14** according to general procedure C. The ^{1}H nmr and hrms spectal data of **23** are identical to those reported above under general procedure B.

17-Hydroxymethyl-1,13-diaza-4,7,10-trioxa-16,19-dithiacycloheneicosane (24).

According to general procedure C, crown ether **24** (0.79 g, 33%) was obtained as a viscous liquid by the reduction of **15** (2.58 g, 6.5 mmole); ^{1}H nmr: δ 2.75 (m, 12H), 3.31 (m, 3H), 3.59 (m, 14H); hrms (fab) calcd. for $C_{15}H_{33}N_2O_4S_2$(M+H)$^+$: 369.1882, found: 369.1880.

Anal. Calcd. for $C_{15}H_{32}N_2O_4S_2$: C, 48.88; H. 8.75. Found: C, 49.01; H, 8.70.

General Procedure D for the Synthesis of Azathiacrown Ethers Containing Two 5-Substitutent-8-hydroxyquinoline as Side Arms 25-32 (Scheme 2).

A solution of 45 ml of anhydrous benzene, 2.0 mmole of macrocyclic ether, 4.2 mmole of 5-substitutent-8-hydroxyquinoline (or 8-hydroxyquinaldine) and paraformaldehyde (0.135 g, 4.5 mmole) was refluxed for 15 hours. The solvent was evaporated under reduced pressure, and the crude product was separated on silica gel with methylene chloride:methanol:ammonium hydroxide = 50:5:1 as eluent.

1,7-Bis(5-nitro-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4,13-dioxa-10,16-dithiacyclooctadecane (25).

Ligand **25** (0.43 g, 28%) was prepared from 0.65 g (2.2 mmole) of **19** and 0.91 g (4.8 mmole) of 5-nitro-8-hydroxyquinoline according to general procedure D. Hexane (80 ml) was added

into the flask and the mixture was ultrasonicated for 3 hours. After 70 ml of hexane was decanted from the container, another 80 ml of hexane was added into the container and the mixture was ultrasonicated for another 3 hours. After 70 ml of hexane was decanted, the remaining hexane was evaporated under reduced pressure to give a low melting solid; ^{1}H nmr: δ 2.95 (t, J = 6.0 Hz, 4H), 2.74-2.80 (m, 12H), 3.61-3.78 (m, 8H), 4.41 (s, 4H), 7.55 (dd, J=4.0, 8.4 Hz, 2H), 8.43 (s, 2H), 8.62 (dd, J=1.4, 4.0 Hz, 2H), 9.21 (dd, J=1.2, 6.6 Hz, 2H); hrms (fab) calcd. for $C_{32}H_{38}N_6O_8S_2$(M)$^+$: 698.2193, found: 698.2182.

Anal. Calcd. for $C_{32}H_{38}N_6O_8S_2$: C, 55.00; H, 5.48. Found: C, 55.19; H, 5.28.

1,10-Bis(8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7,16-trioxa-13,19-dithiacycloheneicosane (26).

According to the general procedure D, compound **26** (0.85 g, 65%) was prepared from 0.69 g (2.0 mmole) of macrocyclic crown ether **22** and 0.65 g (4.5 mmole) of 8-hydroxyquinoline; ^{1}H nmr: δ 2.64 (t, J=4.2 Hz, 4H), 2.83 (m, 12H), 3.62 (m, 12H), 4.01 (s, 4H), 7.22 (m, 2H), 7.35 (m, 4H), 8.12 (d, J=6.6 Hz, 2H), 8.85 (m, 2H); ^{13}C nmr: δ 29.4, 32.4, 53.4, 54.5, 56.5, 69.5, 70.9, 119.5, 120.3, 122.2, 126.2, 127.8, 133.1, 139.9, 149.5, 152.1; hrms (fab) calcd. for $C_{34}H_{45}N_4O_5S_2^+$: 653.2831, found: 653.2822.

Anal. Calcd. for $C_{34}H_{44}N_4O_5S_2$: C, 62.55; H, 6.79. Found: C, 62.40; H, 6.58.

1,10-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7,16-trioxa-13,19-dithiacycloheneicosane (27).

Ligand **27** (0.69 g, 51%) was synthesized from 0.68 g (2.0 mmole) of crown ether **22** and 0.72 g (4.5 mmole) of 5-methyl-8-hydroxyquinoline as a viscous liquid according to the general procedure D; ^{1}H nmr: δ 2.59 (s, 6H), 2.69 (t, J=4.0 Hz, 4H), 2.90 (s, 12H), 3.66 (m, 12H), 3.97 (s, 4H), 7.10 (s, 2H), 7.40 (t, J=4.2 Hz, 2H), 8.24 (d, J=8.6 Hz, 2H), 8.87 (d, J=1.8 Hz, 2H); ^{13}C nmr: δ 16.1, 27.6, 29.8, 51.1, 52.6, 55.0, 67.6, 68.9, 70.0, 116.6, 119.1, 122.1, 125.7, 126.5, 130.8, 137.8, 146.6, 149.3; hrms (fab) calcd. for $C_{36}H_{49}N_4O_5S_2$(M+H)$^+$: 681.3144, found: 681.3135.

Anal. Calcd. for $C_{36}H_{48}N_4O_5S_2$: C, 63.50; H, 7.11. Found: C, 63.67; H, 6.91.

1,10-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7,16-trioxa-13,19-dithiacycloheneicosane (28).

Compound **28** (0.98 g, 64%) was obtained from 0.71 g (2.1 mmole) of crown ether **22** and 0.82 g (4.6 mmole) of 5-chloro-8-hydroxyquinoline according to the general procedure D; mp 109-110.5°; ^{1}H nmr: δ 2.70 (t, J=5.8 Hz, 4H), 2.94 (s, 12H), 3.61-3.71 (m, 12H), 4.03 (s, 4H), 7.45 (s, 2H), 7.49 (q, J=4.2 Hz, 2H), 8.45 (dd, J=1.4, 1.6 Hz, 2H), 8.89 (dd, J=1.4, 1.6 Hz 2H); ^{13}C nmr: δ 27.7, 29.9, 51.1, 52.5, 54.7, 67.5, 68.9, 70.0, 117.7, 118.3, 120.3, 124.3, 125.9, 131.1, 138.0, 147.6, 150.4; hrms (fab) calcd. for $C_{34}H_{43}Cl_2N_4O_5S_2$(M+H)$^+$: 721.2052, found: 721.2036.

Anal. Calcd. for $C_{34}H_{42}Cl_2N_4O_5S_2$: C, 56.58; H, 5.87. Found: C, 56.70; H, 5.77.

1,10-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7-dioxa-13,16,19-trithiacycloheneicosane (29).

Ligand **29** (0.78 g, 66%) was prepared from 0.61 g (1.7 mmole) of crown ether **23** and 0.59 g (3.7 mmole) of 5-methyl-8-hydroxyquinoline according to the general procedure D; ^{1}H nmr: δ 2.54

(s, 6H), 2.74 (s, 4H), 2.82-2.96 (m, 16H), 3.62-3.66 (s, 8H), 3.92 (s, 4H), 7.08 (s, 2H), 7.37 (q, J=4.0 Hz, 2H), 8.18 (dd, J=1.4, 1.4 Hz, 2H), 8.83 (dd, J=1.4, 1.6 Hz, 2H); ^{13}C nmr: δ 18.0, 29.2, 32.3, 53.3, 54.3, 56.7, 69.5, 70.8, 118.3, 120.9, 123.9, 127.5, 128.3, 132.5, 139.5, 148.3, 150.9; hrms calcd. for $C_{36}H_{49}N_4O_4S_3$ (M+H)$^+$: 697.2916, found: 697.2936.

Anal. Calcd. for $C_{36}H_{48}N_4O_4S_3$: C, 62.04; H, 6.94. Found: C, 61.93; H, 6.82.

1,10-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7-dioxa-13,16,19-trithiacycloheneicosane (**30**).

Ligand **30** (0.78 g, 76%) was prepared from 0.51 g (1.4 mmole) of crown ether **23** and 0.55 g (3.1 mmole) of 5-chloro-8-hydroxyquinoline; ^{1}H nmr: δ 2.78 (s, 4H), 2.83-2.99 (m, 16H), 3.66-3.72 (s, 8H), 3.98 (s, 4H), 7.41 (s, 2H), 7.49 (q, J=4.0 Hz, 2H), 8.46 (dd, J=1.8, 1.4 Hz, 2H), 8.90 (dd, J=1.4, 1.8 Hz, 2H); ^{13}C nmr: δ 29.2, 32.2, 53.2, 54.3, 56.2, 69.2, 7.7, 119.1, 120.0, 122.1, 126., 127.6, 132.8, 139.5, 149.2, 151.80; hrms (fab) calcd. for $C_{34}H_{43}Cl_2N_4O_4S_3$(M+H)$^+$: 737.1823, found: 737.1836.

Anal. Calcd. for $C_{34}H_{42}N_4O_4S_3Cl_2$: C, 55.35; H, 5.74. Found: C, 55.51; H, 5.63.

1,13-Bis(8-hydroxyquinolin-7-ylmethyl)-1,13-diaz-4,7,10-tri-oxa-16,19-dithiacycloheneicosane (**31**).

Ligand **31** (57%) was synthesized as a viscous liquid from marocyclic diamine **21** and 8-hydroxyquinoline; ^{1}H nmr: δ 2.76 (s, 4H), 2.80-2.86 (m, 12H), 3.63-3.70 (m, 12H), 3.99 (s, 4H), 7.26-7.30 (m, 4H), 7.35 (q, J=4.0 Hz, 2H), 8.06 (dd, J=1.6, 1.4 Hz, 2H), 8.85 (dd, J=1.8, 1.8 Hz, 2H); ^{13}C nmr: δ 29.1, 32.1, 53.0, 54.2, 56.9, 69.5, 70.7, 117.5 118.9, 121.3, 128.0, 128.4, 135.7, 139.2, 148.8, 152.8; hrms (fab) calcd for $C_{34}H_{45}N_4O_5S_2$(M+H)$^+$: 653.2831, found 653.2816.

Anal. Calcd. for $C_{34}H_{44}N_4O_5S_2$: C, 62.55, H, 6.79. Found: C, 62.38, H, 6.88.

1,13-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-1,13-diaz-4,7,10-trioxa-16,19-dithiacycloheneicosane (**32**).

Ligand **32** (57%) was synthesized as a viscous liquid from marocyclic diamine **21** and 5-methyl-8-hydroxyquinoline; ^{1}H nmr : δ 2.56 (s, 6H), 2.76 (s, 4H), 2.80-2.88 (m, 8H), 2.94-3.01 (m, 4H), 3.66-3.71 (m, 12H), 3.95 (s, 4H), 7.10 (s, 2H), 7.40 (q, J=4.0Hz, 2H), 8.21 (dd, J=1.4, 1.6 Hz, 2H), 8.86 (dd, J=1.6, 1.4 Hz, 2H); ^{13}C nmr: δ 18.1, 29.2, 32.3, 53.1, 54.4, 56.8, 69.8, 70.9, 118.4, 121.0, 124.0, 127.6, 128.4, 132.6, 139.6, 148.4, 153.0; hrms (fab) calcd for $C_{36}H_{49}N_4O_5S_2$(M+H)$^+$: 681.3144, found 681.3152.

Anal. Calcd. for $C_{36}H_{48}N_4O_5S_2$: C, 63.50, H, 7.11, Found: C, 63.43, H, 7.24.

1,10-Bis(8-hydroxyquinolin-2-ylmethyl)-1,10-diaza-4,7,16-trioxa-13,19-dithiacycloheneicosane (**33**) (Scheme 3).

Crown ether **22** (0.92 g, 2.7 mmole) and 5.9 mmole (1.02 g) of 8-hydroxyquinoline-2-carboxaldehyde were added to 60 ml of 1,2-dichloroethane and the mixture was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (1.92 g, 9.0 mmole) was added and the mixture was stirred overnight at room temperature. Saturated sodium bicarbonate solution (50 ml) was then added to quench the reaction and the layers were separated. The water layer was extracted three times with 20 ml portions of methylene chloride. The combined 1,2-dichloroethane

layer and methylene chloride extracts were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the mixture was separated on silica gel (methylene chloride:methanol:ammonium hydroxide = 80:5:1) to give 48% of compound **33**; ^{1}H nmr: δ 2.70 (t, J=4.8 Hz, 4H), 2.96 (m, 12H), 3.64 (m, 12H), 4.04 (s, 4H), 7.15 (s, 2H), 7.28 (d, 2H), 7.40 (m, 2H), 7.69 (d, J=4.2 Hz, 2H), 8.10 (d, J=3.8, Hz, 2H); ^{13}C nmr: δ 30.3, 31.8, 53.8, 55.3, 61.4, 70.1, 70.7, 71.7, 110.2, 117.7, 122.0, 127.3, 127.7, 136.5, 137.5, 152.2, 158.5; hrms (fab) calcd for $C_{34}H_{45}N_4O_5S_2$(M+H)$^+$: 653.2831, found 653.2842.

Anal. Calcd. for $C_{34}H_{44}N_4O_5S_2$: C, 62.55; H, 6.79. Found: C, 62.63; H, 6.60.

1,7-Diaza-4-oxa-10,13,16-trithiacyclooctadecan-8-one (**34**) (Scheme 4).

To a solution of 1.01 g (3.0 mmole) of diamide **11** in 110 ml of dry tetrahydrofuran was added 0.46 g (12.0 mmole) of lithium aluminum hydride at 0-5°. The mixture was stirred for 12 hours at room temperature and then refluxed in a nitrogen atmosphere. The reaction was monitored by thin layer chromatography using methylene chloride:methanol:ammonium hydroxide = 50:4:1 as eluent. When the reaction was completed, the mixture was cooled to 0-5°, and then water, 15% aqueous sodium hydroxide and water were added. The white precipitate was filtered and the solid was washed with three 10 ml portions of methylene chloride. The combined organic extracts were evaporated under reduced pressure to give the crude product which was purified by chromatography on silica gel to give the reduced product as a low melting solid (0.36 g, 37%); ^{1}H nmr: δ 2.78-2.87 (m, 10H), 3.36 (s, 2H), 3.53-3.74 (m, 10H); ^{13}C nmr: δ 30.2, 30.3, 30.9, 35.1, 37.7, 45.8, 46.6, 67.7, 67.7, 69.3, 70.2, 174.2; hrms (fab) calcd. for $C_{14}H_{25}N_2O_2S_3$(M+H)$^+$: 325.1078, found: 325.1086. A satisfactory elemental analysis was obtained for **35**, a derivative of **34**.

1-(5-Chloro-8-hydroxyquinolin-7-ylmethyl)-1,7-Diaza-4-oxa-10,13,16-trithiacyclooctadecan-8-one (**35**).

According to the general procedure D, monosubstituted crown ether **35** (0.88 g, 66%) was synthesized from 0.47 g (2.6 mmole) of 5-chloro-8-hydroxyquinoline and 0.78 g (2.4 mmole) of **34**; mp 139.5-140.5°; ^{1}H nmr: δ 2.70 (t, J=4.8 Hz, 2H), 2.93 (t, J=5.2 Hz, 4H), 2.90 (s, 4H), 3.52 (s, 4H), 3.60 (s, 4H), 3.67 (m, 4H), 3.94 (s, 2H), 7.36 (s, 1H), 7.46 (q, J=1.8Hz, 1H), 8.43 (dd, J=1.2, 1.0 Hz, 1H), 8.84 (dd, J=1.2, 1.2 Hz, 1H); ^{13}C nmr: δ 30.2, 31.7, 32.3, 36.8, 39.8, 54.1, 54.6, 57.3, 68.7, 70.3, 71.0, 72.0, 119.5, 120.3, 122.2, 126.3, 127.5, 132.9, 149.4, 152.4, 169.9.

Anal. Calcd. for $C_{22}H_{30}ClN_3O_3S_3$: C, 51.19; H, 5.86. Found: C, 51.38; H, 6.01.

N,*N*'-Bis(8-hydroxyquinolin-2-ylmethyl)-1,2-bis(2-aminoethoxy)ethane (**36**) (Scheme 5).

Using the method by which compound **33** was synthesized, compound **36** (27%) with a low melting point was prepared from 8-hydroxyquinoline-2-carboxaldehyde and 1,2-bis(2-amino-ethoxy)ethane by reductive amination with sodium triacetoxy-borohydride as reduction agent; ^{1}H nmr: δ 2.88 (t, J=4.6 Hz, 4H), 3.65 (s, 4H), 3.76 (t, J=4.8 Hz, 4H), 4.07 (s, 4H), 7.12-7.24 (m, 6H), 7.35-7.43 (m, 2H), 8.01 (d, J=8.4 Hz, 2H); hrms (fab) calcd. for $C_{26}H_{30}N_4O_4$(M)$^+$: 462.2267, found: 462.2276. A satisfactory elemental analysis was obtained for **37**, a derivative of **36**.

1,10-Bis(8-hydroxyquinolin-2-ylmethyl)-1,10,13,19-tetraaza-4,7,16-trioxacycloheneicosan-11,21-dione (**37**).

According to general procedure A, macrocyclic diamide **37** (0.25 g, 19%) containing two 8-hydroxyquinolines, was obtained from 0.51 g (2.0 mmole) of bis(α-chloroamide) **5** and 0.93 g (2.0 mmole) of diamine **36**; ^{1}H nmr: δ 2.80-2.89 (m, 8H), 3.26-3.36 (m, 8H), 3.58-3.63 (m, 8H), 4.03 (s, 4H), 7.12-7.35 (m, 8H), 7.98 (d, J=6.8 Hz, 2H).

Anal. Calcd. for $C_{34}H_{42}N_6O_7$: C, 63.14; H, 6.55. Found: C, 63.27; H, 6.47.

REFERENCES AND NOTES

[1]   A. Boudou, F. Ribeyre, In Metal Ions in Biological Systems, Sigel, H., Ed.; Vol. **34**; Marcel Dekker: New York, 1997.

[2]   E. Foulkes, Biological Effects of Heavy Metals; CRC Press: Boca Raton, FL, 1990, Vols **I** and **II**.

[3]   J. Lester, Heavy Metals in Wastewater and Sludge Treatment Processes; Press: Boca Raton, FL, 1987, Vol. **I**.

[4]   I. Oehme, S. Prattes, S. O. Wolfveis, and J. G. Mohr, *Tetrahedron,* **47**, 595 (1998).

[5]   K. L. Chau and D. M. Porter, *Anal. Chem*., **62**, 1964 (1990).

[6]   K. Wang, K. Seiler, P. Rusterholz, and W. Simon, *Analyst,* **117**, 57 (1992).

[7]   R. M. Izatt, K. Pawlak, J. S. Bradshaw, and L. R. Bruening, *Chem. Rev*., **95**, 1231 (1995).

[8]   A. Ueno, A. Ikeda, H. Ikeda, T. Ikeda, and F. Toda, *J. Org. Chem*., **64**, 382 (1999).

[9]   U. Oguz and U. E. Akkaya, *Tetrahedron Lett*., **39**, 5857 (1998).

[10]   F. Unob, Z. Asfari, and J. Vicens, *Tetrahedron Lett*., **39**, 2951 (1998).

[11]   D. Marquis, J.-P. Desvergne, and H. Bouas-Laurent, *J. Org. Chem*., **60**, 7984 (1995).

[12]   A. V. Bordunov, J. S. Bradshaw; X. X. Zhang, N. K. Dalley, X. Kou, and R. M. Izatt, *Inorg. Chem.,* **35**, 7229 (1996).

[13]   X. X. Zhang, A. V. Bordunov, J. S. Bradshaw; N. K. Dalley, X. Kou,; and R. M. Izatt, *J. Am. Chem. Soc*., **117**, 11507 (1995).

[14]   L. Prodi, F. Boletta, M. Montalti, N. Zaccheroni, P. B. Savage, J. S. Bradshaw, and R. M. Izatt, *Tetrahedron Lett*., **39**, 5451 (1998).

[15]   L. Prodi, C. Bargossi, M. Montalti, N. Zaccheroni, N. Su, J. S. Bradshaw, R. M. Izatt, and P. B. Savage, *J. Am. Chem. Soc*., **122**, 6769 (2000).

[16]   X. X. Zhang, J. S. Bradshaw, A. V. Bordunov, and R. M. Izatt, *J. Incl. Phenom.* **29**, 259 (1997).

[17]   J. S. Bradshaw; H. C. Song, G. P. Xue, T. R. Bronson, J. A. Chiara, E. K. Krakowiak, P. B. Savage, and R. M. Izatt, *Supramol. Chem.*, **13**, 499 (2001).

[18]   H. C. Song, J. S. Bradshaw, G. P. Xue, T. R. Bronson, J. A. Chiara, E. K. Krakowiak, P. B. Savage, and R. M. Izatt, *ARKIVOC*, **2**, Part 3 ms 0000 (2001) (http://www.arkat-usa.org/journal/Issue9/cont1.htm).

[19]   Z. -X. Yang, J. S. Bradshaw, X. X. Zhang, P. B. Savage, E. K. Krakowiak, N. K. Dalley, N. Su, R. T. Bronson, and R. M. Izatt, *J. Org. Chem.,* **64**, 3162 (1999).

[20]   R. T. Bronson, J. S. Bradshaw, P. B. Savage, S. Fuangswasdi, S. L. Lee, K. E. Krakowiak and R. M. Izatt, *J. Org. Chem.,* **66**, 4752 (2001).

[21]   J. S. Bradshaw, K. E. Krakowiak, and R. M. Izatt, *J. Heterocylic Chem.*, **26**, 1431 (1989).

[22]   K. E. Krakowiak, J. S. Bradshaw, and R. M. Izatt, *J. Org. Chem.*, **55**, 3364 (1990).

[23]   K. E. Krakowiak, J. S. Bradshaw, and R. M. Izatt, *Synlett*., 611 (1993).

[24]   J. S. Bradshaw, K. E. Krakowiak, H. -Y. An, and R. M. Izatt, *J. Heterocylic Chem.*, **27**, 2113 (1990).

[25]   K. -W. Chi, H. -C. Wei, T. Kottke, and R. J. Lagow, *J. Org. Chem.*, **61** 5684 (1998).

[26]   N. Su, J. S. Bradshaw, P. B. Savage, K. E. Krakowiak, R. M. Izatt, S. L. DeWall, and G. W. Gokel, *Tetrahedron*, **55**, 9737 (1999).

[27]   N. Su, J. S. Bradshaw, X. X. Zhang, H. -C. Song, P. B. Savage, G. -P. Xue, K. E. Krakowiak, and R. M. Izatt, *J. Org. Chem.* **64**, 8855 (1999).

[28]   A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, and R. D. Shah, *J. Org. Chem.*, **61**, 3849 (1996).

[29]   D. Pelissard and R. Louis, *Tetrahedron Lett.,* 4589 (1972).