Phenol-Containing Macrocyclic Diamides as New Catalysts in the Highly Regioselective Conversion of Epoxides to β-Hydroxy Thiocyanates

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The regioselective ring-opening reactions of some epoxides with ammonium thiocyanate in the presence of a series of new phenol-containing macrocyclic diamides and also dibenzo-18-crown-6-, 18-crown-6-, benzo-15-crown-5-, and pyridine-containing macrocyclic diamide have been studied. The epoxides were subject to cleavage by NH_4SCN in the presence of these catalysts under mild reaction conditions in various aprotic solvents. In this study, reagents and conditions have been discovered with which the individual β-hydroxy thiocyanates can be synthesized in high yield and with more than 90% regioselectivity. The results can be discussed in terms of a four-step mechanism: (1) formation of complex between catalyst and NH_4SCN, (2) release of SCN^- nucleophile from the complex, (3) reaction of the active nucleophile at the less sterically hindered site in the epoxide, and (4) regeneration of catalyst. The major advantages of this method are as follows: (1) high regioselectivity, (2) simple regeneration of catalyst, (3) its reuse through several cycles without a decrease in activity, and (4) ease of workup of the reaction.

Introduction

Epoxides are one of the most versatile intermediates in organic synthesis, and a large variety of reagents are known for the ring opening of these compounds.[1] Their electrophilic reaction with different nucleophilic anions has been an interesting subject in organic synthesis.[2−7] Between these anions, the reaction of thiocyanate ion with epoxides, in the absence or in the presence of catalyst, is a widely studied and suitable method for the preparation of thiiranes.[8−15] The formation of thiiranes from the reaction of epoxides and thiocyanate ion has been proposed to occur through the intermediacy of the corresponding β-hydroxy thiocyanate, but this intermediate has not been isolated due to its rapid conversion to the corresponding thiirane.[13−17] There are two methods reported in the literature for the synthesis of β-hydroxy thiocyanates. In one method, thiocyanohydrins are prepared by opening of a cyclic sulfate with NH_4SCN to form the corresponding β-sulfate, which is hydrolyzed to the thiocyanohydrines. A second method employed the addition to the epoxide of thiocyanic acid generated in situ at low temperature.[18−21] For these syntheses, it has been reported that the presence of some hydroquinone or DDQ are required to stabilize the produced β-hydroxy thiocyanate and inhibit its conversion to thiirane.[16,22]

Although the reagents such as Ti (O-*i*-Pr)$_4$,[23] $Ph_3P(SCN)_2$,[24] $TiCl_3$ (or $ZnCl_2$),[25] and $Pd(PPh_3)_4$[26] are useful, they are limited to specific oxiranes and are not applicable as versatile reagents in preparation of β-hydroxy thiocyanates.[27]

In conjunction with the ongoing work in our laboratory on the synthesis and complex formation of macrocyclic compounds with different molecules,[28−32] we found that

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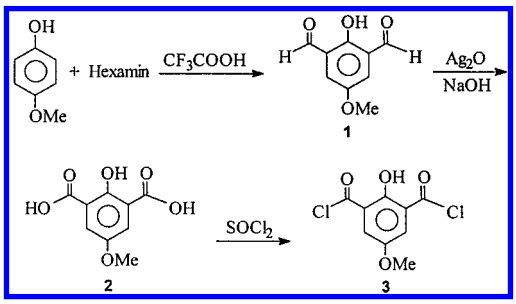
Scheme 1



phenol-containing macrocyclic diamides efficiently catalyzed the addition of ammonium thiocyanate to epoxide to form *β*-hydroxy thiocyanate. Five new phenol-containing macrocyclic diamides as well as dibenzo-18-crown-6-, 18-crown-6-, benzo-15-crown-5-, and pyridine-containing macrocyclic diamide **19**[33] were selected as catalysts in these reactions.

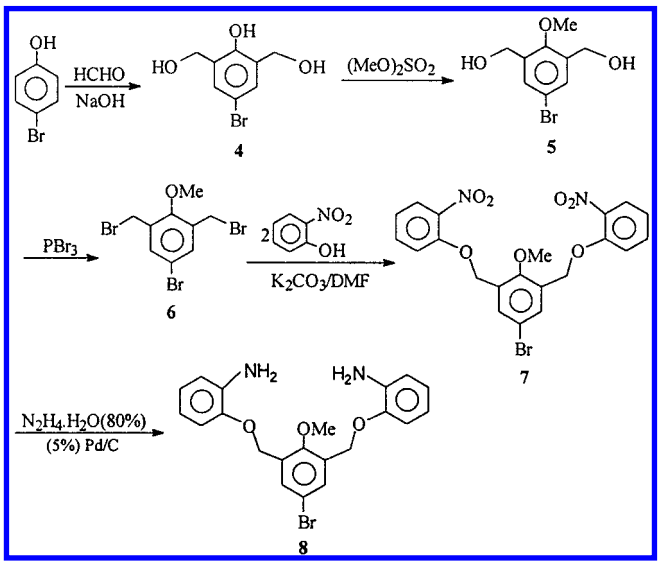
Discussion

(A) Preparation of Catalyst. Although macrocyclic amides are originally regarded as intermediates to prepare aza crowns, only a few procedures have been developed for their preparations. Among these, carboxylic acid derivatives, such as malonic and α,*ω*-dicarboxylic acid esters,[34] labile diacid dichlorides,[35,36] and bis(α-chloroamide)compounds,[37−39] were allowed to react with various diamides under high dilution or for long reaction periods. In previous studies,[28,31] we reported a new efficient synthesis of macrocyclic diamides. No high-dilution technique was required in this method. We applied this approach to the synthesis of dilactams **11**−**15** which contain phenolic groups (Scheme 1).

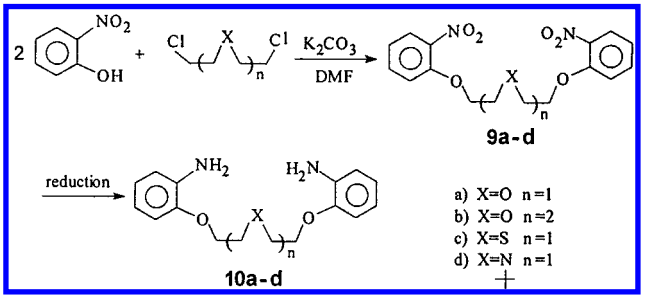
As shown in Scheme 1, *p*-methoxyphenol was reacted with hexamine in trifluoroacetic acid to give yellow needles of 2,6-diformyl-4-methoxyphenol **1** in 32% yield.[40] Dicarboxylic acid **2** was obtained as a pale yellow solid in 60% yield by oxidation of dialdehyde **1** in the presence of Ag_2O in aqueous NaOH solution. Treatment of **2** with thionyl chloride gave 86% yield of dicarboxylic acid dichloride **3**.

The diamine **8** was obtained by reduction of the corresponding dinitro compound **7** with palladium on carbon (5%) and hydrazine in 81% yield (Scheme 2). *p*-Bromophenol reacted with formaline (37% aqueous solution) in

Scheme 2



Scheme 3



the presence of sodium hydroxide followed by protection of the phenolic group with dimethyl sulfate. Treatment of **5** with PBr_3 gave the dibromide **6,** which reacted with *o*-nitrophenol to afford dinitro compound **7**.

The diamino compounds **10a**−**d** were obtained by reduction of the corresponding dinitro compounds **9a**−**d** (Scheme 3). *o*-Nitrophenol reacted with the dichlorides of oligoethylene glycols in the presence of potassium carbonate in dimethylformamide to give the corresponding dinitro compounds **9a**−**d** in the range of 67−85% yields.[41] The cyclization reaction between diacid dichloride **3** and the diamines **8** and **10a**−**d** was performed without using high-dilution techniques. In a preliminary study, the effect of some solvents ($CHCl_3$, CH_3CN, CH_2Cl_2, C_6H_6, acetone) on the yield of the macrocyclization reaction has been investigated, and CH_2Cl_2 has been chosen as the most suitable solvent for these macrocyclization reactions. In addition, the cyclization reaction was carried out with fast addition of a solution of diamine (2 mmol) in dry CH_2Cl_2 (10 mL) into a solution of dicarboxylic acid dichloride **3** (2 mmol) in dry CH_2Cl_2 (10 mL) over 5 s with vigorous stirring at room temperature. The reaction mixture was stirred for further 20 min to give macrocyclic dilactams **11**−**15** in good yields (Scheme 3).

Crown ethers **16**−**19** were also used as catalysts in thiocyanation of epoxides.

(B) Thiocyanation of Epoxides. Epoxides of convenient volatility to allow GC analysis were chosen for study. As catalysts, some phenol-containing macrocyclic-

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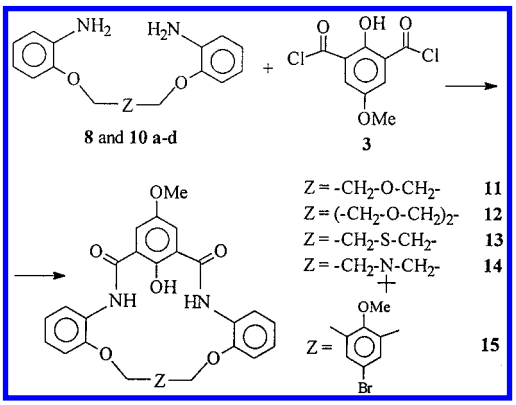
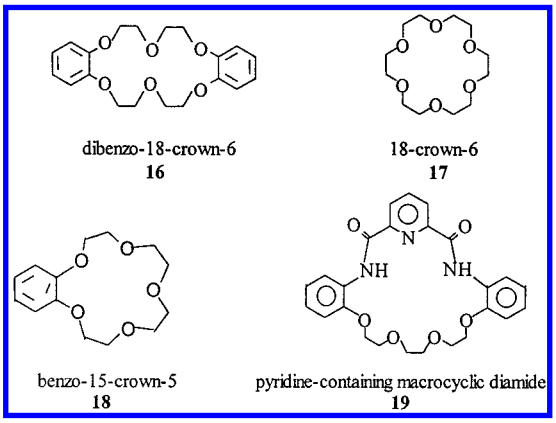
Scheme 4



diamides that were synthesized according to Scheme 4 were used. Also, dibenzo-18-crown-6 **16**, 18-crown-6 **17**, benzo-15-crown-5 **18**, and pyridine-containing macrocyclic diamide **19** were selected to represent some com-

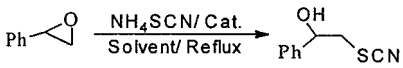


mon crown ether catalysts. The results of the reaction of styrene oxide with thiocyanate ion in the presence of the above catalysts are summarized in Table 1. In each case, cleavage of the epoxide ring occurs, and upon workup, the corresponding thiocyanohydrin was obtained. The catalyst was easily recovered and could be reused several times. By comparison, the cleavage of the styrene oxide with ammonium thiocyanate in the absence of catalyst is given in entry 10 of Table 1. As shown in Table 1, yields of thiocyanation with this new methodology were quite good. Catalysts **11** and **12** were the most effective, and the reactions were completed in 35 and 40 min in the presence of these catalysts respectively (Table 1, entries 1 and 2). In the presence of other catalysts **13**−**19**, the reaction times for thiocyanation at 80 °C are in the rang 50−90 min. However, the reaction of the styrene oxide with an excess of ammonium thiocyanate in the absence of catalyst afforded the corresponding thiirane in 35% yield when the reaction mixture was refluxed for 3 h.

The results of the ring opening of styrene oxide in the presence of macrocycle **11** using various solvents are summarized in Table 1. Thiocyanation reactions proceed very cleanly employing CH_3CN, while those performed in Et_2O and CH_2Cl_2 led to a lower yield of the thiocyanohydrin.

The results obtained with some representative epoxides in the presence of macrocycles **11** and 18-crown-6 **17** as catalyst are summarized in Table 2. On the other

Table 1. Thiocyanative Cleavage of Styrene Oxide with NH_4SCN in the Presence of Various Macrocyclic Compounds in Different Solvent under Reflux Condition



entry	catalyst (0.01 mol %)	solvent	time (min)	yield[a] (%)
1	11	CH_3CN	35	93
2	12	CH_3CN	40	93
3	13	CH_3CN	50	90
4	14	CH_3CN	50	85
5	15	CH_3CN	90	55
6	16	CH_3CN	85	70
7	17	CH_3CN	70	75
8	18	CH_3CN	90	65
9	19	CH_3CN	70	70
10		CH_3CN	190[b]	*c*
11	11	Et_2O	70	*d*
12	11	*t*-BuOH	60	50
13	11	EtOH	60	40
14	11	THF	65	30
15	11	CH_2Cl_2	70	<20
16	11	1,4-dioxane	70	40

[a] Determined by GC. [b] In the presence of excess of NH_4SCN. [c] 35% of the corresponding thiirane was obtained. [d] 25% of the corresponding thiirane was obtained.

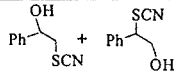
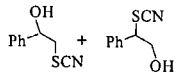
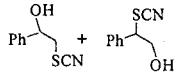
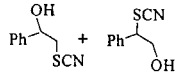
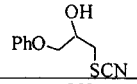
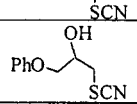
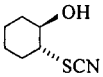
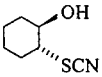
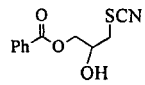
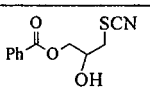
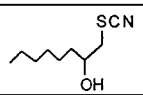
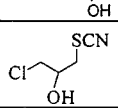
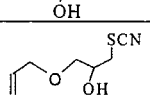
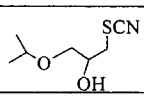
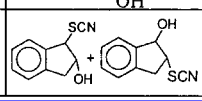
hand, some other methods for conversion of epoxides into the corresponding thiocyanohydrins are given in Table 2 (entries 4−6, 8, and 12). When epoxides were allowed to react in the presence of our catalysts, the yield and the regioselectivity were higher than the observed in all of the reactions conditions studied. An alternative preparation of β-hydroxy thiocyanate by the reaction of styrene oxide with KSCN/18-crown-6 **17** was examined. This route, however, is not a good one for the synthesis of β-hydroxy thiocyanates and gave a 15% of the corresponding thiirane (Table 2, entry 7).

Generally, the optimum amounts of the catalysts were found to be 0.01 mol for 1 mol of epoxides and NH_4SCN. However, other factors can exert a controlling influence, such as (1) steric hindrance of epoxides, (2) the nature of solvent, and (3) electron-donating or -withdrawing groups bonded to the epoxide. Each one can have a pronounced effect on the observed ratio of thiocyanohydrin isomers and overall yield.

The reaction exhibited a stereoselectivity anti as shown for cyclohexene oxide (Table 2, entry 11) in which only the trans isomer was detected. The anti Markovnikov-type[39] regioselectivity was generally observed in these reactions, except for the reactions of styrene oxide (Table 2, entry 1) and indene oxide (Table 2, entry 19), which produced 18% and 20% of the other regioisomer, respectively. The reactions of other epoxides were found to be highly regioselective, and only one isomer was obtained. In these reactions a 5−10% of the corresponding thiiranes was also formed, which could easily isolated by column chromatography.

The regiochemical mode of epoxide cleavage by ammonium thiocyanate in the presence of macrocycle catalyst can be viewed as occurring via nucleophilic attack by thiocyanate ion on the less sterically hindered epoxide carbon. This mechanism closely resembles the S_N2 model for aliphatic nucleophilic displacement. On the basis of our previous study on macrocycle diamides and other works on the complexation of crown ethers and azophenol-dyed crown ethers with elemental halogens, alkaline

Table 2. Reaction of Epoxides with NH_4SCN in the Presence of the Representative Catalyst

Entry	Epoxide	Catalyst (0.01)	Reaction Conditions	Product(s)	Reaction Time(min)	Yield%[a]
1		**11**	NH_4SCN/CH_3CN Reflux		35	93(4:1)
2		**17**	NH_4SCN/CH_3CN Reflux		70	75
3		**11**	$KSCN/CH_3CN$ Reflux		90	10
4		$Pd(PPh_3)_4$[26]	NH_4SCN/N_2 THF/ Reflux		120	35
5		$Ti(O\text{-}^iPr)_4$[23]	NH_4SCN THF/ Reflux		240	30
6		$ZnCl_2$[25]	KSCN THF/ Reflux		180	60
7		**17**	$KSCN/CH_3CN$ Reflux		90	15
8		DDQ	NH_4SCN/CH_3CN Reflux		50	91(1:8)[16]
9		**11**	NH_4SCN/CH_3CN Reflux		45	90
10		**17**	NH_4SCN/CH_3CN Reflux		75	80
11		**11**	NH_4SCN/CH_3CN Reflux		40	95
12		H_2Q[b]	KSCN/ H_3PO_4 H_2O/ Et_2O		-	48[19]
13		**11**	NH_4SCN/CH_3CN Reflux		50	90
14		**17**	NH_4SCN/CH_3CN Reflux		100	80
15		**11**	NH_4SCN/CH_3CN Reflux		80	85
16		**11**	NH_4SCN/CH_3CN Reflux		55	80
17		**11**	NH_4SCN/CH_3CN Reflux		45	85
18		**11**	NH_4SCN/CH_3CN Reflux		65	80
19		**11**	NH_4SCN/CH_3CN Reflux		100	90(1:4)

[a] Determined by GC. [b] Hydroquinone has been used to stabilize 2-hydroxycyclohexyl thiocyanate (see ref 19).

metal ions, ammonium cation, and alkylamines,[28−32,42−45] conversion of epoxide to β-hydroxy thiocyanate occurs according to the following four-step mechanism: The first step involves the formation of a 1:1 molecular complex

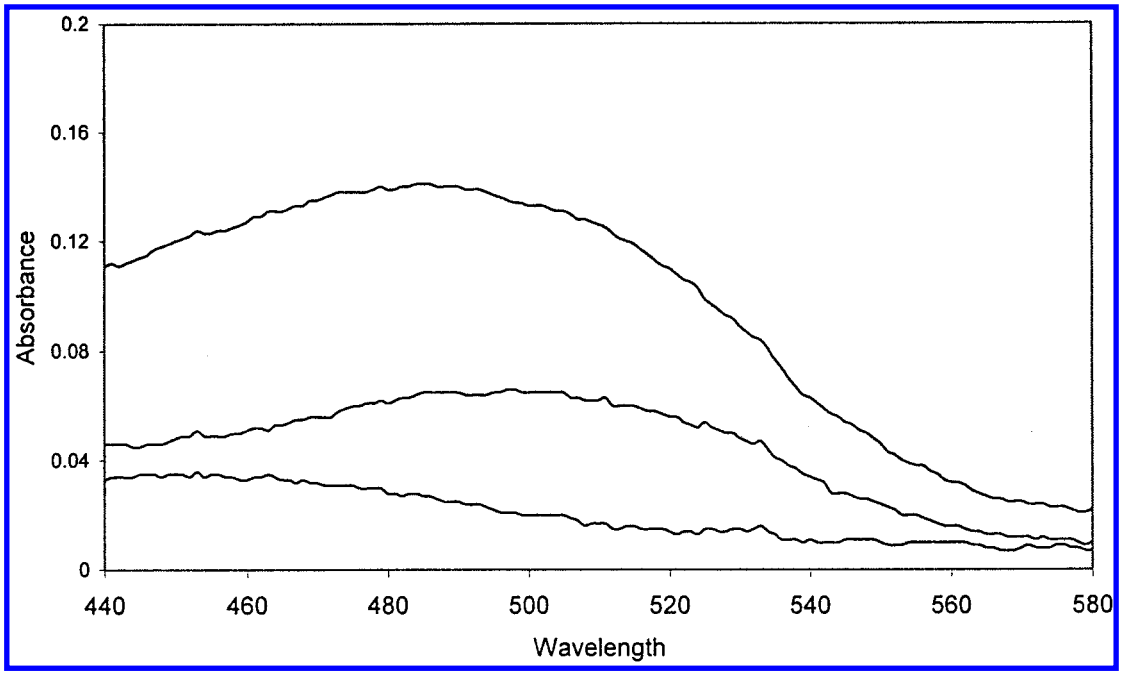


Figure 1. Absorption spectra from bottom to top refer to NH_4SCN, catalyst **11**, and catalyst **11** in the presence of NH_4SCN, in CH_3CN solution.

between macrocycle and NH_4SCN in which thiocyanate ion (SCN^-) exist as a contact ion pair:

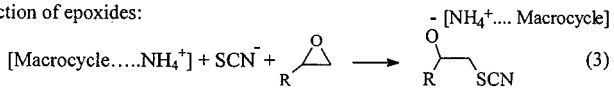
$$\text{macrocycle} + NH_4SCN \rightleftharpoons [\text{macrocycle}....NH_4^+]SCN^- \quad (1)$$

In the second step, this complex is further decomposed to release SCN^- ion into solution as:

$$(\text{macrocycle}....NH_4^+)SCN^- \rightarrow [\text{macrocycle}....NH_4^+] + SCN^- \quad (2)$$

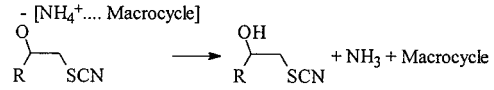
Therefore, in this way, SCN^- ion is produced as a nucleophilic species in the presence of a suitable macrocycle, and in the third step, this ion participates in the ring-opening reaction of epoxides:

reaction of epoxides:



(3)

Finally, the catalyst is regenerated in step 4:



(4)

These steps occur continuously until all of the epoxides and ammonium thiocyanate are consumed, and after workup, the catalyst can be recovered easily.

The variation in yield and rate of epoxide ring opening by SCN^- in the presence of different catalyst **11**−**19** can be rationalized in terms of the suggested mechanism. The macrocycles **11** and **12** are the most active catalysts in these reactions. According to the mechanism, in both macrocycles **11** and **12** a complexation with NH_4SCN and, hence, liberation of SCN^- occurred much faster than with other catalysts. In support of this mechanism, interaction of catalyst **11** with NH_4SCN was followed by UV spectroscopy (Figure 1). This figure shows the electronic absorption spectra of NH_4SCN, catalyst **11**, and catalyst **11** in the presence of NH_4SCN in CH_3CN solution. As we can see, addition of NH_4SCN to catalyst **11** results in the appearance of a new absorption maximum at 485 nm. As is obvious, the catalyst **11**/NH_4SCN interaction will result in a strong absorption shift of about 15 nm toward shorter wavelengths.

In conclusion, we have found that suitable macrocyclic compounds can catalyze the regioselective ring opening of epoxides by ammonium thiocyanate under mild reaction conditions.

Especially noteworthy are the ease of catalyst regeneration and reuse, the compatibility of these reaction conditions with a variety of sensitive functional groups, as well as the convenience of this procedure, which make this synthetic technique highly useful.

Experimental Section

Elemental analyses were performed at the National Oil Co. of Iran, Tehran Research Center.

Preparation of 2,6-Diformyl-4-methoxyphenol (1). 4-Methoxyphenol (5.243 g, 42.2 mmol) and hexamethelenetetramine (11.95 g, 55.1 mmol) were dissolved in anhydrous trifluroacetic acid (60 mL) under N_2 and the mixture stirred for 24 h. The mixture was poured into 4 M HCl (200 mL) and stirred for 10 min, after which time it was extracted with CH_2Cl_2. The combined organic extracts were washed with 4 M HCl, water, and saturated brine, dried (Na_2SO_4), and evaporated to give a yellow crystalline residue. The product was purified by column chromatography to remove baseline impurities and trace amounts of 5-methoxysalicylaldehyde. This gave **1** as yellow needles: yield 2.4 g (32%); mp = 135−136 °C (lit.[40] mp 135−136 °C); IR (KBr) 1144, 1471, 1600, 1675, 1686, 2872, 2978, 3067, 3350 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.85 (s, 3H), 7.50 (s, 2H), 10.21 (s, 2H), 11.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 56.5, 122.8, 123.9, 153.0, 158.4, 192.3.

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Preparation of 4-Methoxyphenol-2,6-dicarboxylic Acid (2).[46] To a mixture of silver oxide (6.5 g, 0.028 mol) and sodium hydroxide (5.7 g, 0.14 mol) in water (50 mL), warmed to 55−60 °C, was added 2,6-diformyl-4-methoxyphenol **1** (2.5 g, 0.014 mol) with stirring. The silver oxide was transformed to fluffy metallic silver, and considerable heat was evolved. Stirring was continued for 10 min, the mixture was filtered, and the precipitated silver was washed with 100 mL of hot water. The solution was acidified with hydrochloric acid and cooled at 10−15 °C. The precipitate was filtered and dried. After recrystallization from ethanol a pale brown solid of dicarboxylic acid **2** was obtained in 60% yield (1.76 g): mp = 148−150 °C dec; IR (KBr) 1152, 1595, 1703, 2820, 3300 cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 3.72 (s, 3H), 7.47 (s, 2H); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 56.0, 117.9, 120.8, 150.4, 156.0, 169.2.

Preparation of 4-Methoxyphenol-2,6-dicarboxylic Acid Dichloride (3).[46] 4-Methoxyphenol-2,6-dicarboxylic acid **2** (2 g, 0.009 mol) was heated in thionyl chloride (10 mL) for 4 h at 50−60 °C. The thionyl chloride was evaporated at low temperature to give **3** as a brown viscous oil in 86% yield (2 g): IR (CH_2Cl_2) 1154, 1460, 1585, 1778, 2958, 3074 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.8 (s, 3H), 7.6 (s, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 57.0, 120.0, 123.6, 152.0, 162.4, 178.2.

4-Bromo-2,6-bis(hydroxymethyl)phenol (4). To an aqueous solution of NaOH (25%, 50 mL) containing *p*-bromophenol (17.3 g, 0.1 mol) and methanol (25 mL) was added formaldehyde (38%, 90 mL) and the mixture stirred for 12 d at room temperature. Then, a mixture of water (50 mL) and acetic acid (15 mL) was added. The reaction mixture was stirred for 4 h at room temperature to give a yellow precipitate. Filtration gave 20 g (86%) of the solid (mp = 155−160 °C). The precipitate was dissolved in 10% aqueous NaOH and decolorized with active charcoal (0.5 g). The filtrate was acidified with 2 M HCl to give crystals that were filtered, washed with water, and dried. The crude product was recrystallized from hot water to gave pale yellow precipitate (10.9 g, 47%): mp = 162−164 °C (lit.[47] mp 163−164 °C); IR (KBr) 1070, 1480, 1590, 3318, 3420 cm^{-1}; ^1H NMR (acetone-d_6, 60 MHz) δ 2.39 (s, 2H), 4.78 (s, 4H), 7.30 (s, 2H).

4-Bromo-2,6-bis(hydroxymethyl)anisole (5). To a solution of 4-bromo-2,6-bis(hydroxymethyl)phenol (**4**), (2.6 g, 11 mmol) in 5% aqueous NaOH (10 mL) was added dropwise dimethyl sulfate (1.5 mL, 15 mmol). After being stirred at 30 °C for 2 h, the reaction mixture was allowed to stand overnight at room temperature. The precipitate was collected by filtration, washed with water, and redissolved in hot water. After removal of the insoluble oil, the clear solution was cooled. The product (1.6 g, 58%) crystallized as white needles: mp = 126−128 °C; after recrystallization from water mp = 130 °C (lit.[48] mp 130 °C); IR (KBr) 1067, 1455, 3030, 3270 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.75 (s, 3H), 4.49 (s, 4H), 7.52 (s, 2H).

4-Bromo-2,6-bis(bromomethyl)anisol (6). To a solution stirred at room temperature of **5** (5.5 g, 22.5 mmol) in 100 mL of dioxane was added over a 30 min period a solution of PBr_3 (50 mmol) in 10 mL of dioxane. After 20 h, 15 mL of H_2O and 200 mL of $CHCl_3$ were added, and the mixture was stirred for 5 min and then neutralized with saturated $NaHCO_3$. The $CHCl_3$ extracts were dried (Na_2SO_4), and after removal of the solvent the residue was purified by column chromatography using petroleum ether (bp = 60−80 °C) as eluent: white crystals (5.11 g); yield 61%; mp = 80−81 °C (lit.[49] 82−83 °C); IR (KBr) 778, 867, 1204, 1580, 3022 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.0 (s, 3H,), 4.46 (s, 4H), 7.48 (s, 2H).

2,6-Bis[2-(*o*-nitrophenoxy)methyl]-4-bromo-1-methoxybenzene (7). A mixture of *o*-nitrophenol (14 g, 0.1 mol) and potassium carbonate (14 g) was stirred in DMF (100 mL) for 2 h. Then, 4-bromo-2,6-bis(bromomethyl)anisol **6** (0.05 mol, 18.65 g) was added dropwise during 1 h, and the mixture was refluxed for 24 h. After cooling, the mixture was poured into ice, and the precipitate was filtered off. The precipitate was washed with distilled water, and the crude product was purified by column chromatography using petroleum ether/ethyl acetate as eluent (2:1) to give white solid **7** (16 g): yield 66%; mp = 185−187 °C; IR (KBr) 670, 741, 778, 865, 1005, 1055, 1091, 1170, 1218, 1285, 1351, 1380, 1461, 1526, 1588, 1608, 2842, 2938, 3072 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.86 (s, 3H,), 5.23 (s, 4H), 7.06−7.18 (m, 4H). 7.55 (dt, 2H, J_1 = 7.3 Hz, J_2 = 1.7 Hz), 7.7 (s, 2H), 7.88 (dd, 2H, J_1 = 8.0 Hz, J_2 = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 63.0, 65.8, 114.9, 118.0, 121.0, 125.9, 131.0, 132.8, 134.0, 141.0, 151.6, 155.0; UV ($CHCl_3$) λ (ϵ_{max}) 321, 346 nm. Anal. Calcd for $C_{21}H_{17}BrN_2O_7$: C, 51.53; H, 3.48; Br, 16.36; N, 5.73. Found: C, 51.23; H, 3.62; Br, 16.57; N, 5.53.

General Procedure for the Preparation of Diamino Compounds 8 and 10a−c. In a two-necked round-bottomed flask equipped with a reflux condenser and a dropping funnel was prepared a suspension of dinitro compound **7** (5.87 g, 0.012 mol) or **9a−c** (0.012 mol), palladium on carbon 5% (0.4 g), and absolute ethanol (200 mL). The mixture was warmed, and while the mixture was stirred magnetically, hydrazine hydrate 80% (10 mL) in ethanol (20 mL) was added dropwise over a 1.5 h period through the dropping funnel with the temperature maintained at about 50 °C. The reaction mixture was refluxed for 2 h and filtered while hot. On cooling, the filtrate gave the corresponding diamino compound after vacuum drying.

2,6-Bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxybenzene (8): white crystals; yield 4.14 g, 81%; mp = 105−106 °C; IR (KBr) 746, 992, 1005, 1041, 1137, 1210, 1282, 1378, 1457, 1505, 1592, 1610, 2880, 2940, 3038, 3382, 3478 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.65 (s, 4H), 3.82 (s, 3H,), 5.1 (s, 4H), 6.6−6.8 (complex, 6H), 6.95 (d, 2H, J = 7.5) 7.47 (d, 2H, J = 7.5); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 63.4, 65.9, 112.6, 115.7, 118.9, 122.1, 125.0, 130.6, 131.0, 137.0, 146.8, 157.1; MS *m*/*z* 430 (M^+ + 2, 0.7), 428 (M^+, 0.7), 350 (19), 242 (14), 210 (100), 182 (23), 133 (32), 122 (26), 119 (39), 91 (79); UV ($CHCl_3$) λ (ϵ_{max}) 309 nm. Anal. Calcd for $C_{21}H_{21}BrN_2O_3$: C, 58.74; H, 4.90; Br, 18.65; N, 6.53. Found: C, 58.61; H, 5.12; Br, 18.83; N, 6.44.

1,5-Bis(*o*-aminophenoxy)-3-oxapentane (10a):[50] white crystals; yield 94%; mp = 65−66 °C; IR (KBr) 1138, 1508, 1605, 3321, 3388 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.58 (s, 4H), 3.88 (t, 4H, J = 4.6 Hz), 4.12 (t, 4H, J = 4.6 Hz), 6.59−6.78 (m, 8H).

1,8-Bis(*o*-aminophenoxy)-3,6-dioxaoctane (10b):[50] white crystals; yield 93%; mp = 48−50 °C; IR (KBr) 1140, 1510, 1608, 3370, 3470 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.67 (s, 4H), 3.77 (s, 4H), 3.85 (t, 4H, J = 4.5 Hz), 4.2 (t, 4H, J = 4.5 Hz), 6.54−6.77 (m, 8H); MS *m*/*z* 333 (M^+ + 1, 7), 332 (M^+, 32), 224 (17), 153 (12), 136 (49), 109 (57), 92 (38), 80 (53), 65 (30), 44 (100).

1,5-Bis(*o*-aminophenoxy)-3-thiopentane (10c):[50] white crystals; yield 89%; mp = 28−29 °C; IR (KBr) 1017, 1508, 1608, 3328, 3408 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.03 (t, 4H, J = 6.5 Hz), 3.73 (b, 4H), 4.20 (t, 4H, J = 6.5 Hz), 6.66−6.84 (m, 8H); MS *m*/*z* 304 (M^+, 3), 196 (13), 168 (23), 123 (18), 105 (100), 80 (32), 61 (53), 45 (65).

***N-tert*-Butylbis[2-(*o*-aminophenoxy)ethyl]amine (10d).**[51] The dinitro compound **9d** (4.0 g, 0.01 mmol) was reduced in a stirred refluxing solution of tin(II) chloride dihydrate (15 g, 0.65 mol) in concentrated hydrochloric acid (50 mL). After 7 h, the reaction mixture was cooled and the precipitate was filtered. A solution of sodium hydroxide (5 N, 200 mL) was added to the filtrate and extracted with CH_2Cl_2. The organic layer was washed with water, dried with sodium sulfate, and evaporated. The residue was crystallized from ethanol to give diamine **10d** as white crystals in 54% (6 g) yield: mp = 50−52 °C; IR (KBr) 1508, 1615, 3355, 3428 cm^{-1}; ^1H NMR ($CDCl_3$,

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250 MHz) δ 1.13 (s, 9H), 3.03 (t, 4H, J = 6.6 Hz), 3.80 (b, 4H), 4.01 (t, 4H, J = 6.6 Hz), 6.55−6.80 (m, 8H).

General Procedure for the Synthesis of Phenol-Containing Macrocyclic Diamides (11−15). A solution of diamine (2 mmol) in dry CH_2Cl_2 (50 mL) was added quickly to a vigorously stirred solution of 4-methoxyphenol-2,6-dicarboxylic acid dichloride **3** (2 mmol) in dry CH_2Cl_2 (50 mL) at room temperature. The mixture was stirred for a further 20 min and then was washed with bicarbonate solution and water. The organic layer was dried over magnesium sulfate, and the solvent was evaporated to give an oily product. The crude product was purified by column chromatography using petroleum ether (bp = 60−80 °C)/ethyl acetate as eluent.

3,15-Diaza-4,5;13,14-dibenzo-21-hydroxy-19-methoxy-6,9,12-trioxabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (11): red viscous oil; yield 68%; IR (neat) 749, 1051, 1259, 1454, 1535, 1602, 1662, 2925, 3288 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.86 (s, 3H), 4.04 (s, 4H), 4.28 (s, 4H), 6.92−7.05 (m, 6H), 8.10 (d, 2H, J = 3.3 Hz), 8.69 (m, 4H), 11.73 (s, 1H); MS m/z 450 (12), 449 (29), 448 (82), 341 (14), 340 (51), 314 (30), 284 (9), 270 (17), 268 (14), 255 (19), 241 (13), 226 (24), 212 (12), 177 (7), 163 (30), 149 (27), 135 (17), 120 (48), 109 (26), 91 (16), 77 (30), 43 (100); UV ($CHCl_3$) λ (ϵ_{max}) 245 (15744), 293.5 nm (9796). Anal. Calcd for $C_{25}H_{24}N_2O_7$: C, 64.65; H, 5.21; N, 6.03. Found: C, 64.97; H, 5.55; N, 5.76.

3,18-Diaza-4,5;16,17-dibenzo-24-hydroxy-22-methoxy-6,9,12,15-tetraoxabicyclo[18.3.1]tetraeicosa-1(24),20,22-triene-2,19-dione (12): red viscous oil; yield 64%; IR (neat) 749, 1051, 1118, 1252, 1461, 1535, 1595, 1662, 2932, 3308 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.80 (s, 4H), 3.88 (s, 3H), 3.97 (t, 4H, J = 4.0 Hz), 4.25 (t, 4H, J = 4.0 Hz), 6.89−7.10 (m, 6H), 8.08 (d, 2H, J = 1.9 Hz), 8.53 (s, 2H), 8.60 (d, 2H, J = 7.8 Hz), 10.84 (s, 1H); MS m/z 510 (M^+ + 2, 8), 509 (M^+ + 1, 21), 508 (M^+, 32), 493 (8), 492 (8), 384 (5), 374 (3), 356 (5), 312 (5), 296 (2), 285 (4), 268 (15), 241 (4), 226 (6), 203 (19), 177 (100), 163 (5), 153 (7), 135 (10), 120 (20), 109 (17), 93 (33), 77 (6); UV ($CHCl_3$) λ (ϵ_{max}) 247 (14838), 351 nm (8584). Anal. Calcd for $C_{27}H_{28}N_2O_8$: C, 63.77; H, 5.55; N, 5.51. Found: C, 63.42; H, 5.91; N, 5.62.

3,15-Diaza-4,5;13,14-dibenzo-21-hydroxy-19-methoxy-9-thia-6,12-dioxabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (13): red solid; mp = 154−156 °C; yield 66%; IR (KBr) 749, 1051, 1252, 1454, 1535, 1602, 1662, 2918, 3301 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.31 (t, 4H, J = 6.3 Hz), 3.86 (s, 3H), 4.37 (t, 4H, J = 6.3 Hz), 7.03−7.06 (m, 6H), 8.08 (s, 2H), 8.65 (m, 4H), 11.7 (s, 1H); MS m/z 480 (M^+, 5), 466 (4), 465 (31), 464 (100), 357 (11), 356 (92), 328 (4), 296 (27), 270 (61), 268 (32), 241 (16), 226 (39), 179 (22), 178 (17), 163 (50), 152 (28), 135 (4), 120 (32), 109 (17), 93 (11), 87 (89), 77 (15); UV ($CHCl_3$) λ (ϵ_{max}) 249.5 (38208), 378 (10480), 510 nm (3792). Anal. Calcd for $C_{25}H_{24}N_2O_6S$: C, 62.49; H, 5.03; N, 5.83; S, 6.67. Found: C, 62.17; H, 5.38; N, 5.52; S, 6.92.

9-*tert*-Butyl-3,9,15-triaza-4,5;13,14-dibenzo-21-hydroxy-19-methoxy-6,12-dioxabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (14): red viscous oil; yield 58%; IR (neat) 749, 1044, 1252, 1508, 1602, 1662, 2925, 3361 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.85 (t, 4H, J = 4.5 Hz), 4.11 (s, 3H), 4.17 (t, 4H, J = 4.5 Hz), 6.97−7.08 (m, 6H), 8.11 (d, 2H, J = 3.3 Hz), 8.64−8.69 (m, 4H), 12.08 (s, 1H); MS m/z 519 (M^+, 5), 505 (12), 504 (38), 503 (16), 489 (4), 447 (6), 339 (50), 325 (12), 296 (17), 282 (18), 270 (66), 255 (13), 241 (10), 226 (14), 212 (6), 177 (4), 163 (33), 148 (5), 135 (9), 120 (19), 109 (18), 91 (8), 77 (14), 41 (100); UV ($CHCl_3$) λ (ϵ_{max}) 246 (19358), 326 (11175), 507 nm (6015). Anal. Calcd for $C_{29}H_{33}N_3O_6$: C, 67.04; H, 6.40; N, 8.09. Found: C, 67.51; H, 6.72; N, 7.67.

10-Bromo-3,18-diaza-4,5;16,17-dibenzo-24-hydroxy-13,22-dimethoxy-6,15-dioxa-tricyclo[12.3.3.1.1]tetraeicosa-1(24),8,10,12,20,22-hexaene-2,19-dione (15): red viscous oil; yield 67%; IR (neat) 749, 1004, 1252, 1454, 1535, 1595, 1662, 2925, 3314 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.75 (s, 3H), 4.04 (s, 3H), 4.92 (d, 2H, J = 9.7 Hz), 5.42 (d, 2H, J = 9.7 Hz), 6.99−7.04 (m, 6H), 7.94 (d, 2H, J = 3.2 Hz), 8.41 (s, 2H), 8.62 (s, 2H), 10.83 (s, 2H), 14.64 (s, 1H); MS m/z 608 (M^+, 7), 512 (14), 511 (40), 510 (57), 496 (3), 402 (4), 372 (6), 359 (7), 344 (7), 270 (51), 268 (51), 255 (11), 241 (10), 226 (35), 212 (8), 210 (12), 198 (7), 169 (13), 163 (16), 133 (43), 119 (38), 109 (46), 105 (42), 91 (100), 78 (25); UV ($CHCl_3$) λ (ϵ_{max}) 374 (8129), 259 nm (19280). Anal. Calcd for $C_{30}H_{25}BrN_2O_7$: C, 59.51; H, 4.16; Br, 13.20; N, 4.63. Found: C, 59.87; H, 3.94; Br, 13.51; N, 4.37.

General Procedure for Conversion of Epoxides to β-Hydroxy Thiocyanate Using Macrocyclic Diamide as Catalyst. To a mixture of epoxide (10 mmol) and NH_4SCN (10 mmol, 0.76 g) in acetonitrile (30 mL) was added a solution of catalyst (0.1 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred under reflux conditions for 35−90 min. The reaction was monitored by TLC or GC. After completion of the reaction, the mixture was filtered and the solvent was evaporated. Chromatography of the crude product was performed on a column of silica gel eluted first with n-hexane in the reaction mixture followed by using CCl_4/CH_2Cl_2 (1:1) for the separation of β-hydroxy thiocyanate as a pale yellow liquid.

Selected Spectral Data for β-Hydroxy Thiocyanates.[16,24,27] **(a) 2-Hydroxy-2-phenylethyl thiocyanate:** IR (neat) ν SCN (2160 cm^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.3 (5H, m), 5.0 (1H, dd), 3.1−3.3 (2H, m), 2.4−2.9 (1H, brs); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 135.8, 129.5, 128.3, 126.2, 113.0, 72.9, 42.4.

(b) 2-Hydroxycyclohexyl thiocyanate: IR (neat) ν SCN (2165 cm^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ 2.95 (1H, m), 2.35 (1H, m), 2.15 (1H, s), 1.80 (2H, m), 1.65 (2H, m), 1.20−1.50 (4H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 110.0, 72.0, 55.0, 34.5, 32.5, 30.5, 27.0.

(c) 3-Phenoxy-2-hydroxypropyl thiocyanate: IR (neat) ν SCN (2163 cm^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.27 (2H, m), 6.92 (3H, m), 5.0 (1H, m), 4.2 (2H, d), 3.64 (2H, d); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 158.0, 130.0, 122.0, 115.1, 114.9, 78.2, 67.2, 33.6.

(d) 3-Allyloxy-2-hydroxypropyl thiocyanate: IR (neat) ν SCN (2158 cm^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ 5.81 (1H, m), 5.1−5.25 (2H, m), 4.7 (1H, brs), 3.98 (3H, m), 3.6 (2H, d), 3.36 (2H, d); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 134.2, 118.0, 117.0, 80.2, 72.9, 69.2, 32.5.

(e) 3-Isopropyloxy-2-hydroxypropyl thiocyanate: IR (neat) ν SCN (2170 cm^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.74 (1H, m), 3.57 (3H, m), 3.33 (2H, d), 3.17 (1H, brs), 1.1 (6H, d, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 114.5, 79.4, 73.2, 67.6, 38.2, 23.0, 22.0.

(f) 3-Chloro-2-hydroxypropyl thiocyanate: IR (neat) ν SCN (2168 cm^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ 4.1 (1H, m), 3.7 (4H, m), 2.64 (1H, brs); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 117.8, 71.2, 46.1, 43.4.

(g) 2-Hydroxyoctan thiocyanate: IR (neat) ν SCN (2162 cm^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.91 (1H, m), 3.15 (1H, dd, J = 13 J = 3.5 Hz), 2.95 (1H, dd, J = 13 J = 7.5 Hz), 2.69 (1H, brs), 1.2−1.6 (10H, m), 0.88 (3H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 113.2, 70.6, 41.5, 36.3, 32.0, 29.4, 25.8, 22.9, 14.4.

(h) 2-Hydroxy-1-thiocyanatoindan: IR (neat) ν SCN (2160 cm^{-1}); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.2−7.5 (4H, m), 5.0 (1H, d), 4.8 (1H, m), 3.55 (2H, d), 3.2−3.5 (1H, brs); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 139.0, 130.0, 128.0, 126.0, 124.0, 120.0, 112.4, 83.7, 50.1, 39.4.

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