mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to yield a brown oil (1.5 g). Column chromatography of this oil on silica gel (ca. 40 g) and elution with 1:1 ethyl acetate/petroleum ether yielded a brown solid/oil mixture (R_f = 0.6 in ethyl acetate). Trituration of this mixture with ether gave **27** (0.090 g, 0.27 mmol, 9%) as a white crystalline solid, mp 153.5–155.5 °C: IR (KBr) 1595, 1530, 1490, 1450, 1440, 1425, 1360, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08–7.97 (m, 2 H), 7.62 (s, 1 H), 7.53–7.37 (m, 3 H), 7.28–7.12 (m, 3 H), 7.06–6.89 (m, 2 H), 4.43 (d, J = 12.7 Hz, 1 H), 4.20 (d, J = 12.8 Hz, 1 H), 3.05–2.28 (m, 4 H), 2.01–1.69 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.9, 155.0, 139.9, 138.1, 130.4, 129.5, 129.1, 128.6, 128.0, 127.8, 126.7, 117.4, 59.2, 31.8, 28.4, 25.0; LRMS (relative intensity) m/z 333 (10, M^+), 91 (100); HRMS calcd for $C_{21}H_{19}NOS$ 333.1187, found 333.1176 ± 0.0033.

2-(Benzylsulfonyl)-3,4-cyclopenteno-6-phenylpyridine (28). To a stirred solution of 3-(benzylsulfonyl)-5-phenyl-1,2,4-triazine (0.78 g, 2.51 mmol) and glacial acetic acid (0.36 mL, 6.29 mmol, 2.5 equiv) in anhydrous methylene chloride (10 mL) at 0 °C under nitrogen was added 1-morpholino-1-cyclopentene (**9b**) (0.50 mL, 3.12 mmol, 1.24 equiv) dropwise. The resulting effervescing solution was stirred at 0 °C under nitrogen for 30 min and then at room temperature for 30 min. The reaction mixture was concentrated by evaporation under reduced pressure to yield a brown oil. Trituration of this oil with ether (20 mL) with cooling yielded **28** (0.40 g, 1.17 mmol, 46%) as a white crystalline solid, mp 178.0–179.5 °C: IR (KBr) 1600, 1530, 1490, 1445, 1430, 1400, 1310, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12–8.00 (m, 2 H), 7.77 (s, 1 H), 7.55–7.39 (m, 3 H), 7.24 (s, 5 H), 4.77 (s, 2 H), 3.12–2.82 (m, 4 H), 2.13–1.80 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.1, 155.1, 138.9, 137.6, 131.3, 131.1, 129.5, 128.7, 128.4, 127.9, 126.8, 119.7, 58.1, 32.4, 30.5, 24.6. Anal. Calcd for $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01; S, 9.18. Found: C, 72.22; H, 5.23; N, 4.13; S, 8.93.

4-Carbomethoxy-6-(4-chlorophenyl)-2-(methylsulfonyl)-pyridine (31). A solution of 5-(4-chlorophenyl)-3-(methylsulfonyl)-1,2,4-triazine[14] (**30**) (0.81 g, 3.00 mmol) and methyl 3-pyrrolidinoacrylate[13] (0.47 g, 3.03 mmol) in anhydrous tetrahydrofuran (25 mL) was heated at reflux (66 °C) under nitrogen for 24 h. The resulting reaction solution was evaporated under reduced pressure, and the residual solid was column chromatographed on silica gel (approximately 40 g) followed by elution with methylene chloride to afford **31** (R_f = 0.4 in methylene chloride) (0.49 g, 1.50 mmol, 50%) as a pale yellow solid, mp 164.5–167.0 °C: IR (KBr) 1725–1715, 1585, 1530, 1480, 1425, 1295, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.50 (s, 1 H), 8.06 (d, J = 8.6 Hz, 2 H), 7.49 (d, J = 8.5 Hz, 2 H), 4.04 (s, 3 H), 3.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.9, 159.0, 157.8, 140.8, 137.0, 134.5, 129.3, 128.4, 122.9, 118.4, 53.3, 39.8. Anal. Calcd for $C_{14}H_{12}ClNO_4S$: C, 51.62; H, 3.71; Cl, 10.88; N, 4.30; S, 9.84. Found: C, 54.41; H, 3.53; Cl, 10.81; N, 4.54; S, 10.10.

Further elution using ethyl acetate yielded crude 5-(4-chlorophenyl)-3-pyrrolidino-1,2,4-triazine (**32**) (0.40 g, 1.5 mmol, 50% crude) as a pale yellow solid. Trituration of this solid in ether provided the analytically pure sample: IR (KBr) 1590, 1570, 1540–1510, 1475, 1455, 1395 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 8.07–8.03 (m, 2 H), 7.49–7.45 (m, 2 H), 3.73 (br m, 4 H), 2.06 (br m, 4 H). Anal. Calcd for $C_{13}H_{13}ClN_4$: C, 59.89; H, 5.03; Cl, 13.60; N, 21.49. Found: C, 59.95; H, 5.03; Cl, 13.82; N, 21.26.

Acknowledgment. We are indebted to Eli Lilly & Company, Indianapolis, IN, for support of this work.

Registry No. **1a**, 99702-42-8; **1c**, 99702-44-0; **1d**, 99702-43-9; **2a**, 99702-45-1; **2c**, 99702-47-3; **2d**, 99702-46-2; **3a**, 118459-16-8; **3b**, 99702-48-4; **3c**, 99702-50-8; **3d**, 99702-49-5; **4a**, 118459-17-9; **4b**, 99702-51-9; **4c**, 99702-53-1; **4d**, 99702-52-0; **5a**, 118459-18-0; **5b**, 99702-54-2; **5c**, 99702-56-4; **5d**, 99702-55-3; **6a**, 118459-19-1; **6b**, 99702-57-5; **6d**, 99702-60-0; **7b**, 99702-58-6; **7c**, 99702-62-2; **7d**, 99702-61-1; **8b**, 99702-59-7; **8c**, 118459-20-4; **8d**, 99702-63-3; **9a**, 7148-07-4; **9b**, 936-52-7; **10**, 22929-52-8; **11**, 106183-62-4; **12**, 106183-61-3; **13**, 14790-45-5; **14**, 99702-65-5; **15**, 99702-64-4; **17**, 118459-06-6; **18**, 118459-07-7; **19**, 118459-08-8; **20**, 118459-09-9; **23**, 117504-57-1; **24**, 118459-10-2; **25**, 118459-11-3; **27**, 118459-12-4; **28**, 118459-13-5; **29**, 90087-77-7; **30**, 105783-78-6; **31**, 118459-14-6; **32**, 118459-15-7; tetrahydrofuran-3-ol, 453-20-3; morpholine, 110-91-8; 5-phenyl-1,2,4-triazine-3-thione, 15969-28-5; pyrrolidine, 123-75-1; 6-chloro-5-methyl-1,2,4-triazine, 118459-21-5.

Synthesis of 2,4(5)-Bis(hydroxymethyl)imidazoles and 2,4(5)-Bis[(2-hydroxyethoxy)methyl]imidazoles: Precursors of 2,4(5)-Connected Imidazole Crown Ethers

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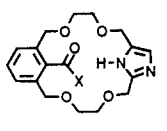
Received September 27, 1988

Two syntheses of 1-[(dimethylamino)sulfonyl]-2,4-bis[(2-hydroxyethoxy)methyl]imidazole, **3**, a precursor to imidazole-containing crown ethers, are described. The first involved hydroxymethylation of 1-benzylimidazole with formaldehyde to afford 1-benzyl-2,5-bis(hydroxymethyl)imidazole (**5**) (20% yield), which was elaborated into **3** in four steps. An alternative and more efficient route involved coupling of diamine **17b** with the imino ether obtained from nitrile **11b** to afford imidazoline **18b**. The imidazoline was found to oxidize under Swern conditions, providing a mild new method of imidazole synthesis. Sulfamylation and debenzylation produced **3**. This approach was also applied to the synthesis of 1-[(dimethylamino)sulfonyl]-2,4-bis(hydroxymethyl)imidazole (**2**). Diol **3** was converted into 2,4-connected imidazole crown ethers, one of which (**4**) formed a crystalline complex with water. The complex structure was determined by X-ray crystallography.

As part of an effort directed toward modeling the enzymatic His-Asp couple, we recently described the synthesis of imidazole-containing crown ether **1** in which the imidazole ring was linked from C-2 to C-4(5).[1] To our knowledge this was the first report of a 2,4(5)-connected imidazole crown ether. This is remarkable given the large number of crown ethers that have been synthesized.[2] The



1: X = OH
4: X = OMe

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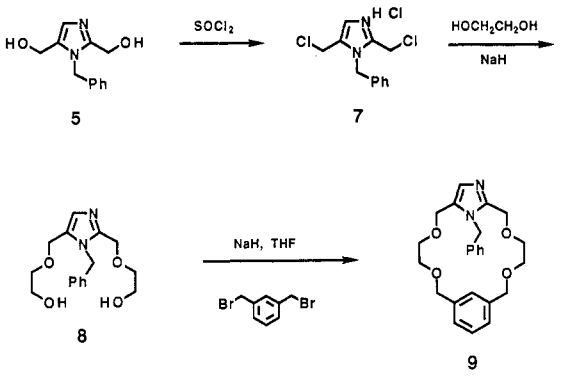
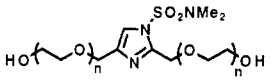
Scheme I



5 7 8 9

prevalence of crown ethers containing other nitrogen heterocycles, such as pyridine,[3] pyrrole,[4] triazole,[5] and pyrimidine,[6] suggested no lack of interest in these compounds but rather a lack of suitable synthetic precursors. Indeed, 2,4(5)-bis(hydroxymethyl)triazole is a known compound,[7] and precursors to the other heterocyclic systems are readily available. A practical synthesis of the analogous 2,4(5)-bis(hydroxymethyl)imidazole, however, has not been reported.

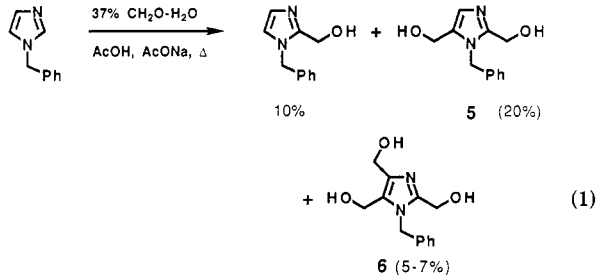


2: n = 0
3: n = 1

In some respects imidazole is a unique heterocyclic subunit for crown ethers since its two tautomeric forms give it "chameleon-like" properties.[8] Thus, the 2,5-tautomer can donate a hydrogen bond to the guest, while the 2,4-form can donate a lone pair to a metal ion or a hydrogen bond. We report here full details of our reported approach to imidazole crown ethers.[1] A low-yielding and inconvenient step in this route necessitated the development of a new approach, and we present here an efficient, alternative synthesis of 1-[(dimethylamino)sulfonyl]-2,4-bis(hydroxymethyl)imidazole (**2**) and 1-[(dimethylamino)sulfonyl]-2,4-bis[(2-hydroxyethoxy)methyl]-imidazole (**3**). Standard procedures allow these compounds to be converted into imidazole-containing crown ethers, one of which (**4**) was found to bind water avidly. The structure of the dihydrate of **4** was determined by X-ray crystallography.

Results and Discussion

Synthesis of 3 by Elaboration of 1-Benzylimidazole. The first synthetic route to **3** was based on functionalization of 1-benzylimidazole. Jones reported the synthesis of 1-benzyl-2-(hydroxymethyl)imidazole in 92% yield by formylation of 1-benzylimidazole with formaldehyde in a sealed tube.[9] With the 2-position blocked by an alkyl substituent, Godefroi reported that in buffered solution the hydroxymethylation would occur in the 5-position.[10] Thus, as shown in eq 1, when 1-benzylimidazole was heated



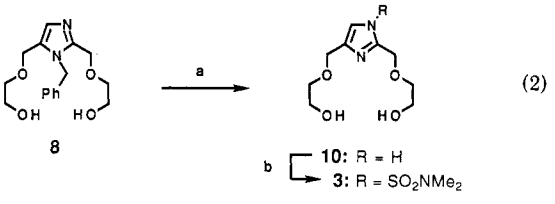
10% 5 (20%)

6 (5-7%) (1)

in a sealed tube at 140 °C for 12 h with 37% formaldehyde, acetic acid, and sodium acetate, three major products were obtained, 1-benzyl-2-(hydroxymethyl)imidazole (10%), 2,5-bis(hydroxymethyl)imidazole (**5**) (20%), and 2,4,5-tris(hydroxymethyl)imidazole (**6**) (5–7%).[11] Attempts to optimize the yield of **5** by increasing reaction time resulted in higher yields of **6** at the expense of the desired product (**5**).

Reaction of **5** with thionyl chloride gave dichloride **7** in 72% yield as its hydrochloride salt (Scheme I). In most cases this labile material was obtained analytically pure without purification and was therefore carried on directly. Reaction of **7** with a large excess of ethylene glycol and sodium hydride produced diol **8** in 66% yield. In a model cyclization, **8** reacted with 1,3-bis(bromomethyl)benzene and sodium hydride (THF, reflux) to give very low yields (ca. 4%) of imidazole macrocycle **9**. The ^{1}H NMR of **9** showed the methylene of the benzyl group to resonate as a very broad singlet at room temperature and a sharp AB quartet at −30 °C, presumably due to hindered rotation resulting from the benzyl group being forced into the center of the macrocycle. This observation explained the low cyclization yield and suggested that the cyclization with methyl 2,6-bis(bromomethyl)benzoate, the precursor to **1**, would meet with even less success.

A transposition of protecting groups was carried out to give a 2,4-disubstituted imidazole, so that the protecting group would be on the exterior of the cyclization product. Thus, hydrogenolysis of **8** at atmospheric pressure (Pd–C) produced unprotected diol **10** in 87% yield (eq 2). Protection of **10** with *N*,*N*-dimethylsulfamoyl chloride and



8 (2)

10: R = H
3: R = SO_2NMe_2

a: H_2, Pd-C; b: Me_2NSO_2Cl, Et_3N, 5% MeOH-CH_2Cl_2

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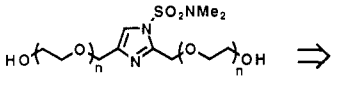
(8) Subunits such as 2,4(5)-linked triazole and 2,6-linked 4-pyridone might exhibit the same behavior, but their tautomeric equilibrium constants are further from unity: Elguero, J.; Marzin, C.; Katritzky, A. R.; Paolo, L. *The Tautomerism of Heterocycles*; Academic: New York, 1976.
(9) Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 383–386.
(10) Godefroi, E. F.; Loozen, H. J. J.; Ludreer-Platje, J. Th. J. *Recueil* **1972**, *91*, 1383–1392.
(11) Reaction of imidazole with formaldehyde at 120–130 °C gives a mixture of hydroxymethylated materials from which none of the 2,4-(5)-bis(hydroxymethyl) isomer was isolated: Alley, P. W. *J. Org. Chem.* **1975**, *40*, 1837–1838.

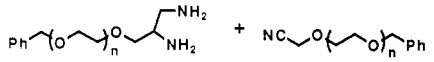
triethylamine in 5% methanol–methylene chloride produced **3** in a 45% yield.[12] The *N,N*-dimethylsulfonamido protecting group was chosen since its bulkiness would favor formation of the 1,2,4-substituted regioisomer. Indeed, a single isomer was obtained and assigned the structure of **3** by analogy with the alkylation regiochemistry seen in 4(5)-substituted imidazoles.[13]

Imidazole **3** met all the requirements of a good cyclization precursor: it was soluble in THF, it had the correct regiochemistry, and it had an easily removable protecting group. However, the overall yield from 1-benzylimidazole was only 3%. This low efficiency, combined with the difficulty in scaling up the formylation of 1-benzylimidazole, led us to search for an alternate route to **3**.

Synthesis of 2 and 3 by Construction of the Imidazole Nucleus. The alternative to functionalizing the imidazole ring by formylation was to form the imidazole itself with the substituents already in place. After exploring a variety of methods, we found that coupling an appropriately substituted diamine with an imino ether to form an imidazoline, followed by oxidation to the imidazole, was most compatible with the required alkoxymethyl substituents. The retrosynthetic analysis for this route is outlined in eq 3.



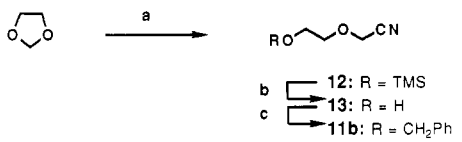
2: n = 0
3: n = 1



(3)

17a: n = 0 **11a**: n = 0
17b: n = 1 **11b**: n = 1

Nitrile **11a** was available by reaction of cyanide with benzylchloromethyl ether.[14] Preparation of **11b** was accomplished in three steps as outlined in eq 4. Opening of 1,3-dioxolane with (trimethylsilyl)cyanide, as described by Olah and co-workers, produced trimethylsilyl protected alcohol **12** in 68% yield.[15] Deprotection with citric acid in methanol[16] produced alcohol **13** (85% yield) and subsequent treatment with sodium hydride and benzyl bromide in dimethylformamide produced the desired nitrile **11b** in 55% yield.

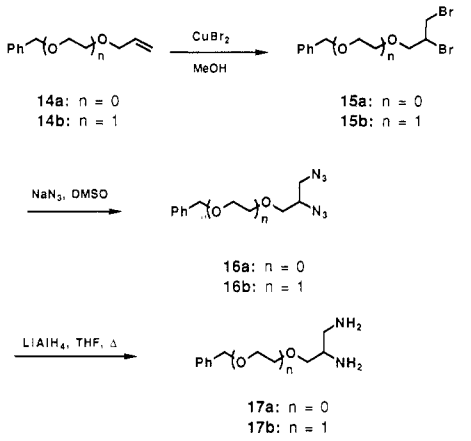


(4)

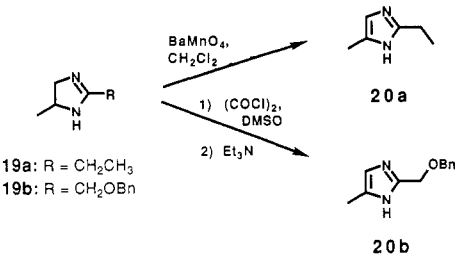
a: TMSCN, ZnI_2; b: citric acid, MeOH; c: $PhCH_2Br$, NaH, DMF

There are numerous methods for the conversion of unactivated alkenes to 1,2-diamines, often through the intermediacy of a 1,2-aminoazide or a 1,2-diazide.[17] The requisite allyl ethers **14a** and **14b** were prepared from the corresponding alcohols and allyl bromide in yields of 83% and 77%, respectively. Treatment of olefin **14** with copper(II) bromide in refluxing methanol[18] produced dibromide **15**, contaminated with less than 10% (^{1}H NMR) of the solvolysis products (Scheme II). Although analytically pure dibromide could be obtained by chromatography on silica gel, this resulted in substantial loss of material, and in most cases the crude product was used directly.

Scheme II



Scheme III



Reaction of dibromide **15** with sodium azide in dimethyl sulfoxide at 65 °C resulted in clean conversion to diazide **16**.[19] The diazide was also unstable to purification and was reduced directly with lithium aluminum hydride in refluxing tetrahydrofuran to give diamine **17**.[19] Conversion of **17b** to the dihydrochloride salt and recrystallization from ethanol–ethyl acetate afforded the analytically pure diamine as a dihydrochloride salt in a 50% overall yield from the allyl ether. Diamine **17a** was particularly air-sensitive (urea formation) but could be purified in 45% overall yield from **14a** as its monohydrogen bromide salt.

Nitrile **11** was converted into its methyl or ethyl imino ether and reacted directly with the corresponding diamine **17** free base.[20] The resultant imidazolines **18a** and **18b** could be isolated as free bases by silica gel chromatography in 72% and 79% yield, respectively. There are numerous reagents for oxidizing imidazolines to imidazoles,[21] including barium manganate, which is used under mild conditions.[22] In our hands none of these methods successfully oxidized 2-[(benzyloxy)methyl]-4-ethylimidazoline

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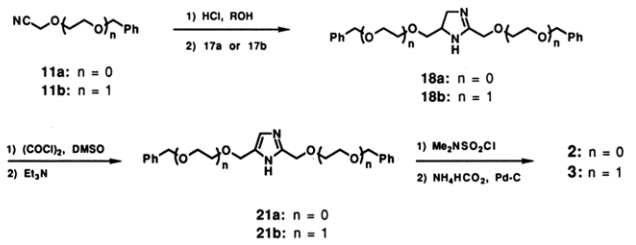
(22) Hughey, J. L., IV; Knapp, S.; Schugar, H. *Synthesis* **1980**, 489–490.

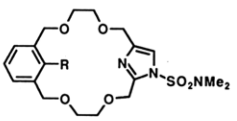
Scheme IV



19b, despite the fact that the latter method successfully converted **19a** to imidazole **20b** in 80% yield (Scheme III). A recent report describing the oxidation of amines to imines using the Swern conditions was successfully applied to our system.[23] Thus, under Swern conditions, imidazoline **19b** was oxidized to imidazole **20b** in 54% yield. Similarly, imidazolines **18a** and **18b** were oxidized to the corresponding imidazoles, **21a** and **21b** in 66% and 60% yield, respectively (Scheme IV). Thus, the Swern conditions provide a mild and particularly efficient method for the conversion of imidazolines to imidazoles.

Protection of the imidazole nitrogen of **21** with *N,N*-dimethylsulfamoyl chloride in benzene gave the corresponding sulfonamides **22a** and **22b** in 86% and 62% yields, respectively. Hydrogenolysis of the benzyl ethers over palladium gave imidazole diols **2** and **3** in 48% and 99% yield, respectively. The overall yield of **3** from allyl ether **14b** was 8%, and importantly, this sequence was easily scaled up allowing multigram quantities of **3** to be synthesized.

Synthesis of Imidazole Macrocycles. Imidazole diol **3** reacted with 1,3-bis(bromomethyl)benzene and sodium hydride in refluxing THF under high dilution conditions (0.01 mM) to give macrocycle **23** (14% yield). Similarly, cyclization of **3** with methyl 2,6-bis(bromomethyl)benzoate produced a low yield of macrocycle **24**. Attempts to optimize the yield of this reaction met with some success. Specifically, it was found that the high temperature usually employed for these cyclizations had a deleterious effect on the yield. Carrying out the cyclization of **3** with methyl 2,6-bis(bromomethyl)benzoate at room temperature afforded macrocylic ester **24** in 61% yield. The (dimethylamino)sulfonyl protecting group in **24** was readily removed with 10% sulfuric acid to give imidazole **4** in 72% yield.[12]



23: R = H
24: R = CO_2Me

X-ray Structure of Imidazole Macrocycle 4·2H$_2$O. The ^{1}H NMR of macrocycle **4** showed the benzylic methylenes to resonate as AB quartets, indicating a nonplanar conformation with hindered inversion of the crown ether. Crystallization from water-saturated ethyl acetate–petroleum ether produced a dihydrate whose structure was determined by X-ray crystallography (Table I).[24] As seen in Figure 1, the ester is in the preferred trans conformation and twisted ca. 61° from planarity with the aromatic ring. The crown likely adopts its nonplanar conformation to avoid transannular contact between the methyl ester and the imidazole moiety.

The bond lengths and angles in the imidazole ring are consistent with a 2,5-tautomeric form.[25] This form allows the imidazole to donate a hydrogen bond to O-28 of the first water molecule, an interaction that is apparent from the close contact between N-23 and O-28 (2.93 Å). Additional close contacts between O-28 and O-15 (Å) and between O-28 and O-29 (Å) indicate this first water molecule to be further bound by donation of a hydrogen bond to a benzylic ether and to the second water molecule. This second water molecule is within 2.94 Å of N-8 of a second molecule of **4**. It is quite clear that one water molecule is nearly in the cavity of the crown while the second water molecule resides in the lattice.

Table I. Details of X-ray Analysis of 4·2H$_2$O

molecular formula	$C_{19}H_{24}H_2O_6 \cdot 2H_2O$
formula/unit cell	4
crystal system	monoclinic
space group	$P2_1/c$
cell parameters	
radiation	Mo λ(Kα) = 0.710 73 Å
a, *b*, *c*, Å	8.021 (3), 27.292 (6), 9.906 (4)
β	106.52°
V, Å^3	2079 (2)
F(000)	880
ρ (calcd), g/cm^3	1.318
μ, cm^{-1}	0.963
approximate size, mm	0.3 × 0.5 × 0.5
intensities measured	3273
intensities processed (R_i = 0.025)	2877
observed reflections ($I > 2.58\sigma(I)$)	1989
R	0.041
R_w	0.051

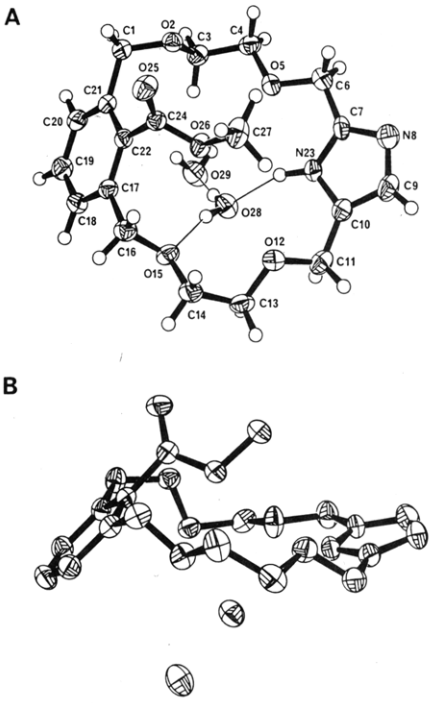


Figure 1. Two ORTEP drawings (A, top view; B, side view with hydrogens removed for clarity) from the X-ray structure of macrocycle **4**-dihydrate. Thermal ellipsoids represent 35% probability contours. See text, Tables I and II, and the paragraph at the end of the paper for full details.

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Table II. Selected Bond Angles, Torsion Angles, and Bond Lengths for 4

Bond Angles, deg			
C(7)–N(8)–C(9)	104.2 (3)	N(8)–C(9)–C(10)	112.0 (3)
C(9)–C(10)–N(23)	103.8 (3)	C(10)–C(7)–N(23)	108.3 (3)
N(8)–C(7)–N(23)	111.8 (3)	C(1)–C(21)–C(22)	121.7 (3)
Torsion Angles, deg			
O(2)–C(1)–C(21)–C(22)	50.1 (4)	O(15)–C(16)–C(17)–C(18)	85.5 (4)
C(21)–C(1)–O(2)–C(3)	71.5 (3)	C(14)–O(15)–C(16)–C(17)	174.0 (3)
C(1)–O(2)–C(3)–C(4)	178.8 (3)	C(13)–C(14)–O(15)–C(16)	164.5 (3)
O(2)–C(3)–C(4)–O(5)	80.8 (3)	O(12)–C(13)–C(14)–O(15)	72.0 (4)
C(3)–C(4)–O(5)–C(6)	178.6 (3)	C(11)–O(12)–C(13)–C(14)	171.3 (3)
C(4)–O(5)–C(6)–C(7)	170.1 (3)	C(10)–C(11)–O(12)–C(13)	162.9 (3)
O(5)–C(6)–C(7)–N(23)	172.2 (3)	O(12)–C(11)–C(10)–C(9)	130.0 (4)

Bond Lengths, Å					
C(7)–N(8)	1.314 (4)	N(8)–C(9)	1.373 (5)	C(9)–C(10)	1.367 (5)
C(10)–N(23)	1.370 (4)	C(7)–N(23)	1.352 (4)	C(22)–C(24)	1.501 (3)

Conclusion

Two syntheses of 1-[(dimethylamino)sulfonyl]-2,4-bis-[(2-hydroxyethoxy)methyl]imidazole (**3**) have been reported. Although the first synthesis is shorter, it is less efficient and difficult to scale up as a result of the low yield and polar mixture of products obtained in the hydroxymethylation of 1-benzylimidazole. The second route to **3** involves a particularly mild and efficient synthesis of the imidazole nucleus, which should have general applicability.

Diol **3** serves as a convenient precursor to imidazole-containing crown ethers. The X-ray structure of the first imidazole crown ether complex (**4**·$2H_2O$) shows that the imidazole moiety acts as a hydrogen-bond donor in complexation of a neutral water molecule. In this respect, the imidazole group is unique in its ability to act as either a donor or an acceptor. It will be interesting if other systems reveal this "chameleon-like" property.

Experimental Section

General. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2), dimethyl sulfoxide (DMSO), and triethylamine were distilled from calcium hydride. Thionyl chloride ($SOCl_2$) was fractionally distilled. Dimethylformamide (DMF) was distilled from magnesium sulfate ($MgSO_4$) under reduced pressure. Ethylene glycol was dried over magnesium sulfate, refluxed with sodium and then distilled. Methanol and ethanol were distilled from their magnesium alkoxides under nitrogen. 2,6-Dimethylbenzoic acid was prepared by the procedure of G. Berger and S. C. J. Olivier[26] and converted into methyl 2,6-bis-(bromomethyl)benzoate according to the literature procedure.[27] Benzyloxyethanol could be obtained from Aldrich or prepared by reduction of 1-(phenylmethoxy)ethanoic acid[28] with diborane–THF complex.[29] All other solvents and reagents were of reagent grade quality and used without further purification. Analytical TLC was performed on 0.2 mm silica 60 coated plastic sheets (EM Science) with F-254 indicator. Flash chromatography was performed on Merck 40–63 μm silica gel as described by Still.[30] Temperatures associated with Kugelrohr distillations are oven temperatures. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected.

^1H NMR and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer and run in chloroform-*d* unless otherwise stated. Chemical shifts are reported in parts per million (ppm) with TMS as an internal reference, and coupling constants are reported in hertz (Hz). Spectra in methanol-d_4 were referenced to the residual protiosolvent peak. The deficit of resonances in some ^{13}C spectra was assumed to result from coincident peaks as the signal-to-noise ratio in each case was high. Mass spectra were obtained on Varian MAT CH-5 and 731 spectrometers. Elemental analyses were performed at the University of Illinois School of Chemical Sciences. The X-ray analysis data was collected on an Enraf-Nonius CAD4 automated κ-axis diffractometer and analyzed by using SHELXS-86.

1-Benzylimidazole-2,5-dimethanol (5). A mixture of 30 g (63 mmol) of 1-benzylimidazole, 16 mL of glacial acetic acid, 21 g of sodium acetate, and 120 mL of 37% formaldehyde was stirred in an Ehrlenmeyer flask until the solution became clear (ca. 20 min). The solution was transferred to a sealed tube and submerged in an oil bath (liquid line 1 in. below oil line), heated at 140 °C, for 12 h. The reaction mixture was concentrated under reduced pressure, 20 mL of water was added, and the solution was concentrated again. This procedure was repeated three times. The resultant thick, yellow oil was made basic with 10 M sodium hydroxide and extracted three times with 500 mL of 10% 2-propanol–chloroform. The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a yellow viscous oil. Flash chromatography (7.5% methanol–CH_2Cl_2) yielded an oil, which upon standing in CH_2Cl_2 gave 8.0 g (20%) of **5** as a white powder: mp 125–126 °C; IR (KBr) 3600–3200, 1495, 1473, 1452 cm^{-1}; ^1H NMR (CD_3OD) δ 7.32–7.22 (m, 3 H, ArH), 7.09–7.07 (m, 2 H, ArH), 6.90 (s, 1 H, H-4), 5.41 (s, 2 H, CH_2N-1), 4.52 (s, 2 H, CH_2-2), 4.39 (s, 2 H, CH_2-5); ^{13}C NMR (CD_3OD) δ 149.82, 138.16, 134.36, 129.81, 128.67, 127.43, 126.86, 57.22, 54.58, 48.1; mass spectrum (EI, 70 eV), *m/z* (relative intensity) 218 (M^+, 18), 109 (10), 91 (100); exact mass calcd for $C_{12}H_{14}N_2O_2$ *m/z* 218.105 52, found *m/z* 218.106 28. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.05; H, 6.45; N, 12.77.

1-Benzylimidazole-2,4,5-trimethanol (6): mp 133–135 °C; ^1H NMR (CD_3OD) δ 7.30 (m, 3 H, ArH), 7.10 (m, 2 H, ArH), 5.45 (s, 2 H, CH_2N-1), 4.56 (s, 2 H, CH_2-2), 4.53 (s, 2 H, CH_2-4), 4.50 (s, 2 H, CH_2-5); ^{13}C NMR (CD_3OD) δ 148.69, 138.47, 138.18, 131.26, 129.80, 128.66, 127.45, 57.27, 57.15, 53.17, 48.23. Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.49; N, 11.28. Found: C, 62.81; H, 6.44; N, 11.26.

1-Benzyl-2,5-bis(chloromethyl)imidazole Hydrochloride (7). To 60 mL (0.82 mol) of thionyl chloride was slowly added 2.45 g (11 mmol) of diol **5**. After the addition was complete, the reaction mixture was stirred for 1 h under a drying tube. The mixture was poured over 250 g of ice while the temperature of the resulting solution was kept below 20 °C. The mixture was extracted three times with 300 mL of 10% 2-propanol–chloroform. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to yield 2.3 g (72%) of **7** as a slightly yellow solid: mp 165 °C dec; IR ($CHCl_3$) 3015, 1522, 1221, 1217, 1209 cm^{-1}; ^1H NMR (CD_3OD) δ 7.88 (s, 1 H, H-4), 7.41 (m, 3 H, ArH), 7.31 (m, 2 H, ArH), 5.69 (s, 2 H, CH_2N-1), 5.06 (s, 2 H, CH_2-2), 4.71 (s, 2 H, CH_2-5); ^{13}C NMR (CD_3OD) δ 145.30, 133.87, 133.42, 130.12, 129.72, 127.77, 121.14, 50.10, 33.80, 32.73; mass spectrum (EI, 70 eV), *m/z* (relative intensity) 256 (3), 254 (M^+, 6), 219 (20), 91 (100); exact mass calcd for $C_{12}H_{12}Cl_2N_2$ *m/z* 254.037 75, found *m/z* 254.037 74. Anal. Calcd for

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$C_{12}H_{12}Cl_2N_2$·HCl: C, 49.42; H, 4.49; N, 9.61; Cl, 36.47. Found: C, 49.37; H, 4.64; N, 9.57; Cl, 36.28.

1-Benzyl-2,5-bis[(2-hydroxyethoxy)methyl]imidazole (8). To a stirred solution of 1.06 g (3.64 mmol) dichloride **7** in 25 mL of ethylene glycol, at 0 °C, was added 300 mg (12.5 mmol) of sodium hydride. The reaction mixture was warmed to room temperature, and after 12 h, it was quenched at 0 °C with 1–2 mL of water. The majority of the ethylene glycol was removed by Kugelrohr distillation at 45–50 °C (1 mm), and the remaining 1–2 mL of liquid was partitioned between 25 mL of a 1% aqueous solution of sodium bicarbonate and 25 mL of chloroform. The aqueous layer was extracted twice with 25 mL of chloroform. The combined chloroform layers were extracted with 50 mL of a 1% aqueous solution of sodium bicarbonate. The aqueous layers were combined and extracted three times with 200 mL of 10% 2-propanol–chloroform. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield an oily, orange solid. Flash chromatography (7.5% methanol–CH_2Cl_2) yielded 735 mg (66%) of **8** as a clear oil: IR (CCl_4) 3680–3343, 3028, 3015, 2928, 1709, 1603, 1454, 1350, 1221, 1217, 1209, 1103, 1055 cm^{-1}; ^1H NMR δ 7.28 (m, 3 H, ArH), 6.99 (m, 3 H, ArH, H-4), 5.31 (s, 2 H, CH_2N-1), 4.52 (s, 2 H, CH_2-2), 4.36 (s, 2 H, CH_2-5), 3.50 (m, 8 H, OCH_2CH_2O), 3.20 (br s, 2 H, OH); ^{13}C NMR δ 146.53, 136.51, 129.43, 128.76, 128.34, 127.69, 125.85, 72.09, 71.04, 64.93, 62.38, 61.41, 61.39, 47.13; mass spectrum (EI, 70 eV), m/z (relative intensity) 306 (M^+, 5), 261 (34), 246 (87), 91 (100); exact mass calcd for $C_{16}H_{22}N_2O_4$ m/z 306.157 94, found m/z 306.157 87.

2,4(5)-Bis[(2-hydroxyethoxy)methyl]imidazole (10). To a solution of 730 mg (2.39 mmol) of diol **8** in 70 mL of 95% ethanol was added 100 mg of 5% palladium on charcoal, and the solution was placed under hydrogen at 1 atm. After 2 h no observable reaction had occurred (TLC), so the catalyst was filtered off, fresh catalyst was added with 3–4 drops of concentrated sulfuric acid, and the reaction was placed under hydrogen at 1 atmosphere. After 9 h, the catalyst was filtered off, and the ethanol was removed under reduced pressure. The resulting oil was dissolved in 5 mL of water and made basic with solid potassium carbonate. The basic solution was extracted three times with 5 mL of 10% 2-propanol–chloroform. The aqueous layer was concentrated under reduced pressure to yield a white solid, which was dissolved in methanol, mixed with silica gel, and concentrated under reduced pressure. The silica gel was washed with 100 mL of 15% methanol–CH_2Cl_2. Concentration under reduced pressure yielded 451 mg (87%) of **10** as a light oil: ^1H NMR (CD_3OD) δ 6.95 (s, 1 H, H-4), 4.50 (s, 2 H, CH_2-2), 4.41 (s, 2 H, CH_2-5), 3.60 (m, 4 H, OCH_2CH_2O), 3.50 (m, 4 H, OCH_2CH_2O); ^{13}C NMR (CD_3OD) δ 147.01, 136.00, 120.26, 73.16, 72.36, 66.61, 66.05, 62.11, 62.01; mass spectrum (EI, 70 eV), m/z (relative intensity) 216 (M^+, 1), 156 (56), 155 (30), 109 (24), 94 (100); exact mass calcd for $C_9H_{16}O_4N_2$ m/z 216.111 01, found m/z 216.111 63.

1-[(*N*,*N*-Dimethylamino)sulfonyl]-2,4-bis[(2-hydroxyethoxy)methyl]imidazole (3). Method A. To a solution of 200 mg (0.93 mmol) of diol **10** in 6 mL of 5% methanol–CH_2Cl_2, under nitrogen, was added 310 μL (2.22 mmol) of triethylamine followed by 238 μL (2.22 mmol) of dimethylsulfamoyl chloride. After 12 h, the solvent was removed under reduced pressure, and the remaining solid was dissolved in 5 mL of water and made basic with solid potassium carbonate. The water was removed under reduced pressure, and the remaining solid was slurried in CH_2Cl_2 and filtered. The filtrate was evaporated under reduced pressure and purified by flash chromatography (7.5% methanol–CH_2Cl_2) to afford 140 mg (45%) of **3** as a clear oil: IR (CCl_4) 3746–3327, 3036, 3011, 2928, 1578, 1458, 1421, 1394, 1215, 1170, 1155, 1113 cm^{-1}; ^1H NMR δ 7.18 (s, 1 H, H-5), 4.78 (s, 2 H, CH_2-2), 4.46 (s, 2 H, CH_2-5), 3.76–3.64 (m, 8 H, OCH_2CH_2O), 2.92 (s, 6 H, SO_2NMe_2); ^{13}C NMR δ 146.47, 137.91, 117.46, 73.38, 72.61, 65.74, 65.40, 61.63, 61.59, 38.24; mass spectrum (FI, 125 °C), m/z 324 ($M^+ + H$), 323 (M^+). Anal. Calcd for $C_{11}H_{21}N_3O_6S$: C, 40.85; H, 6.55; N, 13.00; S, 9.89. Found: C, 40.27; H, 6.32; N, 12.85; S, 9.52.

5-(Trimethylsiloxy)-3-oxapentanenitrile (12). Use of the procedure of Olah[15] (16 h, room temperature) provided after distillation 5.94 g (68%) of **12** as a clear liquid: bp 40–45 °C (0.4 mm); IR (CCl_4) 2959, 2874, 1429, 1252, 1099, 1045 cm^{-1}; ^1H NMR δ 4.32 (s, 2 H, H-2), 3.77 (m, 2 H, H-4), 3.67 (m, 2 H, H-5), 0.13 (s, 9 H, $SiMe_3$). Anal. Calcd for $C_7H_{15}NO_2Si$: C, 48.52; H, 8.73; N, 8.08. Found: C, 48.29; H, 8.45; N, 8.15.

5-Hydroxy-3-oxapentanenitrile (13). To a stirred solution of 480 mg (2.2 mmol) of citric acid in 25 mL of methanol was added 2.5 g (14 mmol) of **12**. After 30 min the solution was carefully neutralized with solid potassium carbonate at 0 °C, and the volume was reduced in vacuo by ca. 50%. To this solution was added 20 mL of brine, and the mixture was washed three times with 40 mL of 10% 2-propanol–chloroform. The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to yield a slightly yellow oil. Kugelrohr distillation gave 1.04 g (71%) of **13** as a colorless oil: bp 55 °C (0.1 mm); IR (CCl_4) 3480, 2932, 2878, 2253, 1439, 1064 cm^{-1}; ^1H NMR δ 4.20 (s, 2 H, H-2), 3.64 (m, 2 H, H-4), 3.58 (m, 2 H, H-5), 2.10 (br s, 1 H, D_2O exch, OH); ^{13}C NMR δ 115.90, 72.61, 60.89, 56.34. Anal. Calcd for $C_4H_7O_2N$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.63; H, 7.03; N, 13.75.

5-(Benzyloxy)-3-oxapentanenitrile (11b). To a stirred slurry of 71 mg (3.0 mmol) of sodium hydride in 2 mL of DMF at 0 °C was slowly added 250 mg (2.5 mmol) of **13**. The solution was warmed to room temperature for 20 min and recooled to 0 °C, and 508 mg (3.0 mmol) of benzyl bromide was added slowly. The reaction was stirred for 6 h, quenched with several drops water, and partitioned between 10 mL of 50% brine–water and 10 mL of petroleum ether. The aqueous layer was washed three times with 10 mL of petroleum ether, and the organic layers were combined, dried over $MgSO_4$, and evaporated to give a yellow oil. Flash chromatography (10% ethyl acetate–petroleum ether) or distillation with a Kugelrohr apparatus gave 258 mg (55%) of **11b** as a clear oil: bp 100 °C (0.25 mm); IR (CCl_4) 3363, 3089, 3067, 2861, 1578, 1548, 1496, 1453, 1438, 1382, 1107, 1053, 1028 cm^{-1}; ^1H NMR δ 7.36–7.32 (m, 5 H, ArH), 4.57 (s, 2 H, H-2), 4.33 (s, 2 H, CH_2O-5), 3.77 (m, 2 H, H-4), 3.67 (m, 2 H, H-5); ^{13}C NMR δ 137.58, 128.26, 127.59, 127.56, 115.88, 73.14, 70.53, 68.79, 56.44; exact mass calcd for $C_{11}H_{13}NO_2$ m/z 191.09462, found m/z 191.09452. Anal. Calcd: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.24; H, 6.64; N, 7.13.

1-(Benzyloxy)prop-2-ene (14a). To a stirred slurry of 4.89 g (0.2 mol) of sodium hydride in 100 mL of dry DMF was added dropwise at room temperature 20 g (0.18 mol) of benzyl alcohol. Foaming occurred, and the slurry was quickly dissolved, resulting in a brown solution, which was stirred until gas evolution had ceased. To the green-brown suspension was added 6.15 g (37 mmol) of dry potassium iodide, followed by the dropwise addition of a solution of 27.9 g (0.2 mmol) of freshly distilled allyl bromide in 20 mL of dry DMF. The reaction mixture was stirred for 16 h, at room temperature, under nitrogen, resulting in a green-yellow solid mass. The mixture was dissolved in 1 L of ice-cold water, and 50 g of sodium chloride was added. The mixture was extracted four times with 500 mL of ether. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Distillation provided 22.73 g (83%) of **14a** as a clear, colorless liquid: bp 50 °C (1 mm) [lit.[31] bp 204–205 °C (760 mm)]; IR (CCl_4) 3030, 2910, 1495, 1460, 1380, 1200, 1080, 1025 cm^{-1}; ^1H NMR δ 7.33 (m, 5 H, ArH), 5.94 (m, 1 H, H-2), 5.30 (dd, 1 H, $J_{1,2}$ = 5.8, $J_{1,1}$ = 1.1, H-1), 5.20 (dd, 1 H, $J_{1,2}$ = 9.4, $J_{1,1}$ = 1.1, H-1), 4.52 (s, 2 H, CH_2O-3), 4.02 (d, 2 H, $J_{2,3}$ = 5.8, H-3); ^{13}C NMR δ 138.26, 134.69, 127.70, 127.56, 126.93, 117.10, 72.08, 71.11; mass spectrum (FI, 100 °C), m/z 148 (M^+); (EI, 70 eV) m/z (relative intensity) 148 (M^+, 1) 91 (36), 79 (20), 42 (100).

6-(Benzyloxy)-4-oxahex-1-ene (14b). Use of the procedure described for **14a** provided upon distillation 4.93 g (77%) of **14b** as a clear colorless liquid: bp 89 °C (1 mm); IR (CCl_4) 3065, 3034, 2860, 1496, 1454, 1354, 1100 cm^{-1}; ^1H NMR δ 7.35 (m, 5 H, ArH), 5.92 (m, 1 H, H-2), 5.28 (m, 1 H, H-1, trans), 5.18 (m, 1 H, H-1, cis), 4.57 (s, 2 H, CH_2O-6), 4.03 (m, 2 H, H-3), 3.62 (s, 4 H, H-5, H-6); ^{13}C NMR δ 138.15, 134.66, 128.28, 127.67, 127.50, 127.03, 117.03, 73.20, 72.20, 69.42, 69.36; mass spectrum (FI, 100 °C), m/z 192 (M^+); (EI, 70 eV) m/z (relative intensity) 192 (M^+, 3), 151 (22), 107 (43), 91 (100), 41 (81). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.52; H, 8.33.

1-(Benzyloxy)-2,3-dibromopropane (15a). A solution of 5.77 g (39 mmol) of **14a** in 10 mL of dry methanol was added to a

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stirred solution of 19.6 g (87.8 mmole) of copper(II) bromide in 40 mL of dry methanol at 25 °C, under nitrogen. The reaction mixture was heated to reflux for 24 h and allowed to cool to room temperature. The reaction mixture was filtered; the solid was washed two times with 10 mL of dry methanol. The filtrate was evaporated under reduced pressure, and the resulting residue was partitoned between 100 mL of petroleum ether and 100 mL of water. The two-phase mixture was filtered, and the solid was washed two times with 25 mL of water and two times with 50 mL of petroleum ether. The aqueous layer from the filtrate was washed three times with 100 mL of petroleum ether. The combined organic extracts were washed with 200 mL of a 5% aqueous solution of sodium bicarbonate and 200 mL of water, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to provide 9.47 g (79%) of crude **15a** as a clear colorless liquid. This material was of sufficient purity for further manipulations. An analytically pure sample was obtained by flash chromatography (CH_2Cl_2–petroleum ether, 1:1): IR (CCl_4) 3060, 3030, 2910, 2870, 1498, 1456, 1362, 1235, 1210, 1100, 1025 cm^{-1}; ^1H NMR δ 7.35 (m, 5 H, ArH), 4.61 (s, 2 H, CH_2O-1), 4.26 (m, 1 H, H-2), 3.84 (m, 4 H, H-2, H-3); ^{13}C NMR δ 137.58, 128.55, 128.00, 127.97, 76.67, 73.50, 49.17, 33.17; mass spectrum (EI, 70 eV), m/z (relative intensity) 310 (M^+ + 4, 12), 308 (M^+ + 2, 25), 306 (M^+, 13), 172 (60), 170 (64), 121 (86), 91 (100), 79 (97). Anal. Calcd for $C_{10}H_{12}OBr_2$: C, 38.96; H, 3.93; Br, 51.88. Found: C, 38.80; H, 3.99; Br, 51.77.

1-(Benzyloxy)-5,6-dibromo-3-oxahexane (15b). Use of the procedure described for **15a** provided 1.45 g (76%) of **15b** as a clear colorless liquid. The product was of acceptable purity for use without further purification. An analytically pure sample was obtained by flash chromatography (1:1 CH_2Cl_2–petroleum ether): IR (CCl_4) 3030, 2901, 1495, 1356 cm^{-1}; ^1H NMR δ 7.34 (m, 5 H, ArH), 4.58 (s, 2 H, CH_2O-1), 4.26 (m, 1 H, H-5), 3.90 (m, 2 H, H-4), 3.82 (m, 2 H, H-6), 3.73 (m, 2 H, H-1), 3.65 (m, 2 H, H-2); ^{13}C NMR δ 138.05, 128.32, 127.64, 127.59, 73.18, 72.24, 70.95, 69.34, 49.11, 33.24; mass spectrum (EI, 70 eV), m/z (relative intensity) 352 (M^+ + 2, 4), 350 (M^+, 2) 107 (48), 91 (100). Anal. Calcd for $C_{12}H_{16}O_2Br_2$: C, 40.94; H, 4.58; Br, 45.39. Found: C, 41.08; H, 4.56; Br, 45.24.

1-(Benzyloxy)-2,3-diazidopropane (16a). A mixture of 0.5 g (1.62 mmol) of **15a**, 0.45 g (6.82 mmol) of sodium azide, and 10 mL of dry DMSO was heated at 65–70 °C for 20 h under nitrogen. After the solution was cooled to room temperature, 20 mL of water was added, and the mixture was extracted four times with 30 mL of petroleum ether. The organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Drying under high vacuum for 16 h provided 0.33 g (88%) of **16a**, which was judged to be >90% pure by ^1H NMR: IR (CCl_4) 3065, 2864, 2108, 1496, 1103, 1028 cm^{-1}; ^1H NMR δ 7.33 (m, 5 H, ArH), 4.56 (s, 2 H, CH_2O-1), 3.67 (m, 1 H, H-2), 3.60 (m, 2 H, H-1), 3.41 (m, 2 H, H-3); ^{13}C NMR δ 137.25, 128.48, 127.94, 127.64, 73.50, 69.59, 60.48, 51.61.

1-(Benzyloxy)-5,6-diazido-3-oxahexane (16b). Use of the procedure described for **16a** provided 0.45 g (88%) of **16b** as a clear yellow liquid, which was judged to be >90% pure by ^1H NMR: IR (CCl_4) 3065, 2866, 2100, 1496, 1103, 1028 cm^{-1}; ^1H NMR δ 7.33 (m, 5 H, ArH), 4.56 (s, 2 H, CH_2O-1), 3.70–3.59 (m, 7 H, H-1, H-2, H-4, H-5), 3.46–3.32 (m, 2 H, H-6); ^{13}C NMR δ 138.00, 129.59, 128.35, 127.65, 73.25, 70.98, 70.85, 69.30, 60.43, 51.60. Anal. Calcd for $C_{12}H_{16}N_6O_2$: C, 52.17; H, 5.79; N, 30.43. Found: C, 52.84; H, 5.91; N, 28.21.

3-(Benzyloxy)propane-1,2-diamine (17a). A solution of 10 g (43 mmol) of **16a** in 75 mL of dry THF was added slowly to a stirred slurry of 6 g (160 mmol) of lithium aluminum hydride in 75 mL of THF at 0 °C. The reaction was heated to reflux for 12 h, cooled to 0 °C, and successively quenched with 6 mL of water, 6 mL of a 15% aqueous solution of sodium hydroxide, and 20 mL of water. The solids were filtered, and the filtrate was evaporated to an oil, which was partitioned between 100 mL of brine and 100 mL of 10% 2-propanol–chloroform. The aqueous layer was washed three times with 100 mL of 10% 2-propanol–chloroform. The organic layers were combined, dried over Na_2SO_4, and evaporated at reduced pressure. The resulting oil was dissolved in 20 mL of ethanol and 100 mL of dry ether, and a stream of dry hydrogen bromide was passed through the solution at 0 °C for 15 min. A white powdery solid precipitated. The solution was stirred at 0 °C for 1 h, and the solid was collected to afford 4.6 g (45%) of **17a** as a monohydrogen bromide salt: mp 93–94 °C; IR (free base, CCl_4) 3427, 3080, 3051, 2982, 1597, 1037, 1018 cm^{-1}; ^1H NMR (CD_3OD) δ 7.29–7.22 (m, 5 H, ArH), 5.44 (s, 5 H, NH), 4.44 (s, 2 H, CH_2O-3), 3.43 (s, 3 H, H-2, H-3), 3.05 (m, 2 H, H-1); ^{13}C NMR (CD_3OD) δ 137.52, 128.43, 127.87, 127.79, 73.25, 72.01, 49.43, 42.30. Anal. Calcd for $C_{10}H_{16}N_2O$·HBr: C, 45.99; H, 6.56; N, 10.73; Br, 30.60. Found: C, 47.26; H, 6.73; N, 10.99; Br, 30.65.

6-(Benzyloxy)-4-oxahexane-1,2-diamine (17b). By use of the procedure described for **17a**, an oil was obtained, which was dissolved in 20 mL of ethanol, and 5 mL of concentrated HCl was added at 0 °C. The mixture was evaporated to dryness and dissolved in 10 mL of ethanol, and 50 mL of ethyl ether was added. The white powder was filtered off and recrystallized from ethanol–ethyl acetate to yield 7.10 g (60%) of **17b**·2HCl as a white powdery solid: mp 140–141 °C dec; IR (free base, CCl_4) 3408, 3049, 2887, 1772, 1734, 1624, 1610, 1176, 1034 cm^{-1}; ^1H NMR (CD_3OD) δ 7.35–7.26 (m, 5 H, ArH), 4.55 (s, 2 H, CH_2O-6), 3.81–3.70 (m, 7 H, H-1, H-2, H-5, H-6), 3.29 (m, 2 H, H-4); ^{13}C NMR (CD_3OD) δ 138.71, 129.23, 128.95, 128.72, 74.05, 71.33, 70.16, 68.55, 49.71, 39.50; mass spectrum (FD, 9 ma), m/z 225 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{20}N_2O_2$·2HCl: C, 48.49; H, 7.46; N, 9.43. Found: C, 48.49; H, 7.41; N, 9.46.

2-Ethyl-4(5)-methyl-2-imidazoline (19a). A stream of dry hydrogen chloride was passed through a solution of 20 g (0.36 mol) of propionyl nitrile in 25 g (0.54 mol) of dry ethanol and 200 mL of dry ether under a fast flow of nitrogen at 0 °C. After 4 h, a white precipitate formed and most of the solvent had evaporated off. Excess solvent and reactants were removed by evaporation under reduced pressure to leave the crude imino ether hydrochloride as a white hygroscopic solid. The residue was dissolved in 100 mL of dry ethanol and cooled to 0 °C under dry nitrogen, and a solution of 26.91 g (0.36 mol) of 1,2-diaminopropane in 50 mL of dry ethanol was added dropwise over 1 h. A white solid rapidly precipitated out of solution during the course of the addition. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The suspension was filtered, and the filtrate was evaporated under reduced pressure to give a white solid. The solid was dissolved in enough 1 M aqueous sodium hydroxide to ensure that the solution was basic (pH 14). The solution was washed four times with 100 mL of CH_2Cl_2, and the combined organic extracts were washed with 200 mL of brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. Distillation provided 20.32 g (50%) of **19a** as a clear colorless liquid: bp 75 °C (1 mm); IR (CCl_4) 3180, 2966, 2860, 1612, 1493, 1010 cm^{-1}; ^1H NMR δ 4.27 (br s, 1 H, D_2O exch, NH), 3.82 (m, 1 H, H-5), 3.69 (t, 1 H, $J_{4,4}$ = 10.4, $J_{4,5}$ = 10.4, H_a-4), 3.15 (dd, 1 H, $J_{4,4}$ = 10.4, $J_{4,5}$ = 7.5, H_b-4), 2.23 (q, 2 H, J = 7.6, CH_2-2), 1.20 (t, 3 H, J = 7.6, CH_3CH_2-2), 1.17 (d, 3 H, J = 6.0, CH_3-5); ^{13}C NMR δ 167.52, 57.15, 56.26, 22.46, 21.59, 10.69; mass spectrum (FI, 100 °C), m/z 112 (M^+); (EI, 70 eV) m/z (relative intensity) 113 (M^+ + 1, 6), 112 (M^+, 100), 97 (83). Anal. Calcd for $C_6H_{12}N_2$: C, 64.24; H, 10.78; N, 24.97. Found: C, 63.98; H, 10.31; N, 24.77.

2-[(Benzyloxy)methyl]-4(5)-methyl-2-imidazoline (19b). Use of the procedure described for **19a** provided 6.70 g (70%) of **19b** as a clear colorless liquid: bp 92 °C (0.1 mm); IR (CCl_4) 3250, 3032, 2965, 2864, 1620, 1496, 1101, 1028 cm^{-1}; ^1H NMR δ 7.32 (m, 5 H, ArH), 5.02 (br s, 1 H, D_2O exch, NH), 4.50 (s, 2 H, $ArCH_2$), 4.15 (s, 2 H, CH_2-2), 3.93 (m, 1 H, H-5), 3.68 (t, 1 H, $J_{4,4}$ = 10.4, $J_{4,5}$ = 10.4, H_a-4), 3.13 (dd, 1 H, $J_{4,4}$ = 10.4, $J_{4,5}$ = 7.8, H_b-4), 1.17 (d, 3 H, J = 6.5, CH_3-5); ^{13}C NMR (CD_3OD) 168.83, 137.50, 129.36, 129.27, 129.02, 74.57, 63.00, 54.42, 52.17, 20.53; mass spectrum (FI, 100 °C), m/z 204 (M^+); (EI, 70 eV) m/z (relative intensity) 204 (M^+, 1), 98 (100), 91 (21). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.61; H, 7.81; N, 13.71.

2,4(5)-Bis[(benzyloxy)methyl]-2-imidazoline (18a). Use of the procedure described for **19a** except substituting dry methanol for ethanol and using the free base of **17a** afforded, after flash chromatography (Et_2NH–MeOH–CH_2Cl_2, 1:5:94), 3.08 g (89%) of **18a** as a clear oil: ^1H NMR δ 7.30 (m, 10 H, ArH), 4.54 (m, 4 H, $ArCH_2$), 4.17 (s, 2 H, 2-CH_2), 4.09 (m, 1 H, H-5), 3.70–3.38 (m, 4 H, H-4, CH_2-5); ^{13}C NMR δ 164.74, 137.88, 137.09, 128.35, 128.26, 127.85, 127.79, 127.58, 73.17, 73.08, 72.94, 66.26 (2 missing); mass spectrum (EI, 70 eV), m/z (relative intensity) 310 (M^+, 1), 150 (22), 132 (75), 91 (100); exact mass calcd for $C_{19}H_{22}N_2O_2$ m/z

310.16812, found m/z 310.16837.

2,4(5)-Bis[[2-(benzyloxy)ethoxy]methyl]-2-imidazoline (18b). Use of the procedure described for **19a** except substituting dry methanol for ethanol and using the free base of **17b** afforded, after flash chromatography (Et_2NH–MeOH–CH_2Cl_2, 1:7:92), 1.96 g (79%) of **18b** as a clear oil: IR (CCl_4) 3373, 3090, 3067, 2864, 1648, 1633, 1103, 1028 cm^{-1}; ^1H NMR (CD_3OD) δ 7.23–7.14 (m, 10 H, ArH), 4.41 (s, 4 H, $ArCH_2$), 4.02 (s, 2 H, CH_2-2), 3.89 (m, 1 H, H-5), 3.52 (m, 8 H, OCH_2CH_2O), 3.36–3.20 (m, 4 H, H-4, CH_2-5); ^{13}C NMR δ 165.33, 137.91, 137.63, 128.50, 127.90, 127.84, 127.77, 127.26, 127.21, 73.87, 73.14, 73.07, 72.98, 70.45, 69.05, 68.98, 66.92, 60.01, 52.77; mass spectrum (FD, 0 ma), m/z (relative intensity) 399 (M^+ + 1, 100); exact mass calcd for $C_{23}H_{30}N_2O_4$ m/z 398.22054, found m/z 398.22108.

2-[(Benzyloxy)methyl]-4(5)-methylimidazole (20b). To a stirred solution of 1.40 g (11 mmol) of oxalyl chloride in 12 mL of CH_2Cl_2, at −70 °C, under nitrogen, was added over 5 min 1.72 g (22 mmol) of dry DMSO in 3 mL of CH_2Cl_2. The mixture was stirred at −70 °C for 5 min. A solution of 2.83 g (13.9 mmol) of **19b** in 3 mL of CH_2Cl_2 was added over 5 min, maintaining the temperature below −60 °C, followed by 5.08 g (50.2 mmol) of dry triethylamine. The reaction mixture was stirred for 1 h. The cooling bath was removed, allowing the mixture to warm to room temperature. The reaction was quenched by addition of 20 mL of water. The aqueous layer was separated and washed four times with 50 mL of CH_2Cl_2. The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford a yellow oil. Purification by flash chromatography (7.5% methanol–CH_2Cl_2) provided 1.69 g of product as a yellow oil, which crystallized as yellow plates on standing. Recrystallization from 75% methanol–hexane provided 1.59 g (57%) of **20b** as white plates: mp 123 °C; IR (CCl_4) 3265, 3065, 3020, 2985, 1616, 1101, 1020 cm^{-1}; ^1H NMR δ 8.88 (br s, 1 H, D_2O exch, H-1), 7.32 (m, 5 H, ArH), 6.67 (s, 1 H, H-5), 4.58 (s, 2 H, CH_2-2), 4.52 (s, 2 H, $ArCH_2$), 2.21 (s, 3 H, CH_3-5); mass spectrum (FI, 100 °C), m/z (relative intensity) 202 (M^+, 100); (EI, 70 eV) m/z (relative intensity) 202 (M^+, 3), 96 (100), 91 (52). Anal. Calcd for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.28; H, 6.98; N, 14.02.

2,4(5)-Bis[(benzyloxy)methyl]imidazole (21a). The crude product obtained using the procedure described for **20b** was purified by flash chromatography (20% petroleum ether–ethyl acetate) to afford 1.79 g (72%) of **21a** as a clear oil: IR (CCl_4) 3462, 3067, 3034, 2860, 1583, 1028, 1005 cm^{-1}; ^1H NMR (500 MHz) δ 7.31–7.25 (m, 10 H, ArH), 6.90 (s, 1 H, H-5), 4.57 (s, 2 H, CH_2-2), 4.52 (s, 2 H, $ArCH_2$), 4.48 (s, 2 H, $ArCH_2$), 4.47 (s, 2 H, CH_2-4); ^{13}C NMR (125 MHz) δ 145.44, 137.95, 137.31, 128.41, 128.31, 128.24, 127.81, 127.50, 72.60, 71.89, 65.39 (4 missing); mass spectrum (EI, 70 eV), m/z (relative intensity) 308 (M^+, 1), 202 (32), 94 (93), 91 (100), 59 (27); exact mass calcd for $C_{19}H_{20}N_2O_2$ m/z 308.15248, found m/z 308.15338.

2,4(5)-Bis[[2-(benzyloxy)ethoxy]methyl]imidazole (21b). The crude product obtained using the procedure described for **20b** was purified by flash chromatography (5% methanol–CH_2Cl_2) to afford 1.13 g (60%) of **21b** as a clear oil: IR (CCl_4) 3464–3294, 3067, 3032, 2864, 1684, 1653, 1053, 1028 cm^{-1}; ^1H NMR δ 9.90 (bs, 1 H, D_2O exch, NH), 7.31–7.27 (m, 10 H, ArH), 6.78 (s, 1 H, H-5), 4.62 (s, 2 H, CH_2-2), 4.52 (s, 4 H, $ArCH_2$), 4.45 (s, 2 H, CH_2-4), 3.70–3.63 (m, 8 H, OCH_2CH_2O); ^{13}C NMR δ 145.60, 137.98, 137.48, 128.33, 128.17, 127.73, 127.60, 127.43, 73.19, 73.02, 69.98, 69.31, 69.20, 69.10, 66.36, 65.59 (3 missing); mass spectrum (FD, 0 ma) m/z (relative intensity) 397 (M^+ + 1, 100); exact mass calcd for $C_{23}H_{28}O_4N_2$ m/z 396.20489, found m/z 396.20484.

1-[(*N*,*N*-Dimethylamino)sulfonyl]-2,4-bis[[2-(benzyloxy)ethoxy]methyl]imidazole (22b). A solution of 1.0 g (2.5 mmol) of imidazole **21b**, 399 mg (2.8 mmol) of *N*,*N*-dimethylsulfamoyl chloride, and 566 mg (5.6 mmol) of triethylamine in 25 mL of dry benzene was stirred at reflux under a nitrogen atmosphere for 2 h. The solvent was removed under reduced pressure; the residue was partitioned between 100 mL of brine and 100 mL of 10% 2-propanol–chloroform. The aqueous layer was washed three times with 100 mL of 10% 2-propanol–chloroform, and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography (20% petroleum ether–ethyl acetate) gave 781 mg (62%) of **22b** as a clear oil: IR (CCl_4) 3034, 2866, 1743, 1691, 1659, 1101, 1053 cm^{-1}; ^1H NMR δ 7.32–7.25 (m, 11 H, ArH, H-5), 4.74 (s, 2 H, CH_2-2), 4.54 (s, 2 H, $ArCH_2$), 4.49 (s, 2 H, $ArCH_2$), 4.46 (s, 2 H, CH_2-4), 3.73–3.60 (m, 8 H, OCH_2CH_2O), 2.80 (s, 6 H, SO_2NMe_2); ^{13}C NMR (125 MHz) δ 144.51, 137.87, 137.73, 128.01, 127.41, 127.28, 118.36, 72.88, 72.79, 69.71, 69.56, 69.11, 68.97, 66.39, 64.56, 37.86 (4 missing); mass spectrum (EI, 70 eV), m/z (relative intensity) 503 (M^+, 3), 137 (20), 108 (26), 91 (100); exact mass calcd for $C_{25}H_{33}N_3O_6S$ m/z 503.20899, found m/z 503.20586.

1-[(*N*,*N*-Dimethylamino)sulfonyl]-2,4-bis[(benzyloxy)methyl]imidazole (22a). The crude product obtained by using the procedure described for **22b** was purified by flash chromatography (35% ethyl acetate–petroleum ether) to afford 2.0 g (86%) of **22a** as a clear colorless oil: IR (CCl_4) 3067, 3034, 2930, 2862, 1558, 1496, 1072, 1028, 1012 cm^{-1}; ^1H NMR (500 MHz) δ 7.36–7.25 (m, 11 H, ArH, H-5), 4.75 (s, 2 H, CH_2-2), 4.63 (s, 2 H, $ArCH_2$), 4.62 (s, 2 H, $ArCH_2$), 4.49 (s, 2 H, CH_2-4), 2.83 (s, 6 H, SO_2NMe_2); ^{13}C NMR (125 MHz) δ 144.95, 138.09, 137.79, 137.30, 128.27, 128.16, 127.95, 127.80, 127.71, 127.62, 118.51, 72.69(2C), 65.58, 64.03, 38.15; mass spectrum (EI, 70 eV), m/z (relative intensity) 415 (M^+, 0.4), 308 (44), 202 (79), 201 (100), 183 (45), 108 (42), 96 (36), 95 (55), 94 (100), 91 (100), 65 (56); exact mass calcd for $C_{21}H_{25}N_3O_4S$ m/z 415.15656, found m/z 415.15713.

1-[(*N*,*N*-Dimethylamino)sulfonyl]-2,4-bis(hydroxymethyl)imidazole (2). A mixture of 1.5 g (3.6 mmol) of **22a**, 1.5 g of 10% palladium on carbon, 1.43 g (18.1 mmol) of ammonium formate, and 40 mL of dry methanol was stirred under a nitrogen atmosphere for 36 h.[32] The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to yield a white solid. Recrystallization of the solid from ethyl acetate yielded 405 mg (48%) of **2** as colorless needles: mp 129–130 °C; ^1H NMR (500 MHz, CD_3OD) δ 7.36 (s, 1 H, H-5), 4.76 (s, 2 H, CH_2-2), 4.50 (s, 2 H, CH_2-4), 2.94 (s, 6 H, SO_2NMe_2); ^{13}C NMR (125 MHz, CD_3OD) δ 149.76, 141.88, 118.61, 58.40, 57.55, 38.67; mass spectrum (EI, 70 eV), m/z (relative intensity) 236 (M^+ + 1, 9), 235 (M^+, 11), 112 (69), 111 (100). Anal. Calcd for $C_7H_{13}N_3O_4S$: C, 35.74; H, 5.57; N, 17.86; S, 13.63. Found: C, 36.03; H, 5.75; N, 17.77; S, 13.43.

1-[(*N*,*N*-Dimethylamino)sulfonyl]-2,4-bis[(2-hydroxyethoxy)methyl]imidazole (3). Method B. To a stirred solution of **22b** in 10 mL of methanol was added 100 mg of 5% palladium on carbon. The heterogeneous solution was placed under a hydrogen atmosphere and stirred for 4 days. The catalyst was filtered through a pad of Celite and washed with ethanol. The filtrate was concentrated under reduced pressure to give 406 mg (97%) of a clear oil whose physical and spectral properties were identical with those of **3** prepared by method A.

23-Benzyl-3,6,13,16-tetraoxa-9,23-diazatricyclo[16.3.1.1^{8,11}]tricosa-1(22),8,10,18,20-pentaene (9). To a stirred suspension of 9 mg (0.36 mmol) of sodium hydride in 4 mL of refluxing THF was added simultaneously a solution of 43 mg (0.16 mmol) of 1,3-bis(bromomethyl)benzene in 2 mL of THF and 50 mg (0.163 mmol) of **8** in 2 mL of THF over 4 h (syringe pump). The reaction was cooled to room temperature and quenched with several drops water, and the solvent was removed under reduced pressure. Flash chromatography (3% methanol–CH_2Cl_2) yielded 3 mg (4.5%) of **9** as an oil: ^1H NMR δ 7.69 (s, 1 H, H-22), 7.29–7.13 (m, 6 H, ArH), 6.99 (s, 1 H, H-10), 6.83–6.80 (m, 2 H, ArH), 5.57 (s, 2 H, CH_2N-23), 4.57 (s, 2 H, H-7), 4.55 (s, 2 H, H-2 or H-17), 4.52 (s, 2 H, H-2 or H-17), 4.34 (s, 2 H, H-12), 3.68–3.47 (m, 8 H, OCH_2CH_2O); MS (FD, 0 ma) m/z 408 (M^+).

9-[(*N*,*N*-Dimethylamino)sulfonyl]-3,6,13,16-tetraoxa-9,23-diazatricyclo[16.3.1.1^{8,11}]tricosa-1(22),8(23),10,18,20-pentaene (23). To a stirred suspension of 11 mg (0.46 mmol) of sodium hydride in 6 mL of refluxing THF was added simultaneously a solution of 22.2 mg (0.07 mmol) of 1,3-bis(bromomethyl)benzene in 3 mL of THF and 50 mg (0.155 mmol) of **3** in 3 mL of THF over 4 h (syringe pump). The reaction was cooled to room temperature and quenched with several drops of water, and the solvent was removed under reduced pressure. The brown residue was slurried in CH_2Cl_2 and filtered, and the filtrate was purified by flash chromatography (2% methanol–CH_2Cl_2) to yield 5 mg (14%) of **23** as an oil: ^1H NMR δ 7.53 (s, 1 H, H-22),

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7.29–7.20 (m, 2 H, ArH), 7.10–7.06 (m, 2 H, ArH, H-10), 4.79 (s, 2 H, H-7), 4.57 (s, 2 H, H-2 or H-17), 4.49 (s, 2 H, H-2 or H-17), 4.46 (s, 2 H, H-12), 3.83–3.77 (m, 4 H, OCH_2CH_2O), 3.71–3.68 (m, 2 H, OCH_2CH_2O), 3.63–3.60 (m, 2 H, OCH_2CH_2O), 2.90 (s, 6 H, NMe_2); MS (FD, 0 ma) m/z 425 (M^+).

Methyl 9-[(*N*,*N*-Dimethylamino)sulfonyl]-3,6,13,16-tetraoxa-9,23-diazatricyclo[16.3.1.1^{8,11}]tricosa-1(22),8-(23),10,18,20-pentaene-22-carboxylate (24). To a stirred suspension of 114 mg (4.97 mmol) of sodium hydride in 120 mL of THF was added dropwise, at ambient temperature, a solution of 730 mg (2.28 mmol) methyl 2,6-bis(bromomethyl)benzoate and 730 mg (2.28 mmol) of **3** in 120 mL of THF over 3 h. The reaction was stirred for 12 h at room temperature, quenched with several drops water, and concentrated under reduced pressure to yield an oily, brown solid. The oil was dissolved in CH_2Cl_2, filtered, and purified by flash chromatography (4% methanol–CH_2Cl_2) to yield 770 mg (61%) of **24** as a light yellow solid: IR (CCl_4) 2920, 1728, 1551, 1003, cm^{-1}; ^{1}H NMR δ 7.33–7.27 (m, 3 H, ArH), 7.13 (s, 1 H, H-10), 4.64 (s, 2 H, H-7), 4.55–4.48 (bs, 4 H, H-2, H-17), 4.38 (s, 2 H, H-12), 3.80 (s, 3 H, CO_2CH_3), 3.59 (m, 8 H, OCH_2CH_2O), 2.84 (s, 6 H, SO_2NMe_2); ^{13}C NMR δ 168.61, 144.79, 137.80, 136.82, 136.73, 132.01, 129.10, 128.58, 128.54, 118.33, 70.94, 70.92, 69.14, 69.07, 68.93, 68.70, 65.76, 64.52, 51.76, 37.97; mass spectrum (FD, ma), m/z 483 (M^+, 100).

Methyl 3,6,13,16-Tetraoxa-9,23-diazatricyclo[16.3.1.1^{8,11}]-tricosa-1(22),8,10,18,20-pentaene-22-carboxylate (4). A solution of 902 mg (1.87 mmol) of **24** in 50 mL of 10% sulfuric acid was heated to 60 °C for 12 h. The pH of the solution was carefully adjusted to pH = 5, at 0 °C, with saturated aqueous sodium bicarbonate. The solution was extracted four times with 100 mL of 10% isopropanol-chloroform. The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a yellow oil. Flash chromatography (4% methanol–CH_2Cl_2) yielded a light yellow solid, which was recrystallized from petroleum ether–ethyl acetate (3:1) to afford 506 mg (72%) of **4** as small off-white needles: mp 79–80 °C; IR (KBr) 3700–3000, 1725 cm^{-1}; ^{1}H NMR δ 7.39–7.25 (m, 3 H, ArH), 6.83 (s, 1 H, H-10), 4.84–4.68 (m, 4 H, $ArCH_2$), 4.49–4.45 (m, 2 H, $ImCH_2$), 4.37–4.31 (m, 2 H, $ImCH_2$), 3.94 (s, 3 H, CO_2CH_3), 3.7–3.6 (m, 8 H, OCH_2CH_2O); ^{13}C NMR δ 169.49, 146.36, 136.85, 136.72, 133.08, 129.74, 129.52, 127.90, 127.86, 126.29, 71.90, 71.59, 70.36, 70.16, 69.86, 68.95, 66.77, 63.33, 52.81; mass spectrum (FD, ma), m/z 376 (M^+, 100). Anal. Calcd for $C_{19}H_{24}N_2O_6 \cdot 2H_2O$: C, 55.32; H, 6.85; N, 6.79. Found: C, 55.18; H, 6.81; N, 6.59. X-ray analysis (see text and paragraph below).

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Registry No. **2**, 118599-61-4; **3**, 115912-73-7; **4**, 115912-74-8; **4**·2H_2O, 118599-85-2; **5**, 115960-26-4; **6**, 118599-62-5; **7**, 118599-63-6; **8**, 115912-72-6; **9**, 118599-64-7; **10**, 118599-65-8; **11a**, 13620-31-0; **11b**, 118599-66-9; **12**, 118599-67-0; **13**, 118599-68-1; **14a**, 14593-43-2; **14b**, 118599-69-2; **15a**, 60276-38-2; **15b**, 118599-70-5; **16a**, 118599-71-6; **16b**, 118599-72-7; **17a**, 118599-73-8; **17a**·HBr, 118599-75-0; **17b**, 118599-74-9; **17b**·2HCl, 118599-76-1; **18a**, 118599-78-3; **18b**, 118599-79-4; **19a**, 931-35-1; **19b**, 118599-77-2; **20b**, 118599-80-7; **21a**, 118599-81-8; **21b**, 118599-82-9; **22a**, 118599-83-0; **22b**, 118599-84-1; **23**, 118599-86-3; **24**, 118599-87-4; Me_2NSO_2Cl, 13360-57-1; $CH_2CH_2C(=NH)OCH_2CH_3$·HCl, 40546-35-8; 1-benzylimidazole, 4238-71-5; benzyl alcohol, 100-51-6; allyl bromide, 106-95-6; 2-(benzoyloxy)ethanol, 622-08-2; propionyl nitrile, 107-12-0; 1,2-diaminopropane, 78-90-0; 1,3-bis(bromomethyl)benzene, 626-15-3; methyl 2,6-bis(bromomethyl)benzoate, 56263-51-5.

Supplementary Material Available: Positional and thermal parameters from the X-ray analysis of compound **4** (5 pages). Order information is given on any current masthead page.

Reactivity of 1,3-Diaryl-2,4-bis(heteroarylimino)-1,3-diazetidines. Formation of N^1,N^2,N^3,N^4,N^5-Pentasubstituted Biguanides

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N^1,*N*^{3}-Di(Ar)-*N*^{2},*N*^{4}-bis(6-methyl-3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazin-4-yl)-*N*^{5}-(*R*)-biguanides **2a–p** were obtained by reacting 1,3-di(Ar)-2,4-bis((6-methyl-3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazin-4-yl)imino)-1,3-diazetidines **1** with several primary amines, piperidine, and 1,1-dimethylhydrazine. The structure of the biguanides was established by a careful ^{1}H and ^{13}C study. To assign unambiguously the NMR signals, NOE difference experiments of compounds **2b** (Ar = 4-Cl-C_6H_4, R = CH_3), **2l** (Ar = R = 4-Cl-C_6H_4), and **2m** (Ar = R = 4-H_3CO-C_6H_4) and 2-D heteronuclear ^{1}H–^{13}C correlation spectrum of **2l** were used. Compound **2a** (Ar = C_6H_5, R = CH_3) was analyzed by X-ray crystallography. Cell constants were 17.1116 (24), 10.4410 (9), and 16.8613 (22) Å; 107.98 (1)°; the space group was $P2_1/c$. Two intramolecular hydrogen bonds determine the conformation of the molecule.

The chemistry of 1,3-diaryl-2,4-bis(arylimino)-1,3-diazetidines, cyclodimers of *N*,*N*′-diarylcarbodiimides,[1] has been little explored; it has been briefly mentioned that these compounds on sequential treatment with phosgene

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