A New, Facile Synthesis of 1,4,7,10-Tetraazacyclododecane: Cyclen

Phillip S. Athey* and Garry E. Kiefer†

The Dow Chemical Company, 2301 N. Brazosport Blvd., B-1222, Freeport, Texas 77541-3257

pathey@dow.com

Received September 12, 2001

This report outlines a new and efficient synthesis of cyclen (1,4,7,10-tetraazacyclododecane, **1**) utilizing bis-imidazoline, **6** (1,1′-ethylenedi-2-imidazoline), with 1,2-dibromoethane. General conditions were developed, allowing for the simple, three-step synthesis of **1** at the multigram scale with an isolated overall yield approaching 65%. The cyclization of **6** produced by the condensation of triethylene tetraamine (TETA) with *N*,*N*-dimethylformamide dimethyl acetal, gave the twelve-membered, imidazolinium, cyclized intermediate bromide salt, **7** (2,3,4,5,6,7,8,8*c*-octahydro-1*H*-4*a*,6*a*,8*a*-triaza-2*a*-azoniacyclopent[*fg*]acenaphthylene), which hydrolyzed to **1** with the use of hot, aqueous caustic. Hydrolysis of **7** under milder conditions formed the 1,4,7,10-tetraazabicyclo[8.2.1]-tridecan-13-one (**20**). Mechanistically, the formation of **7** may be rationalized as involving a diaminocarbene that undergoes an intramolecular carbon−hydrogen insertion.

Introduction

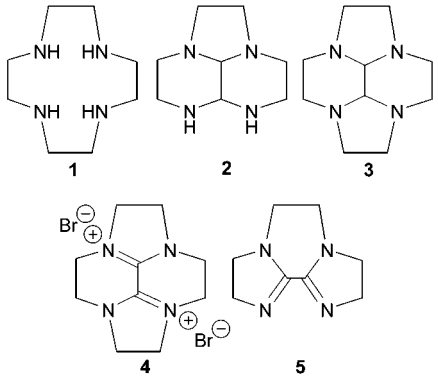
Within the past decade, cyclen (1,4,7,10-tetraazacyclododecane, **1**) has become an important intermediate for the synthesis of diagnostic and therapeutic pharmaceutical agents.[1] One of the fastest growing medicinal uses of cyclen is in the development of MRI contrast agents.[2] More recently, advances in targeted cancer agents such as antibodies and peptides have revived interest in cyclen-based bifunctional chelating agents for therapy.[3]

These new technologies are increasing the demand for **1** on both the commercial and research scale. Accordingly, there is considerable effort being devoted to finding more efficient synthetic strategies to this valuable intermediate.[4−9]

The traditional literature procedure developed by Richman−Atkins for the synthesis **1** involves the formation of tetra-*N*-tosylated cyclen from the macrocyclization of tris-*N*-tosyl diethylenetriamine with *N*-tosyldiethanolamine ditosylate.[10] A variety of procedures for the detosylation have been reported such as treatment with concentrated H_2SO_4 and HBr/AcOH. Over the years, modifications of this process have been reported to help increase the efficiency of this technique.[11−13] However, even with modifications, the use of *N*-tosylates makes for a very cumbersome process.

In an effort to avoid tosylate chemistry, several new synthetic routes to cyclen have been reported.[4−9] Most of the recent work has focused on utilization of the tricyclic intermediate 3*H*,6*H*-ocathydro-2*a*,5,6,8*a*-tetraazacenaphthylene (**2**). Jazwinski and Kolinski initially accomplished the preparation of **2** by treating triethylenetetraamine (TETA) with glyoxal.[14]

Several groups have taken advantage of **2** as a route to **1**, by treating **2** with either dichloro- or dibromoethane to form the tetracyclic precusor **3**.[5−9,15] Hydrolysis of the ethylene bridge has been performed using either a Br_2 oxidation process or a primary amine hydrolysis process. Use of the time-consuming (18 h) oxidation process forms the dicationic, bromide salt (**4**), which can be hydrolyzed under basic conditions (pH 14, autoclave), yielding **1** in 25% overall yield (based on TETA).[6]



Hydrolysis of **3** with primary amines forms **1** in higher yields and has the advantage of being performed in one

† E-mail: gkiefer@dow.com.

(1) (a) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Aza-Crown Macrocycles*: *The Chemistry of Heterocyclic Compounds*; Wiley & Sons: New York, 1993; pp 16−21, 83−85, 157−165. (b) Kumar, K.; Tweedle, M. *Pure Appl. Chem.* **1993**, *65*, 51.

(2) Caravan, P.; Ellison, J. J.; McMurray, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293−2352.

(3) Lui, S.; Edwards, S. D. *Bioconjugate Chem.* **2001**, *12*, 7−34.

(4) (a) Weisman, G. R.; Reed, D. P. *J. Org. Chem.* **1996**, *61*, 5186−87. (b) Weisman, G. R.; Reed, D. P. *Org. Synth.* **2001**, *78*, 73−81.

(5) PCT International WO 96/28433.

(6) (a) Argese, M.; Ripa, G.; Scala, A.; Valle, V. U.S. Patent 6 114 521, 2000. (b) Argese, M.; Ripa, G.; Scala, A.; Valle, V. U.S. Patent 5 886 174, 1999. (c) Argese, M.; Manfredi, G.; Rebasti, F.; Ripa, G. PCT International application WO 00/53588, 2000.

(7) Platzek, J.; Hoyer, K.; Graske, K. D.; Raduechel, B. U.S. Patent 6 156 890, 2000.

(8) Ferrari, M.; Giovenzana, G.; Palmisano, G.; Sisti, M. *Synth. Commun.* **2000**, *30* (1), 15−21.

(9) (a) Herve, G.; Bernard, H.; Toupet, L.; Handel, H. *Eur. J. Org. Chem.* **2000**, *1*, 33−35. (b) Herve G.; Bernard, H.; Le Bris, N.; Le Baccon, M.; Yaouane, J. J.; Handel, H. *Terahedron Lett.* **1999**, *40* (13), 2517−2520.

(10) Atkins, T. J.; Richman, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 2268.

(11) Chavez, F.; Sherry, A. D. *J. Org. Chem.* **1989**, *54*, 2990.

(12) Vriesema, B. K.; Butler, J.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 110.

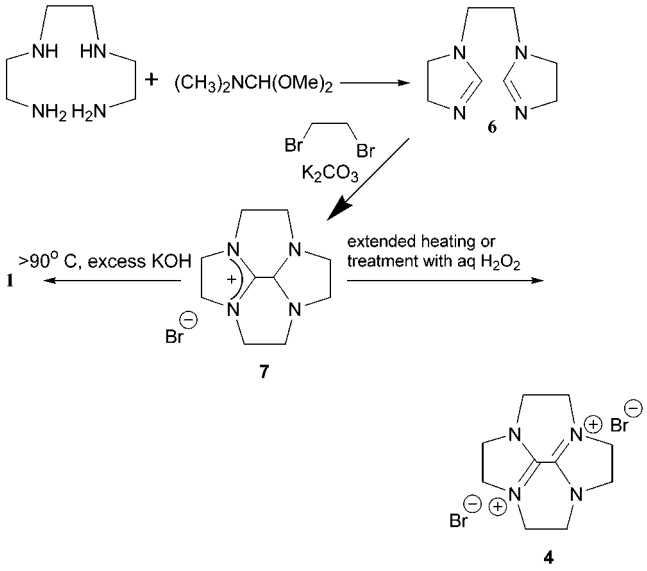
(13) Panette, V.; Yaouanc, J. J.; Handel, H. *Tetrahedron Lett.* **1992**, *33*, 5505−5508.

(14) Jazwinski, J.; Kolinski, R. *Tetrahedron Lett.* **1981**, *22*, 1711.

(15) Weisman, G. R.; Ho, S. C. H.; Johnson, V. *Tetrahedron Lett.* **1980**, *21*, 335−8.

10.1021/jo016111d CCC: $22.00
Published on Web 05/18/2002

Scheme 1



step versus two. For instance, hydroxylamine and hydrazine have both been utilized to generate **1** in yields of 45 and 50−65%, respectively (based on TETA).[5,7] The main disadvantage of this technique is the lengthy reaction time (>20 h).

Weisman and Reed also addressed these issues concerning the synthesis of **1** and reported a unique, nonglyoxal route to **1**.[4] Their approach focused on conversion of TETA to a tricyclic bis-amidine (**5**) that underwent a double reductive ring expansion with DIBALH, yielding **1** in 57%. While this method clearly offers a significant and novel approach to **1**, there remain some drawbacks when considering large-scale production. For instance, the procedure required the use of dithiooxamide, which leads to the generation of hydrogen sulfide and a time-consuming reduction involving DIBALH. Typically, regardless of the synthetic process utilized, final isolation of **1** is achieved via precipitation from basic solution.

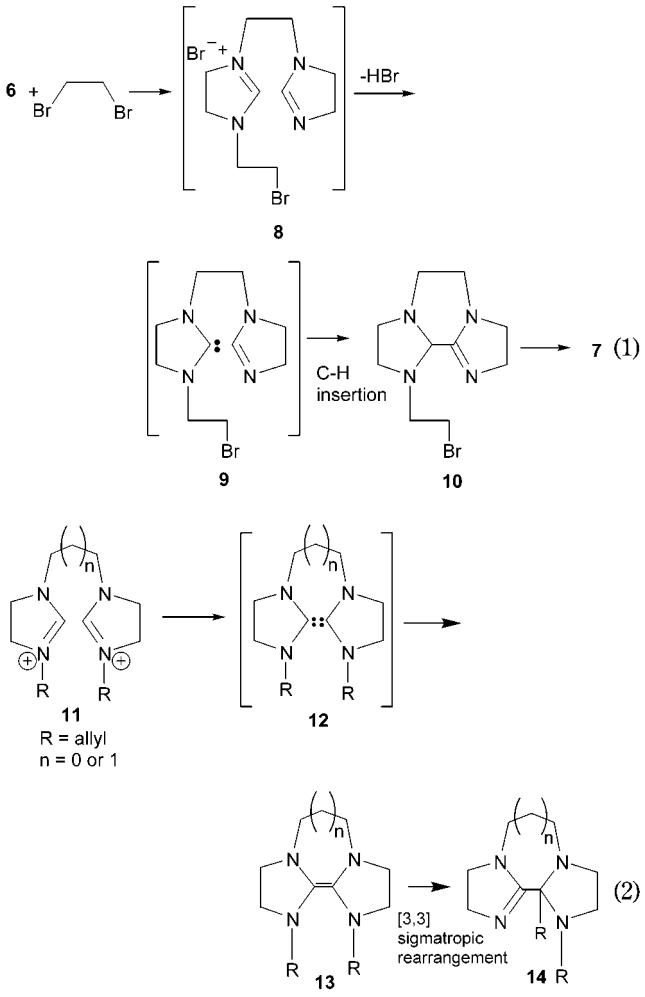
Over the past few years, we have also developed an efficient process for the production of cyclen (**1**) from the cyclization of bis-imidazoline (**6**)[16] with 1,2-dibromoethane that we now report.[17] As in the Weisman−Reed process, the use of bis-amidine chemistry was exploited to perform the cyclization. However, the bis-amidine used was the 1,1′-ethylenedi-2-imidazoline (**6**). Unlike the rigid, tricyclic bis-amidine **5**, bicyclic **6** does not possess a covalent bridge at the unsaturated carbon of the amidine rings.

Results and Discussion

The synthesis of **6** is performed by taking advantage of the reactivity of formamide acetals (Scheme 1).[16] Historically, such reagents have been used to efficiently convert primary amines and primary amides to amidines and acylated amidines, respectively.[18,19] Using this technique, **6** was efficiently prepared under neat reaction conditions in >90% yield following recrystallization.

The macrocyclization of **6** with a dielectrophilic substrate such as 1,2-dibromoethane produced the monoimdazolinium compound **7** in >70% yield. However, extended cyclization reaction times (24 h, DMF) resulted in a new, highly symmetric product, determined to be the dicationic oxamidinium **4**. Compound **4** was also prepared by treating **7** with a dilute aqueous H_2O_2 solution (Scheme 1). The structural nature of **4** was determined by 2-D Hetcor NMR and the single-crystal X-ray structure, with the center carbon framework exhibiting carbon−carbon and carbon−nitrogen bond distances of 1.43 and 1.30 Å, respectively. Finally, the structural analysis of **7** and **4** was further elucidated by reducing both with $NaBH_4$ forming the known bis-aminal, tetraamino ethane macrocycle (**3**). The ^{13}C NMR of **3** was in agreement with the literature values.[15]

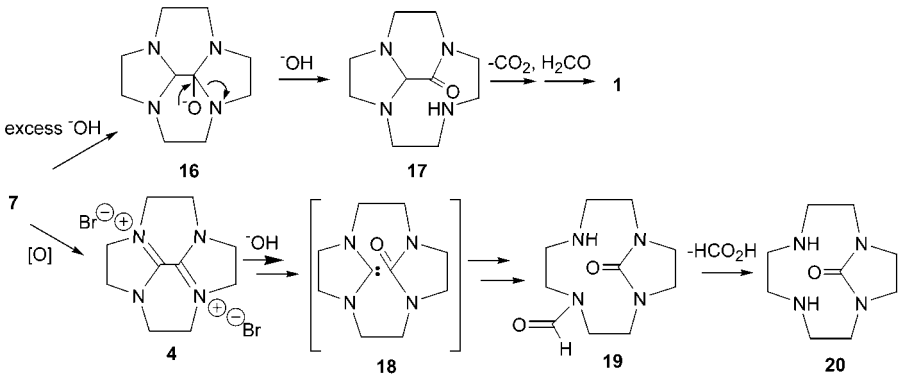
A possible stepwise mechanism for the generation of **7** is outlined in eq 1. Mechanistically, the initial step in the formation of **7** was the alkylation of **6** with 1,2-dibromoethane, producing the imidazolinium intermediate **8**. Intermediates such as **8** are known to be efficient diaminocarbene precursors, generating diaminocarbenes that typically dimerize, yielding tetraaminoethylene derivatives.[20,21] In fact, Lappert has reported the synthesis of endotricyclic tetraaminoethylene **13** (R = allyl; n = 0, 1) via an intramolecular diaminocarbene dimerization and demonstrated the ability of **13** to undergo a [3,3]-sigmatropic rearrangement to form amidine intermediate (**14**), which is similar to **7** (eq 2).[22]



At first glance, a similar mode of mechanistic operation seems plausible for the formation of **7**. However, a carbene dimerization mechanism analogous to that pro-

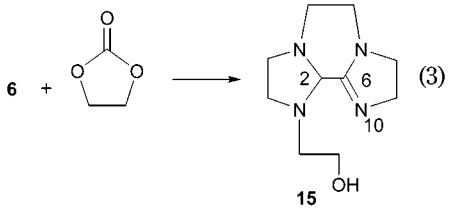
(16) Cetinkaya, E.; Hitchcock, P. B.; Jasim, H.; Lappert, F.; Spyropoulos, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 561.
(17) Athey, P. S.; Kiefer, G. E. U.S. Patent 5 587451, 1996.

Scheme 2



posed for the formation of **13** is not probable here because **6** would have to form a 10-membered ring transition state in the process of generating **13**. A simple, and plausible, alternative is that **8** loses HBr to form carbene **9**, which then undergoes an intramolecular, carbene carbon−hydrogen insertion. Such a process will eventually lead to the electronically neutral intermediate **10** (eq 1). The neutral amidine intermediate **10** may then readily displace the remaining bromide to form **7**. This latter sequence may be the key in trying to understand the efficiency of the formation of **7**. In contrast to the Richman/Atkins methodology, which requires a 12-membered transition state for the final macrocyclic ring closure, the ring-closure reaction of **10** to **7** passes through a conformationally favorable six-membered transition state.

Further investigation of this proposed mechanism was performed by reacting **6** with ethylene carbonate, which demonstrated that the new covalent bond was formed prior to the formation of the macrocyclic ring. The use of such a monoelectrophilic substrate prevents any macrocyclic ring closure but does allow the formation of a tricyclic neutral amidine as discussed and shown in eq 1 (i.e., **10**). Accordingly, upon heating a DMF solution of ethylene carbonate and **6**, we observed the observed major product to be structure **15** (eq 3). The X-ray crystal structure of **15** clearly identifies the bond distance of the imidazoline double bond (C6−N10) and the new carbon single bond (C2−C6) as being 1.28 and 1.50 Å, respectively.



(3)

After the preparation of **7**, the next issue addressed was the deprotection of **7** to yield *free base* cyclen (**1**). Various imidazolinium ions are known to be fairly stable in acidic and neutral media, and some hydrolyze only at elevated pH (>12.0).[18] Accordingly, the use of excess hot alkali hydrolyzed **7** to **1** in >80% yield. The only observed impurity was the urea form of cyclen (**20**), which was the exclusive hydrolysis product of **4**. Under milder conditions, the formation of **20** was observed as the major product. Typically, the isolated cyclization reaction mixture was hydrolyzed without any purification of the salt **7**. The isolation of **1** was achieved by allowing the trihydrate form of **1** to precipitate from the caustic media. Water and trace amounts of salts were removed via azeotropic distillation followed by crystallization from toluene to give **1** in free base form.

Mechanistically, the product distribution of cyclen (**1**) and **20** depends on the partioning of **7** between hydroxide addition to form alkoxide amine **16** and autoxidation to **4** (Scheme 2). Within the literature, the hydrolysis of tetraarylalkylaminoethylenes with strong alkali is known to favor a route involving intermediates such as **16**.[19] Once formed, a stepwise degradation of **17** generates cyclen (**1**).

Under milder conditions, imidazolinium intermediates (i.e., **7**) can undergo autoxidation to produce oxamidinium species such as **4**.[19] Hydrolysis of **4** may proceed through the diaminocarbene intermediate **18**, which ultimately produces **20** (Scheme 2). Although these simple explanations may explain the product formation, the precise mechanistic details will require further delineation to unravel the exact nature of each intermediate involved in the process.

Conclusions

Macrocyclic amines have proven to be extremely valuable as a scaffold for incorporating metal ion binding into larger molecular fragments. Specifically, the kinetic and thermodynamic metal binding characteristics of the 12-membered tetraazamacrocycle are well suited to a wide range of biological applications. In addition, the versatility of this macrocycle continues to grow as new methodology for selective functionalization has appeared. Thus, derivatized forms of cyclen (**1**) are becoming increasingly popular as standard building blocks in applications requiring highly selective metal ion chelation.

As a result of these growing demands and interest, there has been an obvious need to produce **1** at a reasonable cost and in a reproducible and efficient manner. Clearly, several new routes to **1** have appeared over the past five years or so, each claiming certain

(18) *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley & Sons: New York, 1975; pp 285−348.
(19) Lemal, D. M. In *Chemisty of the Amino Group*; Patai, S., Ed.; Interscience: London, 1968; pp 701−48.
(20) Lemal, D. M.; Liu, Y.; Lindner, P. E. *J. Am. Chem. Soc.* **1999**, *121*, 10626−10627.
(21) For a recent review on tetraaminoethylenes and diaminocarbenes, see: Warkentin, J. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; Jai Press: London, 1998; Vol. 2, p 245.
(22) (a) Lappert, M. F. *J. Organomet. Chem.* **1988**, *358*, 185. (b) Lappert, M. F. *J. Org. Chem.* **1989**, *54*, 4684−6.

advantages in overall yield, number of steps, and efficiency.[4−9] Each route has its appeal and is capable of producing **1**. However, with the coupling of dibromoethane and bis-imidazoline (**6**), we have demonstrated that **1** can be easily liberated from the resulting imidazolinium intermediate **7**. The generation of **7** is proposed to be an example of an intramolecular diaminocarbene C−H insertion.

This process is well suited to both laboratory-scale and plant production quantities of **1**. On a lab scale, it is straightforward to produce 50 g of final product in 2 days. On a large production scale, this process is appealing because of the rapid nature of each reaction and the low volume of overall waste produced. We believe this process represents the most predictable approach to cyclen (**1**) with a minimum of procedural development.

Experimental Section

General. Reactions were run under nitrogen with stirring. *Materials: N,N*-Dimethylformamide dimethyl acetal (94%), 1,2-dibromoethane, anhydrous potassium carbonate (325 type mesh), tetrahydrofuran, acetonitrile, and triethyletetraamine (TETA) were purchased commercially. *Instrumentation:* MS data for **7** were collected using a flow injection MS/ESI. GC analyses were performed on a gas chromatograph with a 50 × 33μ capillary column. The temperature program employed was 60 °C for 5 min with an increase to 270 °C at 10 °C. The samples were prepared for GC analysis by removing a small portion of the solution and diluting with 2−3 mL of toluene. The resulting binary solution was rinsed with 50% (w/w) NaOH. NMR data were collected on a 250 MHz instrument. Chemical shifts reported are internally referenced to tetramethylsilane.

1,1′-Ethylenedi-2-imidazoline (6). To a stirred solution of linear TETA (100 g, 0.68 mol) was added *N,N*-dimethylformamide dimethyl acetal (173.37 g, 1.36 mol). The solution was refluxed for 30 min. The reaction mixture was dried in vacuo. The resulting off-white solid was recrystallized from THF. The resulting white solid was filtered under a blanket of nitrogen and isolated in 85% yield (96.3 g, 0.58 mol): mp 107−9 °C; ^{1}H NMR ($CDCl_3$) δ 6.7 (s, 2H), 3.7 (t, 4H), 3.1−3.2 (overlapping signals, 8H) ppm; ^{13}C NMR ($CDCl_3$) δ 157.2 (CH), 55.0 (CH_2), 48.4 (CH_2), 46.4 (CH_2) ppm. MS *m/e* 167 (M + 1, 1), 166 (6), 83 (100), 56 (89).

2,3,4,5,6,7,8,8*c*-Octahydro-1*H*-4*a*,6*a*,8*a*-triaza-2*a*-azoniacyclopent[*fg*]acenaphthylene Bromide Salt (7). A 5 L three-neck round-bottom flask equipped with an overhead mechanical stirrer, a condenser, and a nitrogen inlet was charged with in 2.4 L of acetonitrile, **6** (50 g, 0.30 mol), 1,2-dibromoethane (78.9 g, 0.42 mol), and K_2CO_3 (31.2 g, 0.23 mol). The mixture was heated to reflux while being stirred. After 3 h at reflux, the K_2CO_3 was filtered and the filtrate was dried in vacuo. Typically, the salt was taken up in water without purification and carried on to the hydrolysis step. However, the pure salt form of **7** may be isolated by rinsing the crude solid with a minimal amount of cold acetonitrile, followed by filtration under nitrogen, which yielded a pale yellow solid weighing 35.3 g (0.21 mmol) for a yield of 70%: mp 130 °C dec; ^{1}H NMR (D_2O) δ 4.6 (s, 1H), 3.7−3.9 (m, 4H), 3.3−3.5 (m, 6H), 2.5−3.2 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 162.0 (C), 72.7 (CH), 54.2 (CH_2), 52.4 (CH_2), 45.5 (CH_2), 44.3 (CH_2) ppm. Anal. Calcd for $C_{10}H_{18}N_4Br$: C, 43.96; H, 6.23; N, 20.5; Br, 29.3. Found: C, 43.24; H, 6.38; N, 20; Br, 32.8.

Synthesis of Oxamidinium 4 from 7. The procedure used for the synthesis of **7** was followed with the exception that the DMF solution was heated for 12−14 h at 100 °C (1.14 g, 6.8 mmol of **6**; 1.8 g, 9.58 mmol of 1,2-dibromoethane; 0.71 g, 5.24 mmol of K_2CO_3). The cooled solution was dried in vacuo leaving an amber-colored solid. No further purification of the material was performed: mp 295 °C dec; ^{1}H NMR (D_2O) δ 4.3 (s), 4.0 (s) ppm; ^{13}C NMR (D_2O) δ 46.3 (CH_2), 54.3 (CH_2), 150.6 (C) ppm. X-ray crystallographic analysis information of **4** can be found in Supporting Information.

Synthesis of 4 via Hydrogen Peroxide. The cyclized intermediate **7** (1 g, 3.6 mmol) was dissolved in 10 mL of water. A 10% H_2O_2 aqueous solution was added to the mixture. The solution was heated to reflux. After 30 min, the heat source was removed and the solution was dried in vacuo. No further purification of the material was performed.

Cyclen (1). The cyclized intermediate (**7**, 113 g, 0.41 mol) was dissolved in water to give a total volume of 450 mL and added dropwise to a refluxing solution of 400 mL of caustic (8 equiv, 129 g, 3.3 mol). The caustic solution was heated for an additional 30 min after the addition of **7**. The aqueous caustic solution was gravity filtered while hot. The filtrate was then concentrated (in vacuo) until crystalline **1** was observed in the solution. After the mixture had cooled to ambient temperature, **1** was filtered and the precipitation process was repeated until no further crystallization occurred. The final aqueous filtrate was dried in vacuo, and the remaining cyclen was removed by extractions of the solid residue with hot toluene. The overall yield of (**1**) was 88% (62 g, 0.36 mol): ^{1}H NMR ($CDCl_3$) δ 2.54 ppm; ^{13}C NMR ($CDCl_3$) δ 45.9 ppm; MS *m/e* 174 (M + 1), 173 (2), 128 (8), 104 (45), 85 (100), 56 (80).

Synthesis of 3 (Decahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene) from 7. The cyclized intermediate (**7**, 1 g, 0.0036 mol) was dissolved in a 50:50 MeOH/EtOH solution to give a final volume of 20 mL. $NaBH_4$ was added in small portions to the ethanolic solution. Excess $NaBH_4$ was added, and the solution was refluxed for 1 h. Water was added to the reaction mixture, and the refluxing was continued for an additional 1 h. The solution was dried in vacuo. No further purification of the material was performed. The overall yield was 90% (0.63 g, 0.0032): ^{13}C NMR (D_2O) δ 78.8 (CH), 53.0 (CH_2), 52.0 (CH_2) ppm; MS *m/e* 195 (M + 1), 194 (56), 152 (43), 124 (15), 83 (100), 56 (50).

Synthesis of 3 from 4. The cyclized intermediate (**4**, 0.2 g, 1 mmol) was dissolved in 5 mL of EtOH. $NaBH_4$ was added in small portions to the ethanolic solution. The solution was refluxed for 2 h. The solution was dried in vacuo. No further purification of the material was performed. The yield of (**3**) was quantitative: ^{13}C NMR (D_2O) δ 78.8 (CH), 53.0 (CH_2), 52.0 (CH_2) ppm; MS *m/e* 195 (M + 1), 194 (56), 152 (43), 124 (15), 83 (100), 56 (50).[15]

2,3,5,6,8,9-Hexahydro-diimidazo[1,2-*a*:2′,1′-*c*]pyrazine-1(10*bH*)-ethanol (15). Bis-imidazoline (**6**) (2 g, 12 mmol) and ethylene carbonate (1.06 g, 12 mmol) were dissolved in 100 mL of anhydrous DMF. The resulting solution was heated to 140 °C for 5 h while under nitrogen. The solution was dried in vacuo, leaving a yellow, golden-colored oil. The oil was taken up in CH_2Cl_2 and then rinsed with 2 × 50 mL of 1 N HCl. The pH of the aqueous layer was raised to 13.5−14 with the addition of aqueous NaOH. The basic solution was rinsed with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4. Removal of the solvent left 240 mg of colorless oil. Crystal growth of **15** was accomplished by taking the oil up in diethyl ether and allowing the solvent to slowly evaporate: ^{1}H NMR ($CDCl_3$) δ 2.3−3.7 (m, 17H), 4.4 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 43.19 (CH_2), 45.59 (CH_2), 48.83 (CH_2), 51.31 (CH_2), 52.37 (CH_2), 54.01 (CH_2), 59.64 (CH_2), 61.1 (CH_2), 75.55 (CH), 166.71 (C) ppm; MS *m/e* 211 (M + 1) (3), 210 (21), 180 (32), 138 (100), 124 (26), 97 (25), 83 (12), 56 (31). X-ray crystallographic analysis information of **15** can be found in Supporting Information.

1,4,7,10-Tetraazabicyclo[8.2.1]tridecan-13-one (20). The cyclized intermediate (**6**, 1 g, 5.2 mmol) was dissolved in 15 mL of water. The aqueous solution was added dropwise to a solution of 50% NaOH (10 equiv, 2.04 g, 50 mmol). The solution was stirred for 16 h at ambient temperature and then heated to a reflux for 1 h. When the solution was cooled, **1** precipitated and was filtered. The filtrate was extracted with chloroform (4 × 20 mL). The resulting chloroform solution was dried over K_2CO_3, filtered, and dried in vacuo: ^{1}H NMR ($CDCl_3$) δ 2.4 (br s, 2NH), 2.6 (m, 2H), 2.9 (m, 6H), 3.1 (m, 2H), 3.6 (m, 4H), 4.0 (m, 2H) ppm: ^{13}C NMR ($CDCl_3$) δ 42.0 (CH_2), 44.9 (CH_2), 45.8 (CH_2), 49.6 (CH_2), 165.9 (C) ppm; IR ($CHCl_3$) 2998, 2932,

2895, 1675, 1496, 1455, 1265 cm^{-1}; MS *m*/*e* 199 (M + 1), 198 (12), 155 (100), 142 (37), 126 (18), 113 (53), 99 (33), 85 (45), 70 (25), 56 (73). Anal. Calcd for $C_9H_{16}N_4O$: C, 55.10; H, 8.16; N, 28.57. Found: C, 54.95; H, 7.95; N, 27.78.

Acknowledgment. The authors thank Dr. Khalil A. Abboud from the Department of Chemistry at the University of Florida X-ray crystallography laboratory for the X-ray analysis of **15** and Dr. Won Kim, who at the time was a graduate student at the Department of Chemistry at the University of Texas at Dallas, for the X-ray crystallographic analysis of **4**. We also thank Professor Gary Weisman from the University of New Hampshire for his insightful discussion with regard to the mechanism and structure of intermediate **4**.

Supporting Information Available: ^{13}C NMR and ^{1}H NMR spectra (250 MHz) of **7**, 2D Hetcor spectrum of **4**, flow injection MS/ESI conditions and spectra of **7**, and tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **4** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016111D