A Versatile Intermediate for the Preparation of C-Functionalized Azamacrocycles and Application to the Synthesis of the Potent Anti-HIV Agent (±)JM2936

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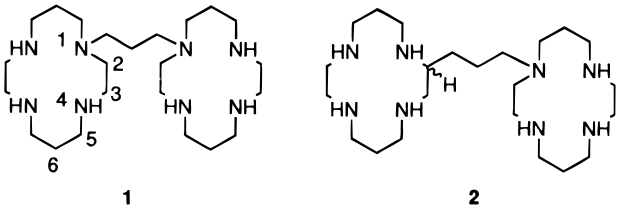
Introduction

Recently we reported the discovery of a novel series of bis-tetraazamacrocycles, such as the bicyclam JM2763 (**1**) (Figure 1), that exhibit potent and selective inhibition of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) replication with a unique mechanism of action.[1] In addition to high antiviral potency, dimers of tetraazamacrocycles linked at a single nitrogen position are particularly attractive drug candidates due to their synthetic accessability. By modification of established literature procedures[2] we were able to prepare and report the structure−activity relationship of an extensive series of N-linked bis-tetraazamacrocycles in which the macrocyclic ring size was varied from 12−16 members per ring.[3] As part of our ongoing efforts to understand the structural features required for potent anti-HIV activity in this class of compounds, we have investigated the effect of connecting the 1,4,8,11-tetraazacyclotetradecane ([14]aneN_4, cyclam) ring system(s) at carbon rather than nitrogen positions,[4] and this paper reports the synthetic methodology we have used to achieve this goal exemplified by the synthesis of (±)JM2936 (**2**). To our knowledge, JM2936 is also the first example of a bis-tetraazamacrocycle that is unsymmetrical due to the nonidentical covalent connection of the rings at carbon and nitrogen positions.[5]

Background

Due to the high kinetic stability exhibited by lanthanide, transition metal, and radiometal complexes of



1 **2**

Figure 1.

tetra- and pentaazamacrocycles, cyclam is one of several azamacrocyclic ring systems which have received considerable recent attention for other biomedical applications such as NMR imaging,[6] mimics of superoxide dismutase,[7] and diagnostic/therapeutic nuclear medicine.[8] From a synthetic standpoint, several groups have prepared C-functionalized tetraazamacrocycles intended as "bifunctional chelating agents" for nuclear medicine applications. In order to covalently attach a radiometal chelating agent to tumor-selective monoclonal antibodies for cancer imaging, the azamacrocycle must be modified on the periphery with a single protein reactive functional group while maintaining the ligands necessary for strong radiometal complexation. To this end, the cyclam ring has been functionalized at nitrogen positions by N-alkylation[9] and at the 5- and 6-carbon positions by macrocyclization reactions of linear tetraamines with substituted α,β-unsaturated esters[10,11] and malonates.[3a,11−15] The corresponding 2-carbon substituent can be introduced into the cyclam ring by macrocyclization of an ethylenediamine or amino acid synthon containing the desired C-substituent.[16,17] This approach has been widely exemplified for the construction of C-functionalized [12]aneN_4 macrocycles[16,18] (using the identical precursor required for the construction of 2-substituted

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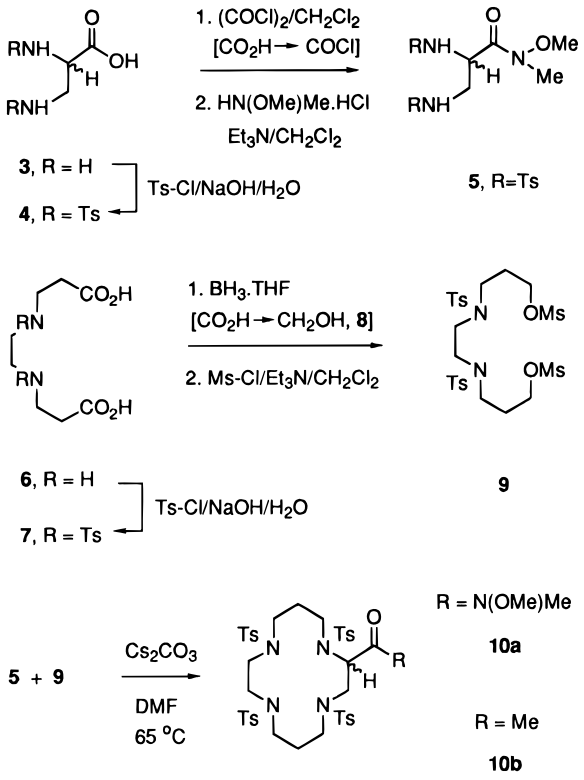
cyclams) in which the key macrocyclization step is the aminolysis of esters or reaction of deprotonated tosylamides with bis-electrophiles (the Richman−Atkins cyclization[19]).

However, these collective routes suffer from at least one of several disadvantages: (a) the reported (protected) functional groups chosen for incorporation are only compatible with a small number of post-macrocyclization functional group transformations; (b) the macrocyclization reaction is low yielding; and (c) each azamacrocycle is constructed with a fixed carbon substituent connecting the functional group to the azamacrocyclic ring, thus limiting the opportunities for divergency of the side chain from a single macrocyclic intermediate. From our perspective, it was desirable to incorporate a versatile functional group directly upon the carbon backbone which is stable to the macrocyclization conditions, and is also capable of C−C bond forming reactions on the fully-constructed azamacrocyclic ring. Based on the reports of Burrows[20] and Guglielmetti[21] on the synthesis of C-functionalized cyclams, in conjunction with our own experience with the synthesis of azamacrocycles,[3] the Richman−Atkins cyclization methodology remains one of the most efficient methods for construction of azamacrocyclic rings and has the added advantage that the *p*-toluenesulfonamido group is stable to a wide variety of post-macrocyclization reaction conditions. We herein report that all of our compatibilty requirements were satisfied by the incorporation of a C-appended, *N*-methoxy-*N*-methylamide (Weinreb amide[22]) within an ethylenediamine synthon which not only withstands the deprotonated tosylamide macrocyclization conditions but also serves as a convenient and versatile carbonyl equivalent for further structural modification on the azamacrocyclic (cyclam) ring.

Results and Discussion

The convergent synthesis of the requisite fully protected 2-(*N*-methoxy-*N*-methylcarboxamido)cyclam derivative **10a** was accomplished in six steps from commercially available amino acids as illustrated in Scheme 1. Tosylation of 2,3-diaminopropionic acid (**3**) in dioxane/H_2O in the presence of sodium hydroxide gave the acid (**4**) in 93% yield. Reaction of **4** with excess oxalyl chloride in CH_2Cl_2 and a small volume of DMF gave the corresponding acid chloride which was immediately converted

Scheme 1



to the Weinreb's amide **5** by reaction with *N*,*O*-dimethylhydroxylamine hydrochloride in CH_2Cl_2 in the presence of Et_3N (overall yield 81% from **4**). The left-hand precursor **9** of the azamacrocycle **10a** was obtained in a straightforward manner in three steps from ethylenediaminedipropionic acid (**6**) in an overall 76% yield. Tosylation of **6** (under identical conditions to **3**) gave the diacid **7** which was reduced with BH_3·THF giving the diol **8**. Derivatization of **8** with methanesulfonyl chloride under standard conditions gave the dimesylate **9**. Macrocyclization to give **10a** was accomplished by a modified Richman−Atkins procedure: dropwise addition of a DMF solution of **9** to a solution of **5** in DMF (final concentration 0.022 M) containing excess Cs_2CO_3[23] maintained at a temperature of 65 °C gave the fully protected azamacrocycle **10a** in a 70% isolated yield following purification by column chromatography on silica gel. Under these reaction conditions, we saw no evidence for formation of the *N*-methylamide of **10a** (or **5**), a byproduct observed by a number of groups when certain *N*-methoxy-*N*-methylamides were reacted with hindered and/or highly basic nucleophiles.[24]

The cyclam derivative **10a** undergoes chelation controlled nucleophilic addition reactions with good specificity characteristic of *N*-methoxy-*N*-methylamides.[25] For example, addition of 3.5 equiv of methyllithium to a solution of **10a** in THF at −78 °C followed by quenching the reaction mixture with water gave the methyl ketone **10b** in 76% isolated yield.[26] Alternatively, the amide **10a** can be reduced with 1.5 equiv of $LiAlH_4$ (or DIBAL-H)

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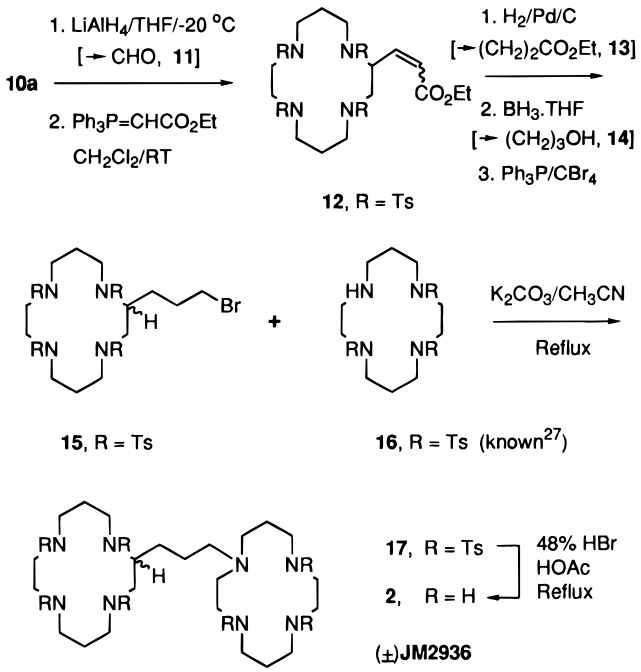
Scheme 2



in THF at −20 °C to give the aldehyde **11** (the corresponding alcohol byproduct could not be detected in the ^{1}H NMR of the crude **11**) which was used for the synthesis of (±)JM2936 (**2**) as shown in Scheme 2. The crude product **11** was homologated with (carbethoxymethylene)triphenylphosphorane (1.0 equiv) at room temperature in CH_2Cl_2 to give a 86:14 (*E:Z*) mixture of α,β-unsaturated esters **12** in 64% overall yield from **10a**. A two-step reduction of **12** with H_2/Pd/C (to give the ester **13**) followed by BH_3·THF gave the alcohol **14** which was subsequently converted to the corresponding bromide **15** in 85% yield by reaction with CBr_4/PPh_3 in refluxing benzene. To complete the synthesis of the desired bistetraazamacrocycle, bromide **15** was reacted with 4,8,-11-tris(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane (**16**)[27] in refluxing CH_3CN in the presence of excess K_2CO_3 to give the heptatosyl protected dimer **17**. Finally, deprotection of the *p*-toluenesulfonamido groups by hydrolysis with 48% aqueous HBr/acetic acid at reflux gave (±)JM2936 (**2**) which precipitated from the reaction mixture as the octahydrobromide salt.

In summary, we have presented a general and convenient method for the introduction of substituents on the carbon backbone of azamacrocycles via a Weinreb amide attached to the periphery of a single macrocyclic intermediate. Since the Weinreb amide is introduced into the ring from an amino acid precursor, and nucleophilic additions occur without loss of enantiomeric purity,[25] this method is also applicable to the synthesis of optically pure azamacrocycles.

Experimental Section

General. See reference 3 for general experimental procedures. ^{1}H NMR spectra were recorded at 300 MHz. The starting materials, ethylenediaminedipropionic acid dihydrochloride (**6**) and 2,3-diaminopropionic acid monohydrochloride (**3**) were obtained from TCI America (Portland, OR).

***N,N*-Bis(*p*-toluenesulfonyl)-*N,N′*-bis(2-carboxyethyl)ethylenediamine (7).** In a three-necked round-bottomed flask equipped with a pH electrode and a mechanical stirrer was placed **6** (5.0 g, 18.0 mmol), dioxane (30 mL), and H_2O (120 mL). A dropping funnel containing 1 N NaOH was placed on the flask, and the pH was adjusted by titration to pH 9 during which time the mixture became homogeneous. An ice bath was placed under the flask and solid *p*-toluenesulfonyl chloride (7.6 g, 39.7 mmol) was added in small portions over 30 min with vigorous stirring. The reaction mixture was maintained at pH 9 for 6 h by titration with NaOH then more *p*-toluenesulfonyl chloride was added (1.5 g). Stirring was continued with pH monitoring for 3 h and then stirred overnight while warming to room temperature during which time the pH had dropped to pH 6 and product had precipitated. NaOH was added until unreacted *p*-toluenesulfonyl chloride alone remained suspended and was filtered off. The pH of the filtrate was lowered to pH 4 with 1 N HCl and cooled in an ice bath. The white solid which precipitated was collected by filtration, washed with H_2O, and dried giving **7** (8.10 g, 88%) as a white solid; mp 204−205 °C; ^{1}H NMR ($CDCl_3$/MeOH-d_4) δ 2.45 (6H, s), 2.62 (4H, t, J = 7.2 Hz), 3.29 (4H, s), 3.42 (4H, t, J = 7.2 Hz), 7.36 (4H, m), 7.73 (4H, m). Anal. Calcd for $C_{22}H_{28}N_2O_8S_2$: C, 51.55; H, 5.52; N, 5.46. Found: C, 51.48; H, 5.53; N, 5.46.

***N,N′*-Bis(*p*-toluenesulfonyl)-2,3-diaminopropionic Acid (4).** In a similar manner, **3** (5.0 g, 0.036 mol) gave **4** (13.6 g, 93%) as a white solid: mp 227−228 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.37 (3H, s), 2.39 (3H, s), 2.61 (1H, m), 2.77 (1H, m), 3.82 (1H, m), 7.29−7.36 (4H, m), 7.51−7.61 (4H, m), 7.69 (1H, m), 8.99 (1H, d, J = 9.0 Hz). Anal. Calcd for $C_{17}H_{20}N_2O_6S_2$: C, 49.50; H, 4.89; N, 6.79. Found: C, 49.23; H, 4.86; N, 6.78.

***N,N′*-Bis(*p*-toluenesulfonyl)-*N,N′*-bis(3-hydroxypropyl)ethylenediamine (8).** To a stirred solution of **7** (25.0 g, 0.049 mol) in anhydrous THF (300 mL) under argon at 0 °C was added BH_3·THF dropwise (Aldrich, 500 mL, 1.0 M solution in THF, 10 equiv), and the mixture was stirred overnight at room temperature. The excess BH_3·THF was evaporated at reduced pressure and the residue treated with 5% HCl giving a white suspension. The pH of the mixture was adjused to pH 9 with 1 N NaOH and extracted with CH_2Cl_2 (3 × 200 mL). The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give **8** (22.6 g, 96%) as a white solid: mp 134−135 °C; ^{1}H NMR ($CDCl_3$) δ 1.79 (4H, m), 2.20 (1H, br s), 2.44 (6H, s), 3.25 (4H, t, J = 6.6 Hz), 3.30 (4H, s), 3.73 (4H, m), 7.33 (4H, m), 7.69 (4H, m). Anal. Calcd for $C_{22}H_{32}N_2O_6S_2$: C, 54.52; H, 6.65; N, 5.78. Found: C, 54.29; H, 6.59; N, 5.72.

***N,N′*-Bis(*p*-toluenesulfonyl)-*N,N′*-bis[[(methanesulfonyl)oxy]propyl]ethylenediamine (9).** To a stirred suspension of **8** (22.5 g, 0.047 mol) in CH_2Cl_2 (500 mL) containing Et_3N (16.2 mL) was added methanesulfonyl chloride (7.91 mL, 2.2 equiv) dropwise at 0 °C, and the mixture was allowed to warm to room temperature overnight during which time it became yellow and homogeneous. The solution was washed with saturated aqueous $NaHCO_3$ (3 × 100 mL) and brine (2 × 100 mL) and then dried ($MgSO_4$) and evaporated under reduced pressure. The solid residue was recrystallized from EtOAc to give **9** (26.8 g, 90%) as a white crystalline solid: mp 148−149 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (4H, m), 2.45 (6H, s), 3.06 (6H, s), 3.23 (4H, t, J = 6.9 Hz), 3.28 (4H, s), 4.30 (4H, t, J = 5.7 Hz), 7.35 (4H, m), 7.69 (4H, m); DCI MS m/z 641 (35, M), 391 (93), 295 (39), 235 (52), 157 (100). Anal. Calcd for $C_{24}H_{36}N_2O_{10}S_4$: C, 44.98; H, 5.66; N, 4.37. Found: C, 44.85; H, 5.63; N, 4.35.

2,3-Bis[(*p*-toluenesulfonyl)amino]-*N*-methoxy-*N*-methylpropanamide (5). To a stirred suspension of **4** (8.0 g, 19.4 mmol) in anhydrous CH_2Cl_2 (200 mL) under argon at 0 °C was added oxalyl chloride (Aldrich, 2 M solution in CH_2Cl_2, 97.0 mL) dropwise followed by DMF (1.0 mL). The mixture was allowed to warm to room temperature over 5 h during which time it became orange and homogeneous. The excess oxalyl chloride was evaporated under reduced pressure and anhydrous CH_2Cl_2 added (200 mL), and the mixture was evaporated once again. This procedure was repeated three times and the residual oil was then placed on a high-vacuum pump for 30 min giving a yellow foam. Anhydrous CH_2Cl_2 (200 mL) was added once again under argon with stirring, and the solution was cooled to 0 °C. *N,O*-Dimethylhydroxylamine hydrochloride (Aldrich, 18.9 g, 10

(26) Although the *p*-toluenesulfonamido group is considered "unstable" with respect to alkyllithium and Grignard reagents, we have found that a large excess of the reagent and elevated temperatures are required for deprotection: See Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*, 2nd ed., John Wiley & Sons, 1991. Similarly, the *N*-methyl amide of **10a** was not observed, see reference 24.

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equiv) was added in one portion followed by anhydrous Et_3N dropwise until all of the *N*,*O*-dimethylhydroxylamine hydrochloride had dissolved. The solution was then allowed to stir overnight at room temperature during which time the orange color had faded. The solvent was evaporated under reduced pressure and the residue partitioned between EtOAc and saturated aqueous $NaHCO_3$, and the organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The solid white residue was dissolved in a minimum volume of EtOAc and triturated with ether giving **5** (7.10 g, 81%) as a white solid: mp 197−198 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (3H, s), 2.44 (3H, s), 3.01 (4H, s overlapping m), 3.24 (1H, m), 3.46 (3H, s), 4.24 (1H, m), 5.09 (1H, m), 5.68 (1H, d, J = 8.4 Hz), 7.26−7.32 (4H, m), 7.66−7.73 (4H, m); DCI MS *m*/*z* 456 (100, M), 302 (42), 172 (26). Anal. Calcd for $C_{19}H_{25}N_3O_6S_2$: C, 50.09; H, 5.53; N, 9.22. Found: C, 50.20; H, 5.50; N, 9.19.

2-(*N*-Methoxy-*N*-methylcarboxamoyl)-1,4,8,11-tetrakis-(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane (10a). To a stirred solution of **5** (7.10 g, 0.0156 mol) and cesium carbonate (12.72 g, 2.5 equiv) in anhydrous DMF (550 mL) maintained at 65 °C (oil bath temperature) was added dropwise a solution of **9** (10.0 g, 1.0 equiv) in DMF (150 mL) over 24 h under argon. The mixture was allowed to stir at 65 °C for 48 h and then allowed to cool and evaporated under reduced pressure. The residue was partitioned between EtOAc and H_2O, and the organic layer was separated, washed exhaustively with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product as a white solid. Purification by column chromatography on silica gel (EtOAc/hexane, 1:1) gave **10a** (9.5 g, 70%) as a white foam: mp 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 1.61−1.92 (2H, br m), 2.25 (2H, br m), 2.43−2.45 (12H, m), 2.85−2.97 (4H, br m), 2.99 (3H, s), 3.04−3.50 (7H, br m), 3.52 (6H, s overlapping m), 5.31 (1H, m), 7.26−7.40 (8H, m), 7.66−7.79 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.42, 25.62, 29.76, 44.85, 47.57, 48.36, 49.06, 50.59, 56.90, 61.30, 127.34−127.89, 129.39−129.77, 133.53, 134.69, 135.30, 136.98, 143.51, 143.97, 166.79; FAB MS *m*/*z* 905 (35, M + H), 904 (56, M), 748 (100), 659 (100). Anal. Calcd for $C_{41}H_{53}N_5O_{10}S_4$: C, 54.42; H, 5.86; N, 7.74. Found: C, 54.42; H, 5.89; N, 7.68.

2-(2-Carbethoxyethenyl)-1,4,8,11-tetrakis(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane (12). To a stirred solution of **10a** (1.50 g, 1.66 mmol) in THF (50 mL) under argon at −20 °C was added $LiAlH_4$ (Aldrich, 1.0 M solution in THF, 2.48 mL, 1.5 equiv) dropwise, and the mixture was stirred at this temperature for 30 min and then quenched with 5% HCl (10 mL). The mixture was extracted with EtOAc (3 × 50 mL), and the combined extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated under reduced pressure to give **11** as a white foamy solid: ^{1}H NMR ($CDCl_3$) δ 1.72−2.02 (4H, m), 2.44 (12H, m), 2.81−3.64 (12H, m), 4.18 (2H, dd, J = 15.7, 5.1 Hz), 4.40 (1H, t, J = 5.1 Hz), 7.26−7.35 (8H, m), 7.60−7.78 (8H, m), 9.76 (1H, s). This was used without further purification. The solid was dissolved in anhydrous CH_2Cl_2 (50 mL) under argon, (carbethoxymethylene)triphenylphosphorane (Aldrich, 578 mg, 1.0 equiv) was added, and the mixture was stirred overnight at room temperature. The solution was evaporated under reduced pressure and purified directly by column chromatography on silica gel (EtOAc/hexane, 1:1) giving a white foamy solid identified by ^{1}H NMR as an 86:14 (*E*:*Z*) mixture of **12** (0.96 g, 64%): mp 110−111 °C; ^{1}H NMR ($CDCl_3$) [*trans*-isomer] δ 1.29 (3H, t, J = 6.9 Hz), 1.70−2.01 (4H, m), 2.41 (3H, m), 2.44 (9H, s), 3.04 (6H, br m), 3.20−3.45 (8H, br m), 4.16 (2H, q, J = 6.9 Hz), 4.40 (1H, m), 5.75 (1H, d, J = 15.9 Hz), 6.85 (1H, dd, J = 15.9, 8.1 Hz), 7.29−7.35 (8H, m), 7.65−7.70 (8H, m); FAB MS *m*/*z* 915 (63, M + H), 869 (27), 760 (100), 606 (52).

2-((2-Carbethoxyethyl)-1,4,8,11-tetrakis(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane (13). To a solution of **12** (0.96 g) in EtOAc/MeOH (1:1, 60 mL) was added palladium on carbon (Aldrich, 10%, 500 mg), and the mixture was hydrogenated on a Parr apparatus at 50 psi for 48 h. The mixture was filtered through Celite and evaporated under reduced pressure, giving **13** as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.2 Hz), 1.60−1.90 (6H, br m), 2.15 (2H, br m), 2.44 (12H, m), 2.80−3.60 (15H, br m), 4.05 (2H, q, J = 7.2 Hz), 7.26−7.34 (8H, m), 7.65−7.80 (8H, m). This was used directly in the next step.

2-(3-Hydroxypropyl)-1,4,8,11-tetrakis(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane (14). The white foam from above was dissolved in anhydrous THF (50 mL) with stirring under argon, and BH_3·THF (Aldrich, 1.0 M solution in THF, 5.0 equiv, 6.3 mL) was added. The mixture was heated to reflux for 5 h and then allowed to cool and evaporated to dryness under reduced pressure, and the residue was quenched with 5% HCl (10 mL). The white suspension was made basic with 1 N NaOH until pH 9 and then extracted with EtOAc (3 × 50 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 7:3) giving **14** (820 mg, 90% from **12**): mp 119−120 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (2H, br m), 1.75−2.04 (6H, br m), 2.44 (12H, s), 2.70−3.41 (15H, br m), 3.46 (2H, m), 7.26−7.35 (8H, m), 7.63−7.75 (8H, m); FAB MS *m*/*z* 875 (100, M + H), 719 (80), 565 (32). Anal. Calcd for $C_{41}H_{54}N_4S_4O_9$: C, 56.22; H, 6.17; N, 6.40. Found: C, 56.17; H, 6.21; N, 6.32.

2-(3-Bromopropyl)-1,4,8,11-tetrakis(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane (15). **14** (600 mg, 0.69 mmol), triphenylphosphine (451 mg, 2.5 equiv), and carbon tetrabromide (570 mg, 2.5 equiv) were heated to reflux in benzene (50 mL) for 5.0 h and then allowed to cool and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:1), giving **15** (550 mg, 85%) as a white foamy solid: mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (2H, br m), 1.60−2.00 (6H, br m), 2.44 (12H, s), 2.90 (2H, m), 3.05−3.49 (15H, br m), 7.31−7.35 (8H, m), 7.63−7.75 (8H, m); FAB MS *m*/*z* 939 (97, M^{81}Br + H), 937 (87, M^{79}Br + H), 783 (100), 627 (34). Anal. Calcd for $C_{41}H_{53}N_4S_4O_8Br$: C, 52.45; H, 5.65; N, 5.97. Found: C, 52.58; H, 5.72; N, 5.85.

1′,4,4′,8,8′,11,11′-Heptakis(*p*-toluenesulfonyl)-1,2′-(1,3-propanediyl)bis(1,4,8,11-tetraazacyclotetradecane) (17). To a solution of **15** (200 mg, 0.21 mmol) and 4,8,11-tris(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane[27] (**16**, 141 mg, 1.0 equiv) in CH_3CN (10 mL) was added anhydrous K_2CO_3 (58 mg, 2.0 equiv), and the mixture was heated to reflux with stirring for 8 days under argon. The mixture was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel (EtOAc/hexane, 6:4) to give **17** (200 mg, 62%) as a white foamy solid: mp 135−136 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (6H, br m), 2.90 (6H, br m), 2.20 (2H, br m), 2.42 (21H, br m), 2.50 (2H, br m), 2.80−3.61 (29H, br m), 7.26−7.32 (14H, m), 7.64−7.80 (14H, m); FAB MS *m*/*z* 1519 (100, M + H), 1363 (31), 1209 (8). Anal. Calcd for $C_{72}H_{94}N_8S_7O_{14}$: C, 56.84; H, 6.18; N, 7.37. Found: C, 57.26; H, 6.39; N, 7.06.

1,2′-(1,3-Propanediyl)bis(1,4,8,11-tetraazacyclotetradecane) Octahydrobromide Dihydrate [(±)JM2936, 2]. **17** (550 mg) was dissolved in a mixture of acetic acid and hydrobromic acid (Aldrich, 48% aqueous, 50 mL) (3:2) and heated to reflux for 4 days during which time a white crystalline solid precipitated. The mixture was allowed to cool, and the solid was collected by filtration, washed with acetic acid and then ether, and dried *in vacuo* to give **2** (275 mg, 70%) as a white powder: mp 270−271 °C dec.; ^{1}H NMR (D_2O) δ 1.40 (2H, m), 1.50−1.95 (10H, br m), 2.60−2.80 (2H, m), 2.80−3.50 (31H, br m); FAB MS *m*/*z* 524 (89, MH + H^{81}Br), 522 (100, MH + H^{79}Br), 442 (68, M + H). Anal. Calcd for $C_{23}H_{52}N_8$·8HBr·2H_2O: C, 24.55; H, 5.69; N, 9.96. Found: C, 24.57; H, 5.75; N, 9.64.

Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **10b**, **11**, **12**, and **13** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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