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# N-Functionalization of Poly(ethylene glycol)-Linked Mono- and Bis-dioxocyclams as Potential Ligands for $Gd^{3+}$

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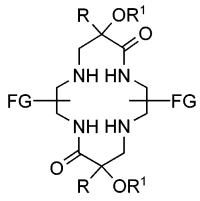
A number of highly functionalized dioxocyclams with acetic acid side chains on the secondary amine sites and ethylene glycol side chains on 6 and 13-positions (**12a**, **12b**) or a tetra(ethylene glycol) side chain linking the 6 and 13 positions (**15**) were synthesized and characterized, as was a bis-dioxocyclam bridged across the 6 and 13 positions by tetra(ethylene glycol) groups (**16**). These were screened for their ability to complex $Gd^{3+}$. Only ligands **15** and **16**, having tetra(ethylene glycol) groups, formed such complexes.

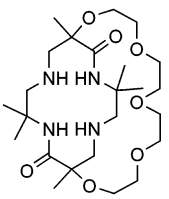
## Introduction

Polyazamacrocycles with acetic acid side chains pendant from ring amino groups are excellent ligand systems for lanthanides (e.g., $Gd^{3+}$) and have found extensive research and commercial application for the development of magnetic imaging contrast agents.[1] A majority of macrocyclic contrast agents are based on the cyclen (1,4,7,10-tetraazacyclododecane) ring system with various coordinating side chains attached at ring amino groups,[1a,c,d,2] although a number of acyclic ones are in use as well.[1a,b] Considerably larger, polyfunctional systems which can complex more than one $Gd^{3+}$ have also been developed.[3]

Recent studies in these laboratories have resulted in efficient syntheses of variously substituted dioxocyclams (**1**)[4] as well as poly(ethylene glycol)-capped dioxocyclams (**2**) and bridged bis-dioxocyclams (**3**).[5] Further functionalizations of these macrocycles to provide new ligands as potential contrast agents are presented below.




**1**

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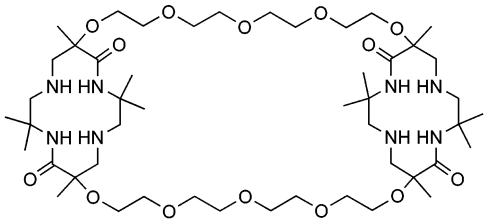


**3**

## Results and Discussion

Studies were initiated by introduction of acetic acid side chains into the previously synthesized[4] *C*-2 symmetric (**4a**) and centrosymmetric (**4b**) monocyclams, which occurred cleanly upon treatment with *tert*-butyl bromoacetate and Hünigs base (eq 1). Macrocycle **4b** was considerably less reactive than **4a**, with 56% of **4b** being recovered. (The yield based on recovered starting material was 92%.) Cleavage of the *tert*-butyl esters to the free acids was achieved by heating in formic acid. However, diacids **6a** and **6b** were quite insoluble in most solvents, including neutral water, so more soluble derivatives were sought.

Photolysis of **7**[6] in the presence of Cbz-protected dimethylimidazoline produced protected azapenam **8** in good yield (Scheme 1).[4] Hydrogenolysis of the Cbz group

(1) (a) Caravan, P.; Ellison, J. J.; McMurray, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293−2352. (b) Bianchi, A.; Calabi, L.; Corana, F.; Fontana, S.; Losi, P.; Maiocchi, A.; Paleari, L.; Valtancoli, B. *Coord. Chem. Rev.* **2000**, *204*, 309−393. (c) Lukes, I.; Kotek, J.; Vojisek, P.; Hermann, P. *Coord. Chem. Rev.* **2001**, *216−217*, 287−312. (d) Jacques, V.; Desreux, J.-F. *Chemistry of Contrast Agents in Magnetic Resonance Imaging*; Wiley: Chichester, 2001; pp 157−191.

(2) (a) Aime, S.; Cravatto, G.; Crich, S. G.; Giovenzana, G. B.; Ferrari, M.; Palmisano, G.; Sisti, M. *Tetrahedron Lett.* **2002**, *43*, 783−786. (b) Aime, S.; Botta, M.; Frullano, L.; Crich, S. G.; Geninatti, G. G.; Pagliarin, R.; Palmisano, G.; Sirtori, F. R.; Sisti, M. *J. Med. Chem.* **2000**, *43*, 4017−4024. (c) Zhang, S.; Kuangcong, S. A. D. *Angew. Chem., Int. Ed. 38*, 3192−3184. (d) Baker, W. C.; Choi, M. J.; Hill, D. C.; Thompson, J. L.; Petillo, P. A. *J. Org. Chem.* **1999**, *64*, 2683−2689.

(3) (a) Inoue, M. B.; Santa Cruz, H.; Inoue, M.; Fernando, Q. *Inorg. Chem.* **1999**, *38*, 1596−1602. (b) Ranganathan, R.; Fernandez, M. E.; Kang, S. I.; Nunn, A. D.; Ratsep, P. C.; Pillai, K. M. R.; Zhang, X.; Tweedle, M. F. *Invest. Radiol.* **1998**, *33*, 779−797. (c) Mondry, A.; Starynowicz, P. *Inorg. Chem.* **1997**, *36*, 1176−1180.

(4) (a) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010−5017. (b) Dumas, S.; Lastra, E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3368−3379.

(5) Puntener, K.; Hellman, M. D.; Kuester, E.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 8301−8306.

(6) Hafner, A.; Hegedus, L. S.; DeWeck, G.; Hawkins, B.; Doetz, K. H. *J. Am. Chem. Soc.* **1988**, *110*, 8413−8421.

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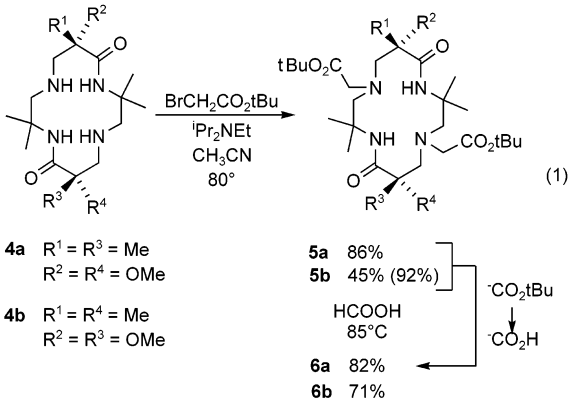
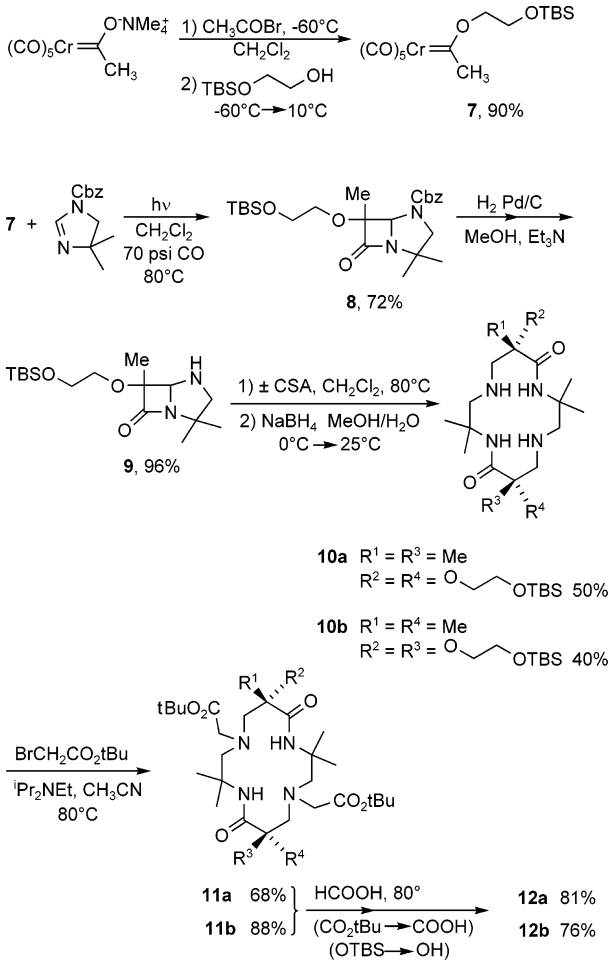


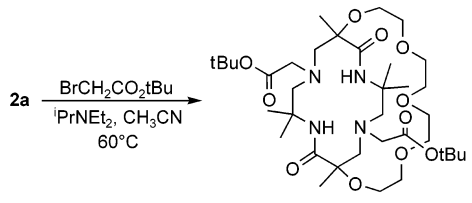

gave free azapenam **9** in excellent yield. Acid-catalyzed dimerization followed by reduction with sodium borohydride gave a 1:1 mixture of dioxocyclams **10a** and **10b**, which were easily separated by flash chromatography. N-Alkylation with *tert*-butyl bromoacetate followed by heating in neat formic acid gave free acids **12a** and **12b** in good yield.

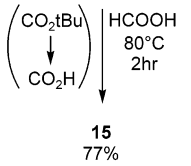
These were substantially more soluble than the corresponding *O*-methyl acids **6a** and **6b**, easily dissolving in methanol, water, and even THF. Recrystallization from methanol/ether gave X-ray quality crystals. An X-ray crystal structure of **12a** was obtained, and a stereoview of it is shown in Figure 1. The amide oxygens and the carboxylates form a potential binding pocket for lanthanides.

Of particular interest were tetra(ethylene glycol)-capped (**2**) and -bridged (**3**) dioxocyclams. These compounds are freely soluble in most solvents, including water, and have amine, amide oxygen, and ether oxygen ligands to bind to lanthanides.[3] Introduction of acetic acid side chains would give charged ligating sites to mitigate the charge on the metal and increase binding. N-Alkylation of **2** and **3** with *tert*-butyl bromoacetate gave di-and tetraesters **13** and **14**, respectively, in good yield (eqs 2 and 3). Cleavage of the esters with formic acid gave free di- and tetraacids **15** and **16** in fair yield. These were fully characterized and their structures determined by single-crystal X-ray diffraction (Figure 2). For the "basket" diacid **15**, the carboxylate groups flank the cavity formed by the polyether chain, while the amide oxygens project outward from the face of the macrocycle. (The lattice also contained a molecule of water). For the bis-cyclam tetraacid **16** two potential lanthanide coordination pockets are evident.

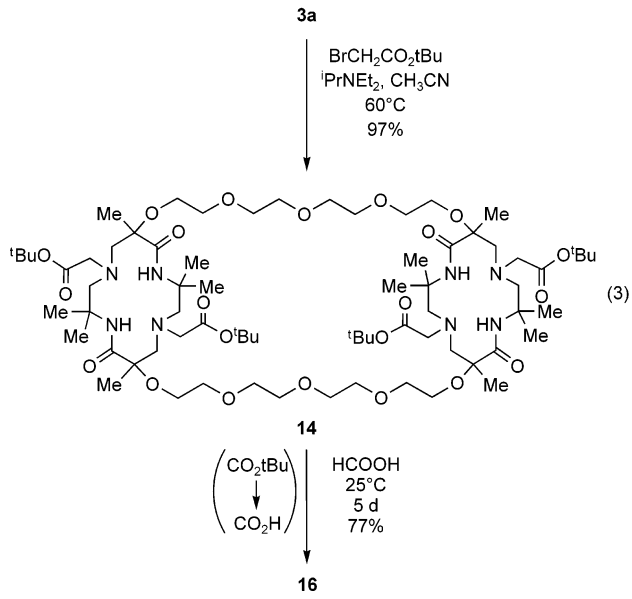
**SCHEME 1**




(2)




(3)

Finally, a more highly functionalized system was synthesized starting with optically active imidazoline **17**[7] (Scheme 2). Photolysis with tetra(ethylene glycol)-linked

(7) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586−3591.

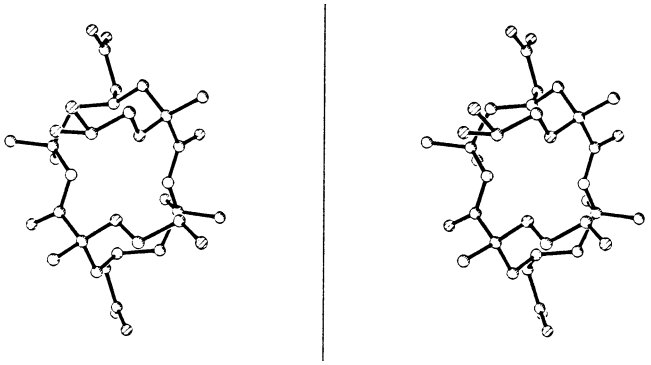
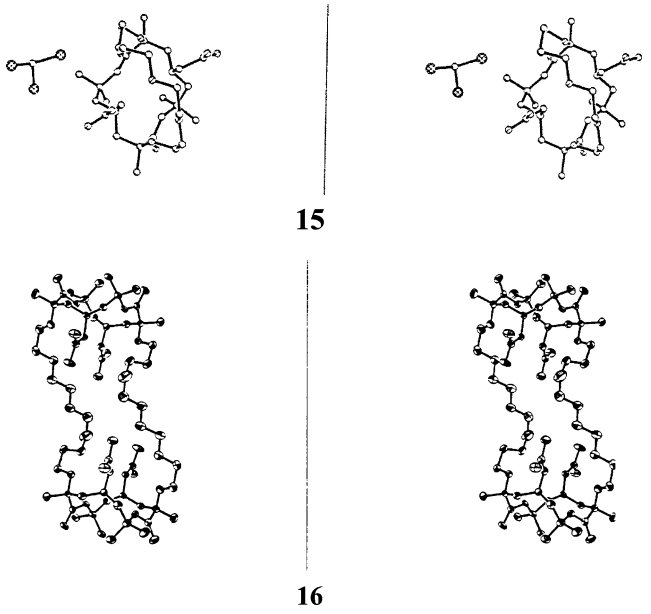


**FIGURE 1.** Stereoview of diacid **12a**.



**15**

**16**

**FIGURE 2.** Stereoviews of compounds **15** and **16**.

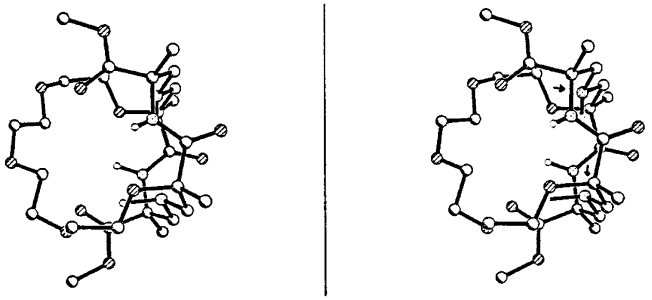
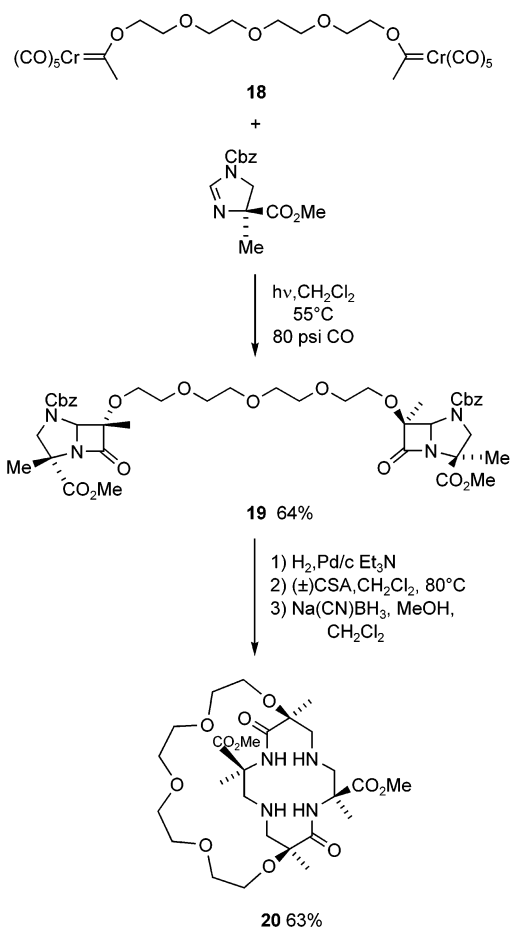


**FIGURE 3.** Stereoview of compound **20** (arrows indicate amine N's).

bis-carbene complex **18** produced protected bis-azapenam **19** in fair yield. Removal of the Cbz group by hydrogenolysis followed by acid-catalyzed cyclization produced "basket" dioxocyclam **20** in modest yield. All attempts to alkylate the secondary amine groups with *tert*-butyl bromoacetate failed. An X-ray structure of **20** was obtained. Examination of a stereoview of the compound (Figure 3) shows that these groups are somewhat inaccessible, accounting for the lack of reactivity.

**SCHEME 2**




One motivation for synthesizing these ligands was to screen them for their ability to complex $Gd^{3+}$ for ultimate use as magnetic resonance imaging contrast agents. Previous studies[5] had shown that the tetra(ethylene glycol)-containing cyclams **2** and **3** did complex $Gd^{3+}$ (from infrared and mass spectrometric data), but only weakly in most cases. Addition of acetic acid side chains to the secondary amines should add additional coordination sites similar to those found in commercial contrast agents (see above).

Macrocycles **6a**, **6b**, **12a**, and **12b** failed to complex $Gd^{3+}$ under a variety of conditions. This is somewhat surprising since these systems had many features found in commercial contrast agents, e.g., tetrazamacrocycles with pendant acetic acid side chains. The major structural differences—ring size (12 vs 14), nitrogen functionality (tetraamine vs diamine diamide), and number of acetic acid side chains (three or four vs 2)—apparently are sufficient to reduce the $Gd^{3+}$ complexation ability of **6** and **12**.

In contrast, treatment of "basket" diacid **15** with $Gd_2(CO_3)_3$ in 10% aq HCl for 2 days at 100 °C produced an off-white solid. The positive-ion electrospray mass spectrum[8] had a base peak of *m*/*z* 617, corresponding to the

(8) For recent examples of the use of electrospray mass spectroscopy for the characterization of gadolinium complexes, see: (a) Chen, Q.-Y.; Luo, Q.-H.; Zheng, L.-M.; Wang, Z.-L.; Chen, J.-T. *Inorg. Chem.* **2002**, *41*, 605−609. (b) Colette, S.; Amekraz, B.; Madic, C.; Berthon, L.; Cote, G.; Moulin, C. *Inorg. Chem.* **2003**, *42*, 2215−2226.

(9) Fischer, E. O.; Maâsböl, A. *Chem. Ber.* **1967**, *100*, 2445−2448.

free ligand. A set of peaks centered at *m*/*z* 774 with a relative abundance of 40% corresponds to $[L + Gd - 2H]^+$, the dicarboxylate $Gd^{3+}$ monocation. The isotopic distribution of the peak cluster corresponded to that calculated for $C_{28}H_{47}GdN_4O_{11}$ which is $[L + Gd - 2H]^+$. The high-resolution exact mass measurement of the 774 peak had a value of 774.2575 compared to a calculated value of 774.2561 for $C_{28}H_{48}N_4O_{11}Gd^{160}$. Negative-ion electrospray mass spectroscopy gave again, a base peak of *m*/*z* 617 with set of peaks centered around *m*/*z* 844 with a relative abundance of 35%. The isotopic distribution of this peak cluster corresponded to that calculated for $C_{28}H_{48}Cl_2GdN_4O_{11}$, from $[L + GdCl_2 - 2H]^-$ corresponding to $Gd^{3+}$ coordinated to two carboxylates of the ligand and two chlorides from the HCl used in its preparation.

Treatment of bis cyclam tetraacid **16** with $Gd_2(CO_3)_3$ in water at 95 °C for 20 h followed by treatment of the precipitate with 10% aq HCl produced an off-white solid. The positive ion electrospray mass spectrum had a parent ion of *m*/*z* 619, corresponding to $(L)^{2+}$, a peak of 45% relative abundance at *m*/*z* 1237 corresponding to $L^+$, a cluster of peaks (5% relative abundance) centered around *m*/*z* 1392 corresponding to $[L + Gd - 2H]^+$, with an isotopic distribution corresponding to that calculated for $C_{56}H_{98}GdN_8O_{22}$, and a very small cluster of peaks (relative abundance < 2%) centered around *m*/*z* 774, corresponding to $[L + 2Gd]^{2+}$, again with an isotopic distribution calculated for that fragment. The negative-ion electrospray mass spectrum had similar features with a base peak *m*/*z* 1235 corresponding to free ligand and a cluster of peaks (25% relative abundance) centered around *m*/*z* 1390 corresponding to $[L + Gd - 4H]^-$, again with the calculated isotope distribution.

Analytical TLC of both Gd complexes indicated there was no free ligand in the bulk material subjected to electrospray mass spectroscopy. Their infrared spectra showed no shift in the CO stretching frequency of the amides indicating that these moieties were not involved in binding.

In summary, a number of highly functionalized dioxocyclams were prepared and screened for their ability to complex $Gd^{3+}$. Only those having poly(ethylene glycol) appendages formed such complexes, and the amide groups appear *not* to be involved in metal ion complexation. Since attempts to grow X-ray quality crystals failed and since mass spectroscopic studies suggest relatively weak binding of $Gd^{3+}$ (the base peak is that of free ligand), further physical studies were not pursued.

## Experimental Section

**(6*S**,13*S**)-8,15-*N*,*N*′-Diacetic Acid 3,3,6,10,10,13-Hexamethyl-6,13-dimethoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione Di-*tert*-butyl Ester (5a).** Dimethoxycyclam **4a** (73 mg, 0.206 mmol) was dissolved in $CH_3CN$ (2 mL). *tert*-Butyl bromoacetate (122 μL, 0.825 mmol) and Hunig's base (158 μL, 0.906 mmol) were added dropwise. The clear solution was warmed to 70 °C overnight (14h ). The reaction was warmed to 85 °C for 2.5 h and then allowed to cool to ambient temperature. The solution was concentrated in vacuo and the residue dissolved in $CH_2Cl_2$ (30 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL). The combined aqueous layers were extracted with $CH_2Cl_2$ (20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (10 g $SiO_2$, 1:1 to 2:1 EtOAc/Hex) gave diester **5a** (106 mg, 86%) as a white, foamy solid: mp 146−147 °C; FTIR (neat) $\nu$ 3323, 1733, 1657 $cm^{-1}$; $^1H$ NMR $\delta$ 8.46 (s, 2H), 3.41 (m, 4h), 3.25 (s, 6H), 3.09 (d, $J$ = 15.2 Hz, 2H, 2.84 (d, $J$ = 7.3 Hz, 2H), 2.79 (d, $J$ = 7.3 Hz, 2H), 2.39 (d, $J$ = 15.2 Hz, 2H), 1.44 (s, 6H), 1.41 (s, 18H), 1.21 (s, 6H), 1.18 (s, 6H); $^{13}C$ NMR $\delta$ 173.5, 171.5, 82.7, 80.9, 67.4, 61.4, 59.7, 55.4, 48.7, 28.2, 25.2, 23.7, 18.4; MS (FAB) *m*/*z* calcd for $C_{30}H_{57}N_4O_8$ ($M^+ + 1$) 601.42, found 601.37. Anal. Calcd for $C_{30}H_{57}N_4O_8$: C, 59.97; H, 9.40; N, 9.33. Found: C, 60.14; H, 9.28; N, 9.25

**(6*R**,13*S**)-8,15-*N*,*N*′-Diacetic Acid 3,3,6,10,10,13-hexamethyl-6,13-dimethoxy-1,4,8,11-tetraazacytclotetradecane-5,12-dione Di-*tert*-butyl Ester (5b).** Dimethoxycyclam **4b** (39 mg, 0.110 mmol) was dissolved in $CH_3CN$ (3 mL). *tert*-Butyl bromoacetate (81 μL, 0.55 mmol) and Hunig's base (131 μL, 0.77 mmol) were added dropwise. The clear solution was heated overnight (19 h) at 80 °C. The orange solution was allowed to cool to ambient temperature. The reaction solution was concentrated in vacuo. The residue was dissolved in $CH_2Cl_2$ (30 mL) and washed with 10% $NaOH_{aq}$ solution (2 × 15 mL) and $H_2O$ (15 mL) and brine (15 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (10 g $SiO_2$, 4−10% MeOH/$CH_2Cl_2$) gave recovered **4b** (22 mg) along with diester **5b** (30 mg, 45% yield, 92% based on recovered starting material) as a white solid: mp 178−181 °C; FTIR (neat) $\nu$ 3325, 1734, 1668 $cm^{-1}$; $^1H$ NMR $\delta$ 7.22 (s, 2H), 3.48 (s, 4H), 3.23 (s, 6H), 3.06−2.99 (m, 6H), 2.70 (d, $J$ = 14.6 Hz, 2H), 1.44 (s, 18H), 1.37 (s, 6H), 1.33 (s, 6H), 1.28 (s, 6H); $^{13}C$ NMR $\delta$ 172.4, 171.1, 82.2, 80.9, 66.2, 61.8, 58.8, 53.9, 50.8, 28.3, 26.9, 25.5, 19.6; MS (FAB) *m*/*z* calcd for $C_{30}H_{57}N_4O_8$ ($M^+ + 1$) 601.42, found 601.34. Anal. Calcd for $C_{30}H_{57}N_4O_8$: C, 59.97; H, 9.40; N, 9.33. Found: C, 60.36; H, 9.39; N, 9.48.

**(6*S**,13*S**)-8,15-*N*,*N*-Diacetic Acid 3,3,6,10,10,13-Hexamethyl-6,13-dimethoxy-1,4,8,11-tetrazacyclotetradecane-5,12-dione (6a).** Diester **5a** (47 mg, 0.08 mmol) was heated at 85 °C overnight in 3.0 mL of formic acid. The reaction was cooled to room temperature, concentrated under vacuum, and dried under high vacuum. Trituration with $CHCl_3$/MeOH followed by drying gave 31 mg (82%) of an off-white solid. This material was insoluble in most solvents including neutral water. For this reason, no further purification or characterization was attempted.

**(6*R**,13*S**)-8,15-*N*,*N*-Diacetic Acid 3,3,6,10,10,13-Hexamethyl-6,13-methoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione (6b).** The same procedure was followed with **5b** (107 mg, 0.18 mmol, 5 mL formic acid) to yield 67 mg (77%) of **6b** as a white powder. It was only soluble in hot aqueous HCl and was not further characterized.

**TBDMS-Protected Chromium Alkoxycarbene Complex 7.** Methyl tetramethylammonium "ate" complex (2.63 g, 8.5 mmol) was dissolved in 60 mL of dry $CH_2Cl_2$ under an argon atmosphere, and the solution was cooled to −60 °C. Acetyl bromide (0.63 mL, 8.5 mmol) was added dropwise, and the resulting solution was allowed to stir at −60 °C for 30 min. Then TBDMS-monoprotected ethylene glycol was added to the solution in 5 mL of dry $CH_2Cl_2$. The resulting solution was slowly warmed to −10 °C over 4.5 h. The reaction mixture was filtered through a pad of silica gel, and the solvent was removed in vacuo. The resulting dark orange oil was then adsorbed onto silica gel and purified by column chromatography on silica gel (hexane/EtOAc 9:1) to give 1.78 g (90%) of complex **7** as a yellow-orange oil: $^1H$ NMR $\delta$ 5.0 (bs, 2H) 4.15 (t, $J$ = 4 Hz, 2H), 2.98 (s, 3H), 0.91 (s, 9H), 0.11 (s, 6H).

This material was used without further characterization since it was somewhat unstable.

**Protected Azapenam 8.** Cbz-protected dimethyl imidazoline (0.54 g, 2.34 mmol) in 5 mL of $CH_2Cl_2$ was transferred into a pressure tube under argon via a cannula, and the mixture was thoroughly degassed by three freeze−pump−thaw cycles under argon. The tube was then filled with CO (75 psi)

and vented three times, pressurized with 75 psi of CO, and placed in an 80 °C photochemical reactor for 3 days. After this period, the CO was vented and the light yellow solution concentrated under vacuum, diluted with 100 mL of methanol, and cooled for several hours at −20 °C to precipitate $Cr(CO)_6$. After filtration through Celite and concentration under vacuum, the golden brown oil was purified by flash chromatography (Si gel) (4:1 → 1:1 → 0:1 hexane/ethyl acetate) to give protected azapenam **8** (0.77 g, 72% yield) as a mixture of Cbz rotomers. This material was deprotected without further purification: FT IR (neat) $\nu$ 1776, 1718 $cm^{-1}$; $^1H$ NMR (mixture of Cbz rotomers) $\delta$ 7.30 (m, 5H), 5.14 (m, 3H), 3.72 (m, 5H), 3.14 (d, $J$ = 7 Hz, 1H), 1.62 (s, 3H), 1.18 (m, 6H), 0.86 (s, 12H), 0.08 (s, 6H); $^{13}C$ NMR $\delta$ 173.4, 153.5, 135.8, 128.7, 128.4, 128.3, 128.1, 90.2, 75.1, 74.6, 67.8, 67.6, 62.5, 61.3, 60.9, 60.6, 29.9, 26.2, 22.9, 22.1, 18.6, 14.4, 14.1, −4.9.

**(5*R**,6*S**)-6-*tert*-Butyldimethylsiloxyethoxy-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]heptane-7-one (9).** Azapenam **8** (910 mg, 1.91 mmol) was dissolved in MeOH (25 mL) and transferred to an oven-dried pressure tube. Triethylamine (300 $\mu$L) was added and the system flushed with argon. 10% Palladium on carbon (468 mg) was added and the system flushed with $H_2$ (3 × 75 psi). The system was pressurized with $H_2$ (75 psi) and stirred at ambient temperature for 2 h. After the system was flushed with argon, the mixture was filtered through Celite, rinsed with EtOAc, and concentrated in vacuo. Purification by flash chromatography (10 g $SiO_2$, 9:1 → 4:1 $CH_2Cl_2$/$Et_2O$) gave azapenam **9** (600 mg, 96%) as a clear oil: FTIR (neat) $\nu$ 3357, 1751 $cm^{-1}$; $^1H$ NMR $\delta$ 4.76 (s, 1H), 3.80−3.60 (m, 4H), 3.06 (d, $J$ = 11.0 Hz, 1H), 2.62 (d, $J$ = 11.3 Hz, 1H), 2.27 (br s, 1H), 1.56 (s, 3H), 1.31 (s, 3H), 1.10 (s, 3H), 0.89 (s, 9H), 0.067 (s, 6H); $^{13}C$ NMR $\delta$ 78.2, 67.5, 62.8, 62.2, 61.1, 26.1, 25.1, 21.9, 20.6, 18.6, 15.0, −4.99, −5.01; MS (FAB) $m/z$ calcd for $C_{16}H_{33}N_2O_3Si$ ($M^+$ + 1) 329.23, found 329.25. Anal. Calcd for $C_{16}H_{33}N_2O_3Si$: C, 58.50; H, 9.82; N, 8.53. Found: C, 58.53; H, 9.69; N, 8.73.

**(6*R**,13*S**)- and (6*S**,13*S**)-3,3,6,10,10,13-Hexamethyl-6,13-bis-*tert*-butyldimethylsilyloxyethoxy-1,4,8,11-tetraazacyclotetradeca-7*E*,14*E*-diene-5,12-dione.** Azapenam **9** (2.03 g, 6.18 mmol) was dissolved in $CH_2Cl_2$ (70 mL) and the solution transferred to an oven-dried pressure tube. (±)-Camphorsulfonic acid (215 mg, 0.93 mmol) was added and the tube fitted with a pressure head. The solution was heated to 120 °C and then cooled to 80 °C and stirred 2 h. The reaction solution was allowed to cool to ambient temperature and washed with a 5% aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 75 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated to give the bis-imine cyclam (2.03 g) as a viscous oil, which was used without further purification: FTIR (neat) $\nu$ 3416, 1682 $cm^{-1}$; $^1H$ NMR $\delta$ 7.64 (s, 2H), 7.42 (s, 2H), 7.53 (s, 2HO), 7.00 (s, 2H) 4.05 (t, $J$ = 11.7 Hz, 4H), 3.83−3.70 (m, 10H), 3.57−3.32 (m, 6H), 3.37 (d, $J$ = 11.0.4 Hz, 2H), 1.50 (s, 6H), 1.48 (s, 6H), 1.46 (s, 6H), 1.38 (s, 6H), 1.37 (s, 6H), 1.30 (s, 6H), 0.90 (s, 36H), 0.078 (s, 24H); $^{13}C$ NMR $\delta$ 170.2, 169.6, 167.5, 167.1, 82.0, 81.2, 68.2, 67.0, 66.2, 63.0, 62.9, 54.4, 54.0, 27.0, 26.3, 25.3, 26.2, 26.2, 26.2, 26.1, 26.1, 25.9, 25.4, 25.1, 22.4, 19.2, 18.7, 18.7, −4.87, −4.91, −4.95; MS (FAB) $m/z$ calcd for $C_{32}H_{65}N_4O_6Si_2$ [$M^+$ + 1] 657.44, found 657.51.

**(6*S**,13*S**)- and (6*R**,13*S**)-3,36,10,10,13-Hexamethyl-6,13-bis-*tert*-butyldimethylsilyloxyethoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione (10a and 10b).** The crude bis-imine cyclam (2.03 g, 3.09 mmol) was dissolved in MeOH (250 mL) and $H_2O$ (50 mL). The solution was cooled to 0 °C. Sodium borohydride (3.51 g, 92.8 mmol) was added in small portions over 2 h. The reaction was allowed to warm to ambient temperature overnight. The murky solution was concentrated in vacuo to remove MeOH. The white slurry was diluted with a 5% aqueous solution of $NaHCO_3$ (150 mL) and extracted with $CH_2Cl_2$ (3 × 150 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (100 g $SiO_2$, 90:10:1 → 80:20:1 Hex/EtOAc/$Et_3N$) gave *meso*-**10b** (820 mg, 40% yield) and (*d*,*l*)-**10a** (1.02 g, 50%) as a white solid and viscous oil, respectively. *meso*-**10b**: mp 128−129 °C; FTIR (neat) $\nu$ 3228, 1664 $cm^{-1}$; $^1H$ NMR $\delta$ 8.35 (s, 2H), 3.72 (t, $J$ = 5.1 Hz, 4H), 3.56−3.49 (m, 2H), 3.38−3.31 (m, 2H), 2.85 (br t, $J$ = 11.5 Hz, 4H), 2.66 (t, $J$ = 11.0 Hz, 2H), 2.36 (dd, $J$ = 10.2, 11.4 Hz, 2H), 1.76 (s, 2H), 1.37 (s, 12H), 1.28 (s, 6H), 0.89 (s, 18H), 0.059 (s, 12H). Anal. Calcd for $C_{32}H_{69}N_4O_6Si_2$: C, 58.14; H, 10.37; N, 8.48. Found: C, 58.31; H, 10.26; N, 8.61.

(*d*,*l*)-**10a**: FTIR (neat) $\nu$ 3416, 1681 $cm^{-1}$; $^1H$ NMR $\delta$ 6.84 (s, 2H), 3.77 (dd, $J$ = 4.8, 5.5 Hz, 4H), 3.57−3.41 (m, 6H), 2.83 (d, $J$ = 12.4 Hz, 2H), 2.59 (d, $J$ = 11.7 Hz, 2H), 2.05 (d, $J$ = 11.4 Hz, 2H), 1.38 (s, 6H), 1.29 (s, 6H), 1.22 (s, 6H), 0.92 (s, 18H), 0.092 (s, 12H); $^{13}C$ NMR $\delta$ 172.2, 80.0, 64.2, 63.1, 56.4, 56.4, 42.9, 27.3, 26.1, 26.0, 25.8, 25.3, 19.5, 18.7, −4.87, −4.95. Anal. Calcd for $C_{32}H_{69}N_4O_6Si_2$: C, 58.14; H, 10.37; N, 8.48. Found: C, 58.03; H, 10.19; N, 8.47.

**(6*S**,13*S**)-8,15-*N*,*N*′-Diacetic Acid 3,3,6,10,10,13-Hexamethyl-6,13-bis-*tert*-butyldimethylsiloxyethoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione Di-*tert*-butyl Ester 11a.** Dioxocyclam **10a** (150 mg, 0.227 mmol) was dissolved in $CH_3CN$ (3 mL). Hunig's base (168 $\mu$L, 0.999 mmol) and *tert*-butyl bromoacetate (134 $\mu$L, 0.908 mmol) were added dropwise, and the clear solution was warmed to 65 °C overnight. The reaction was warmed to 90 °C for 2 days. The orange solution was allowed to cool to ambient temperature and concentrated in vacuo. The residue was dissolved in $CH_2Cl_2$ (15 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (15 mL) and $H_2O$ (15 mL). The combined aqueous layers were extracted with $CH_2Cl_2$ (15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (10 g $SiO_2$, 2:1 → 1:1 Hex/$Et_2O$) gave diester **11a** (138 mg, 68%) as a viscous oil: FTIR (neat) $\nu$ 3347, 1735, 1658 $cm^{-1}$; $^1H$ NMR $\delta$ 8.12 (s, 2H), 3.81 (t, $J$ = 7.3 Hz, 4H), 3.65−3.48 (m, 6H), 3.23 (d, $J$ = 15.4 Hz, 2H), 2.90 (d, $J$ = 15.0 Hz, 2H), 2.80 (d, $J$ = 15.0 Hz, 2H), 2.52 (d, $J$ = 15.4 Hz, 2H), 1.45 (s, 24H), 1.29 (s, 6H), 1.26 (s, 6H), 0.88 (s, 18H), 0.049 (s, 12H); $^{13}C$ NMR $\delta$ 172.7, 171.3, 83.8, 80.9, 67.2, 64.0, 61.8, 60.8, 59.9, 55.8, 29.4, 28.3, 25.9, 25.5, 24.0, 19.5, 18.4, −5.2; MS (FAB) $m/z$ calcd. for $C_{44}H_{89}N_4O_{10}Si_2$ [$M^+$+ 1] 889.61, found 889.83. Anal. Calcd for $C_{44}H_{89}N_4O_{10}Si_2$: C, 59.42; H, 9. 97; N, 6. 30. Found: C, 59.60; H, 9.73; N, 6.26.

**(6*R**,13*S**)-8,15-*N*,*N*′-Diacetic Acid 3,3,6,10,10,13-hexamethyl-6,13-bis-*tert*-butyldimethylsiloxyethoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione Di-*tert*-butyl Ester (11b).** Dioxocyclam **10b** (150 mg, 0.227 mmol) was dissolved in $CH_3CN$ (2 mL). Hunig's base (168 $\mu$L, 0.999 mmol) and *tert*-butyl bromoacetate (134 $\mu$L, 0.908 mmol) were added dropwise, and the clear solution was warmed to 90 °C for 24 h. The orange solution was allowed to cool to ambient temperature and concentrated in vacuo. The residue was dissolved in $CH_2Cl_2$ (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and $H_2O$ (20 mL). The combined aqueous layers were extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (10 g $SiO_2$, 2:1 Hex/$Et_2O$) gave diester **11b** (178 mg, 88%) as a yellow solid: mp 104−106 °C; FTIR (neat) $\nu$ 3405, 1733, 1676 $cm^{-1}$; $^1H$ NMR $\delta$ 6.96 (s, 2H), 3.74−3.42 (m, 12H), 3.20−3.13 (m, 4H), 2.94 (d, $J$ = 15.0 Hz, 2H), 2.63 (d, $J$ = 14.2 Hz, 2H), 1.44 (s, 18H), 1.32 (s, 6H), 1.30 (s, l2H), 0.88 (s, 18H), 0.045 (s, 12H); $^{13}C$ NMR $\delta$ 172.9, 171.2, 82.5, 80.6, 64.6, 64.4, 62.5, 60.0, 57.4, 53.7, 29.4, 28.2, 27.1, 26.0, 21.0, 18.3, −5.2; MS (FAB) $m/z$ calcd. for $C_{44}H_{89}N_4O_{10}Si_2$ [$M^+$ + 1] 889.61, found 889.82. Anal. Calcd for $C_{44}H_{89}N_4O_{10}Si_2$: C, 59.42; H, 9.97; N, 6.30. Found: C, 59.55; H, 9.76; N, 6.38.

**(6*S**,13*S**)-8,15-*N*,*N*′-Diacetic Acid 3,3,6,10,10,13-Hexamethyl-6,13-bis-$\beta$-hydroxyethoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione (12a).** Diester **11a** (92 mg, 0.10 mmol) was dissolved in 3 mL of formic acid and heated at 80 °C for 2 h. The solution was cooled, concentrated in a vacuum,

azeotroped with 3 × 5 mL of toluene, and dried under high vacuum. The white powder was dissolved in hot ethyl acetate. On cooling and standing, a white precipitate formed (46 mg, 81%): $^1$H NMR $\delta$ 8.27 (br s, 2H), 4.53 (m, 2H), 4.25 (m, 2H), 4.04 (d, $J$ = 12 Hz 1H), 3.45−3.73 (m, 6H), 3.02−2.84 (m, 12H), 1.45 (s, 6H), 1.30 (s, 6H), 1.29 (s, 6H). This material was characterized by single-crystal X-ray diffraction.

**(6*R**,13*S**)-8,15-*N*,*N*-Diacetic Acid 3,3,6,10,10,13-Hexamethyl-6,13-bis-hydroxyethoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione (12b).** Prepared by the above procedure from 128 mg (0.14 mmol) of **11b** and 5 mL of formic acid to give 60 mg of **12b** as a white powder: $^1$H NMR $\delta$ 8.12 (s, 2H), 6.2 (br s, 4H), 4.50 (m, 2H), 4.32 (m, 2H), 3.7−3.9 (n, 6H), 3.20 (m, 4H), 3.05 (m, 2H), 1.56 (s, 6H), 1.35 (s, 6H), 1.33 (s, 6H).

**Dioxocyclamdiacetic Acid *tert*-Butyl Ester 13.** Hunig's base (211 $\mu$L, 1.21 mmol) was added dropwise to a solution of dioxocyclam **2**[5] (146 mg, 0.291 mmol) and $CH_3CN$ (1.8 mL). *tert*-Butyl bromoacetate (175 $\mu$L, 1.18 mmol) was added, and the clear solution was warmed to 40 °C overnight. After 16 h, the temperature was increased to 55 °C for 24 h. The heat was removed and the reaction allowed to cool to ambient temperature. $CH_2Cl_2$ (15 mL) was added and the solution washed with $H_2O$, 5% aqueous NaOH, and $H_2O$. The aqueous layers were combined and extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica (10 g $SiO_2$, 5% MeOH/$CH_2Cl_2$) to give impure product. Purification by column chromatography on silica (10 g $SiO_2$, 100% $CH_2Cl_2$ to 5% MeOH/$CH_2Cl_2$) gave pure diester **13** as a white solid (150 mg, 70% yield): mp 164−165 °C; FTIR (neat) $\nu$ 3384, 1667, 1724 cm$^{-1}$; $^1$H NMR $\delta$ 7.57 (br s, 2H), 3.98−3.58 (m, 18H), 3.36 (d, $J$ = 18.3 Hz, 2H), 3.15 (d, $J$ = 14.8 Hz, 2H), 3.00 (d, $J$ = 14.6 Hz, 2H), 2.88 (d, $J$ = 14.8 Hz, 2H), 2.62 (d, $J$ = 14.6 Hz, 2H), 1.46 (s, 18H), 1.37 (s, 6H), 1.33 (s, 6H), 1.27 (s, 6H); $^{13}$C NMR $\delta$ 172.4, 171.7, 83.0. 80.7, 71.0, 70.5, 70.0, 67.9, 63.1, 62.6, 59.4, 54.5, 28.4, 26.4, 25.0 19.7; HRMS (FAB) *m*/*z* calcd for $C_{36}H_{67}N_4O_{11}$ (M + 1) 731.4806, found 731.4813. Anal. Calcd for $C_{36}H_{67}N_4O_{11}$: C, 59.16; H, 9.10; N, 7.67. Found: C, 59.32; H, 8.98; N, 7.61. Structure determined by single-crystal X-ray diffraction.

**Dioxocylamdiacetic Acid 15.** Diester **13** (36 mg, 0.0492 mmol) was dissolved in formic acid (5 mL). The flask was fitted with a reflux condenser and the solution warmed to 80 °C. After 2 h, the solution was cooled to ambient temperature and concentrated in vacuo. The residue was recrystallized from 1:4 $CHCl_3$/Hex to give diacid **15** as colorless prisms (16 mg, 52%). The mother liquor was concentrated and the residue recrystallized as above to give an additional 5 mg of (total yield 77%): mp 225 °C dec; FTIR (neat) $\nu$ 3368, 1655, 1724 cm$^{-1}$; $^1$H NMR $\delta$ 7.67 (br s, 2H), 4.01−3.85 (m, 6H) 3.76−3.49 (m, 14H), 3.04 (br d, $J$ = 12.3 Hz, 2H), 2.88 (d, $J$ = 14.3 Hz, 2H), 2.87−2.79 (m, 2H), 2.51 (d, $J$ = 14.3 Hz, 2H), 1.38 (s, 6H), 1.30 (s, 6H), 1.28 (s, 6H); $^{13}$C NMR $\delta$ 172.8, 171.8, 81.6, 71.2, 70.5, 69.4, 63.4, 61.5, 60.7, 54.3, 29.7, 26.0, 24.3, 20.2; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{51}N_4O_{11}$ (M + 1) 619.3554, found 619.3552. Structure determined by single-crystal X-ray diffraction.

**Bis-dioxocyclamtetraacetic Acid *tert*-Butyl Ester 14.** $CH_3CN$ (500, $\mu$L) was added to dioxocyclam **3**[5] (43 mg, 0.043 mmol) followed by Hunig's base (67 $\mu$L, 0.39 mmol) and *tert*-butyl bromoacetate (50.8 $\mu$L, 0.344 mmol). The solution was heated to 60 °C for 24 h. The reaction mixture was cooled to ambient temperature and diluted with $CH_2Cl_2$ (15 mL). The solution was washed with $H_2O$, 5% aqueous NaOH, and $H_2O$. The combined aqueous layers were extracted with $CH_2Cl_2$ (10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica (7.5 g $SiO_2$, 100% $CH_2Cl_2$ to 2% MeOH/$CH_2Cl_2$ to 5% MeOH/$CH_2Cl_2$) to give tetraester **14** as an off-white solid (61 mg, 97% yield): mp 119−123 °C; FTIR (neat) $\nu$ 3340, 1730, 1652 cm$^{-1}$; $^1$H NMR $\delta$ 8.02 (br s, 4H), 3.81−3.47 (m, 36H), 3.36 (d, $J$ = 18.6 Hz, 4H), 3.17 (d, $J$ = 15.3 Hz, 4H), 2.87 (d, $J$ = 14.4 Hz, 4H), 2.82 (d, $J$ = 15.3, 4H), 2.60 (d, $J$ = 14.4 Hz, 4H), 1.44 (s, 12H), 1.43 (s, 36H), 1.27 (s, 12H), 1.23 (s, 12H); $^{13}$C NMR $\delta$ 172.8, 171.4, 83.9, 81.0, 70.7, 70.6, 69.4, 66.7, 61.4, 61.9, 59.7, 55.6, 28.3, 25.6, 24.3, 19.7; MS (FAB) *m*/*z* calcd for $C_{72}H_{133}N_8O_{22}$ (M + 1) 1461.95, found 1462.04, calcd for $C_{72}H_{132}N_8O_{22}$ ($M^+$) 1460.94, found 1461.02. Anal. Calcd for $C_{72}H_{132}N_8O_{22}$: C, 59.16; H, 9.10; N, 7.67. Found: C, 59.27; H, 8.96; N, 7.59.

**Bis-dioxocyclamtetraacetic Acid 16.** Formic acid (12 mL) was added to tetraester **14** (430 mg, 0.29 mmol). The solution was heated at reflux for 4 h and cooled to 25 °C. The reaction was diluted with $CH_2Cl_2$ and concentrated in vacuo to give tetraacid **16** as a light brown residue. Recrystallization from methanol/ether gave 279 mg (77%) of **16** mp 152 °C dec; FTIR (neat) $\nu$ 3361, 1635, 1646, 1652 cm$^{-1}$; $^1$H NMR $\delta$ 8.17 (br s, 4H), 4.10 (d, $J$ = 17.1 Hz, 4H), 3.94−3.34 (m, 36H), 3.04−2.50 (m, 16H), 1.41 (s, 12H), 1.28 (s, 24H); $^{13}$C NMR $\delta$ 173.4, 171.7, 81.8, 70.8, 70.2, 68.7, 64.7, 63.5, 62.5, 61.1, 54.4, 26.1, 24.2, 20.1; HRMS (FAB) *m*/*z* calcd for $C_{56}H_{101}N_8O_{22}$ (M + 1) 1237.7030, found 1237.7064. Structure determined by single-crystal X-ray diffraction.

***N*-Carbonylbenzyloxy-bis-azapenam 19.** Chiral imidazoline **17**[7] (0.75 g, 6.35 mmol) and bis-chromium carbene complex **18**[5] (2.00 g, 3.17 mmol) were dissolved in $CH_2Cl_2$ (100 mL) and placed in a Pyrex pressure tube under argon. After three freeze−thaw degassings, the red-brown solution was purged with 80 psi of CO (3×) then pressurized to 80 psi CO and irradiated with 2 × 500 W halogen lamps at 55 °C. After 16 h, the light green reaction solution was removed from the photoreactor and the solvent removed in vacuo. MeOH (100 mL) was added to the residue, and the solution placed in a −20 °C freezer for 2 h. The mixture was filtered through a pad of Celite to remove precipitated chromium hexacarbonyl. The resulting filtrate was concentrated in vacuo and the resulting crude material purified by column chromatography on silica (200 g $SiO_2$, 50% to 60% EtOAc/Hex) to give azapenam **19** (1.73 g, 64% yield) along with recovered imidazoline (0.308 g, 73% yield of **19** based on recovered imidazoline): FTIR (neat) $\nu$ 1716, 1739, 1780 cm$^{-1}$; $^1$H NMR $\delta$ 7.35 (m, 10H), 5.27−5.08 (m, 6H), 4.36 (br d, $J$ = 11.0 Hz, 2H), 3.73 (s, 6H), 3.74−3.56 (m, 16H), 3.24 (br d, $J$ = 11.0 Hz, 2H), 1.80 (s, 6H), 1.24 (s, 6H); $^{13}$C NMR $\delta$ 172.3, 170.5, 152.7, 135.5, 128.3, 128.1, 127.8, 90.3, 75.8, 70.4, 70.3, 69.8, 65.3, 65.1, 58.3, 52.9, 17.7, 14.0; HRMS (FAB) *m*/*z* calcd for $C_{42}H_{54}N_4O_{15}$ ($M^+$) 854.3586, found 854.3602.

**Deprotection of 19.** A solution of protected azapenam **19** (1.06 g, 1.24 mmol) in MeOH (80 mL) was transferred to an oven-dried pressure tube. Palladium on carbon (l0 wt %, 500 mg) and triethylamine (800 $\mu$L) were added, and the reaction flask was flushed with argon. A pressure head was fitted onto the flask and the reaction purged with $H_2$ (3 × 60 psi) before pressurizing to 75 psi $H_2$. The reaction was stirred at ambient temperature for 2 h. The reaction mixture was then filtered through Celite and concentrated in vacuo. The residue was dissolved in $CH_2Cl_2$ (30 mL) and washed with a 5% aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a clear oil (0.66 g, 90%) which was used in the next reaction without further purification: $[\alpha]^{21}{}_D$ −116 ($c$ = 1.38, $CHCl_3$); FTIR (neat) $\nu$ 3350, 1761, 1738 cm$^{-1}$; $^1$H NMR $\delta$ 4.84 (d, $J$ = 6.6 Hz, 2H), 3.80 (m, 2H), 3.74−3.58 (m, 16H), 3.68 (s, 6H), 2.62 (m, 2H), 2.39 (m, 2H), 1.68 (s, 6H), 1.25 (s, 6H); $^{13}$C NMR $\delta$ 175.0, 171.8, 89.9, 79.9, 70.5, 70.4, 70.2, 66.0, 65.3, 60.5, 52.6, 17.2, 14.6; MS (FAB) *m*/*z* calcd for $C_{26}H_{43}N_4O_{11}$ (M + 1) 587.29, found 587.22.

**Chiral Bis-dioxocyclam 20.** Crude azapenam **19** (0.66 g, 1.13 mmol) was dissolved in $CH_2Cl_2$ (80 mL) and transferred to an oven-dried pressure tube. (±)-Camphorsulfonic acid (43 mg, 0.19 mmol) was added and the reaction vessel fitted with a pressure head. The solution was stirred and warmed to 100 °C for 1 h and then cooled to 80 °C and stirred overnight. The

reaction was washed with a 5% aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 80 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was used in the next reaction without further purification: FTIR (neat) $\nu$ 3383, 1741, 1676 $cm^{-1}$; $^1H$ NMR $\delta$ 8.02 (s, 4H), 7.57 (s, 4H), 4.09 (d, $J$ = 12.4 Hz, 4H), 3.91 (dd, $J$ = 12.4 Hz, $J$ = 1.45 Hz, 4H), 3.89−3.38 (m, 44H), 1.65 (s, 12H), 1.49 (s, 12H); $^{13}C$ NMR $\delta$ 173.5, 169.9, 166.8, 81.2, 70.8, 70.7, 70.4, 65.3, 63.2, 60.9, 53.0, 21.1, 20.3.

The crude material was dissolved in 1:1 $MeOH/CH_2Cl_2$ (60 mL) and treated with a crystal of bromocresol green indicator. Sodium cyanoborohydride (0.34 g, 5.41 mmol) was added in one portion and the deep blue solution cooled to 0 °C. A saturated methanolic solution of HCl was added dropwise to the reaction mixture to maintain a deep green color. Stirring was continued at 0 °C for 1 h, and then the ice bath was removed and the reaction stirred at ambient temperature overnight (methanolic HCl added as necessary to maintain the green color). Saturated methanolic HCl was added to acidify the reaction, producing rapid gas evolution. Once gas evolution had ceased, the mixture was diluted with a 10% aqueous solution of NaOH (50 mL) and the layers separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 75 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica (50 g $SiO_2$, 2% to 5% $MeOH/CH_2Cl_2$) gave dioxocyclam **20** (0.39, 63% over 2 steps) as colorless crystals: mp 152−154 °C; $[\alpha]^{21}_D$ +46.0 ($c$ = 1.03, $CHCl_3$); FTIR (neat) $\nu$ 3392, 3275, 1739, 1679 $cm^{-1}$; $^1H$ NMR $\delta$ 8.10 (s, 2H), 3.78 (s, 6H), 3.78−3.41 (m, 16H), 2.90−2.55 (m, 8H), 1.57 (s, 6H); $^{13}C$ NMR $\delta$ 174.1,172.0, 79.5, 70.4, 70.3, 69.7, 62.1, 61.1, 54.7, 53.2, 52.9, 21.4, 19.3; MS (FAB) $m/z$ calcd for $C_{26}H_{46}N_4O_{11}$ ($M^+$ + l or $MH_2^{2+}$) 591.32, found 591.18. Anal. Calcd for $C_{26}H_{46}N_4O_{11}$: C ,52.87; H, 7.85; N, 9.49. Found: C, 53.01; H, 7.61; N, 9.26.

**Gadolinium Salt of Dioxocyclam Diacid (15).** Dioxocyclam diacid **15** (26 mg, 0.041 mmol) was dissolved in 10% aq HCl (1.5 mL), and $Gd_2(CO_3)_3$ (27 mg, 0.054 mmol) was added portionwise. The mixture was heated to reflux for 2 days and cooled to room temperature, and the solvent was removed under reduced pressure. Dissolution in water followed by lyophilization gave an off-white solid: FTIR (neat) $\nu$ 3364, 1652, 1635 $cm^{-1}$; High-resolution MS ($ES^+/CH_3(N-H_2O)$ calcd for $C_{28}H_{48}N_4O_{11}Gd^+$ 774.2561, found 774.2575.

**Gadolinium Salts of Bis-dioxocyclam Tetraacid (16).** Bis-dioxocyclam tetraacid **16** (20.6 mg, 0.0166 mmol) was dissolved in $H_2O$ (1 mL). Gadolinium carbonate hydrate (24.7 mg, ∼0.0499 mmol) was added and the white slurry stirred at ambient temperature. The reaction flask was fitted with a condenser and the reaction warmed to 95 °C for 20 h. The white slurry was cooled to ambient temperature and filtered through a plug of Celite/glass wool. The filter cake was treated with a 10% aqueous solution of HCl (5 mL) causing gas evolution. The clear solution was collected and concentrated in vacuo to an off-white powder: FTIR (neat) $\nu$ 3342, 1652, 1634 $cm^{-1}$; MS ($ES^-/CH_3CN-H_2O$) calcd for $C_{56}H_{96}GdN_8O_{22}^-$ 1390.58, found 1390.6; MS ($ES^+/CH_3CN-H_2O$) calcd for $C_{56}H_{98}GdN_8O_{22}^+$ 1392.60, found 1392.6, calcd for $C_{56}H_{96}Gd_2N_8O_{22}^{2+}$ 774.26, found 774.26, calcd for $C_{56}H_{99}GdN_8O_{22}^{2+}$ 696.80, found 697.7.

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**Supporting Information Available:** $^1H$ spectra for compounds **7**, **8**, **12b**, and **19** and $^{13}C$ NMR spectra for compound **8**. For compounds **12a**, **13**, **15**, **16**, and **20**, ORTEP diagrams, crystal data and structure refinement parameters, atomic coordinates, bond lengths and bond angles, torsion angles, anisotropic displacement coefficients, and H-atom coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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