Synthesis and Metal Complexation Reactions of Bis-Dioxocyclams from Photochemical Reaction of Bis-Chromium Alkoxycarbene Complexes with Imidazolines

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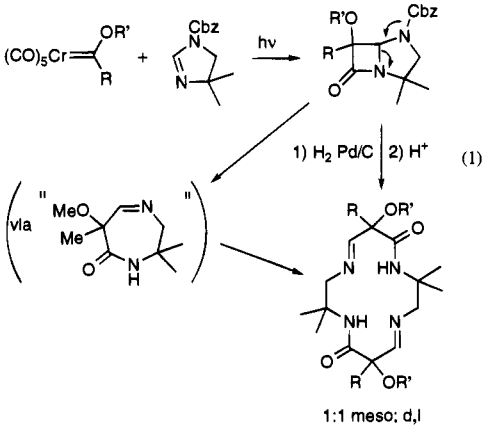
Received October 19, 1994[⊗]

Abstract: Bis-chromium alkoxycarbene complexes, bridged via the alkoxy groups, underwent photochemical cycloaddition to protected imidazolines to give protected bis-azapenams. Deprotection followed by treatment with acid produced bis-dioxocyclams bridged top and bottom with four-, five-, six-, and twelve-atom α,ω-diol linkages. These bis-dioxocyclam ligands formed mono- and bis-nickel(II) complexes. The five-atom bridged system ($-O(CH_2)_3O-$) was characterized by X-ray crystallography and had a number of unusual features.

Introduction

Fourteen-membered tetraazamacrocycles (cyclams) are versatile ligands in coordination chemistry, able to stabilize unusual geometries and oxidation states of transition metals, particularly those of the first row, although other metals such as aluminum, zinc, cadmium, and even technetium also form complexes with these ligands.[1] Dioxocyclams belong to a subgroup which is claimed to be structurally intermediate between oligopeptides and saturated polyamines and which has also been extensively investigated.[2] Bis-cyclams connected by a single bridging group between two ring carbons or nitrogens[3] have been prepared, and the redox chemistry of their homoleptic dimetal complexes has been studied.[4] Bis-cyclams attached through nitrogen by a three-carbon bridge have potent and selective anti-HIV activity,[5a] while bis-nickel(II) complexes of bis-cyclams attached by an eight-atom diether link at the 6 and 6′ carbons had greater anti-HIV activity and lower toxicity than either free bis-cyclam.[5b] Bis-2,4-dioxocyclams attached at the 3-position were synthesized, along with their copper complexes, and their redox chemistry was studied.[6]

These types of tetraazamacrocycles are usually synthesized by the condensation of diamines with diketones or tetraamines with dihalides, ditosylates, or diesters.[1] Recently, an unusual and efficient synthesis of 5,12-dioxocyclams via acid-catalyzed dimerization of azapenams was reported from these laboratories (eq 1).[7] Herein, we report the synthesis of bis-dioxocyclams



linked top and bottom by alkoxy bridges, starting with bis-azapenams.

Results and Discussion

The general approach involves the selective dimerization of bis-azapenams produced photochemically from bis-chromium alkoxycarbene complexes. The requisite bis-carbene complexes[8] **1**−**4** were synthesized in a straightforward manner by treatment of the corresponding acetoxycarbene complex[9] with diols at low temperature (eq 2). These complexes were purified by column chromatography in the air and were stable and easily handled.

[⊗] Abstract published in *Advance ACS Abstracts*, February 15, 1995.

(1) For reviews, see: (a) Busch, D. H. *Acc. Chem. Res.* **1978**, *11*, 392. (b) Kimura, E. *J. Coord. Chem.* **1986**, *15*, 1. (c) Ito, T.; Kato, M.; Yamashita, M.; Ito, H. *J. Coord. Chem.* **1986**, *15*, 29. (d) Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: London, 1989. (e) Kimura, E. *Tetrahedron* **1992**, *48*, 6175. (f) For extensive lists of diverse references, see: Kimura, E.; Haruta, M.; Koike, T.; Shionoya, M.; Takenouchi, K.; Iitaka, Y. *Inorg. Chem.* **1993**, *32*, 2779. (g) Busch, D. H.; Alcock, N. W. *Chem. Rev.* **1994**, *94*, 585.

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(3) (a) Kajiwara, T.; Yamaguchi, T.; Kido, H.; Kawabata, S.; Kuroda, R.; Ito, T. *Inorg. Chem.* **1993**, *32*, 4990 and references therein. (b) Urfer, A.; Kaden, T. A. *Helv. Chim. Acta* **1994**, *77*, 23.

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(5) (a) De Clercq, E.; Yamamoto, N.; Pauwels, R.; Baba, M.; Schols, D.; Nakashima, H.; Balzarini, J.; Debyser, Z.; Murrer, B. A.; Schwartz, D.; Thornton, D.; Bridger, G.; Fricker, S.; Henson, G.; Abrams, M.; Picker, D. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 5286. (b) Inouye, Y.; Kanomori, T.; Yoshida, T.; Bu, X.; Shionoya, M.; Koike, T.; Kimura, E. *Biol. Pharm. Bull.* **1994**, *17*, 243.

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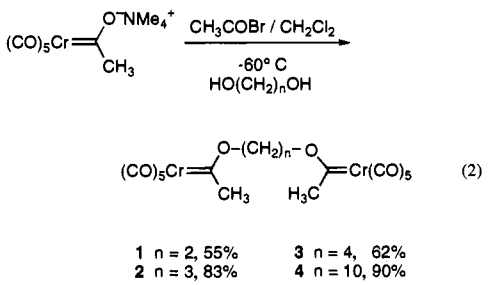
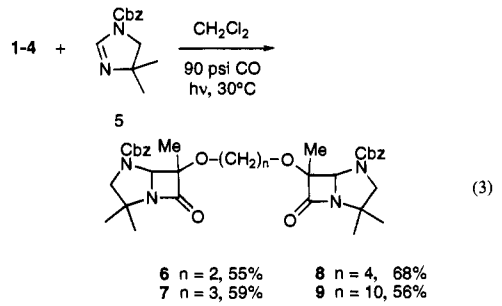
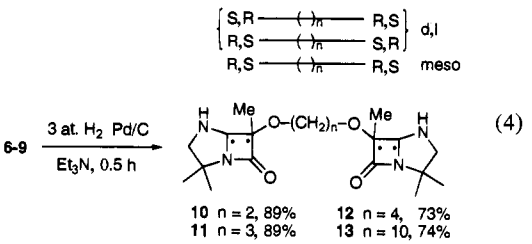


Photolysis of carbene complexes **1**−**4** with protected imidazoline **5** produced protected bis-azapenams **6**−**9** in fair yield as 1:1 mixtures of racemic diastereoisomers[10] at the two alkoxy−methyl centers (eq 3). Because of the presence of these



diastereoisomers as well as rotational isomers of the Cbz protecting groups, these compounds were difficult to separate at this stage, and the ^{1}H NMR spectra were too complex to be of value in assessing the ratios of diastereoisomers. A small portion of each crude reaction mixture was subjected to the deprotection sequence, and the diastereoisomeric ratio was then easily assessed by integration of the signals due to the methine protons of the respective diastereoisomers. The exception to this was compound **7** (n = 3), for which the *d,l* diastereoisomer could be isolated by crystallization while the meso remained in the mother liquor (see below).

The N-protecting group was readily removed under mild hydrogenolysis conditions in the presence of triethylamine, to prevent cleavage to the diazepinone,[7] and the free bis-azapenams **10**−**13** were obtained in good isolated, purified yields as 1:1 mixtures of diastereoisomers (eq 4), setting the stage for the key dimerization step, the complexity of which requires some comment for clarity.



The dimerization is thought to occur by acid-catalyzed cleavage of the azapenam to give an unstable seven-membered cyclic imine (which destroys one of the two chiral centers of the azapenam), followed by dimerization. When the reaction starts with a racemic mono-azapenam, a 1:1 mixture of the racemic *d,l* (*R,R*; *S,S*) and meso (*R,S*) mono-cyclam is obtained (see eq 1).[7] With bis-azapenams, the situation is stereochemically much more complex. Direct dimerization of the mixture

(10) The β-lactam-forming reaction always produces the same *relative* stereochemistry at the two adjacent chiral centers, with the alkyl substituent of the carbene and the nitrogen of the imidazoline ring cis (see ref 7). This results in the production of two sets of diastereoisomers for the bis-azapenams, the racemic *d,l* pair and the meso.

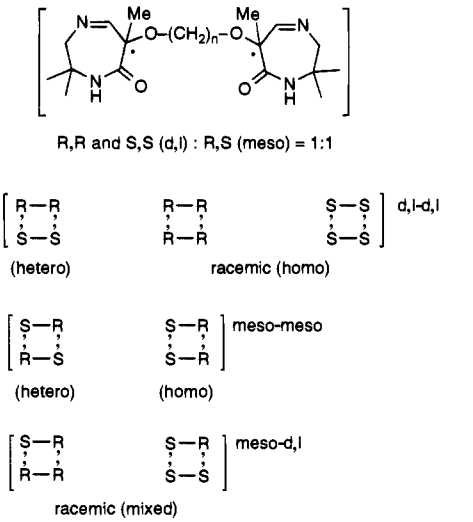
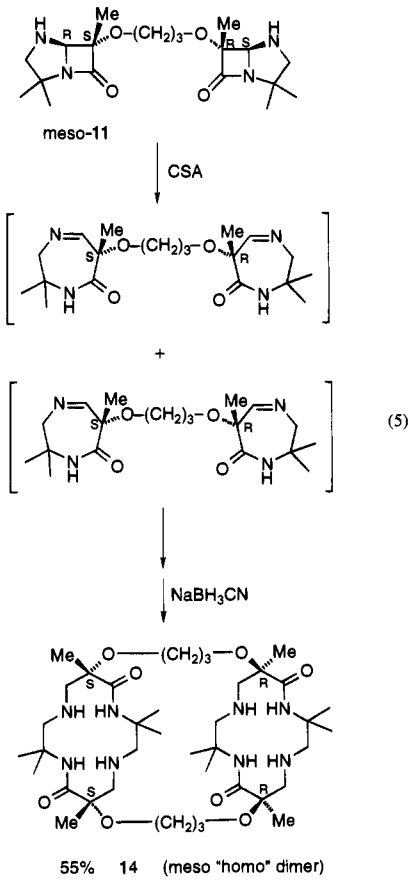


Figure 1. Dimerization of bis-azapenams.

of diastereoisomers in eq 4 could lead to *seven* possible isomeric bis-cyclams, two sets of which are racemic (Figure 1). The ability to separate the diastereoisomers of bis-azapenam **11** (n = 3) at the protected stage provided an opportunity to study the dimerization process under substantially simplified circumstances. For this reason, dimerization studies commenced with separated meso and *d,l* diastereoisomers of **11**.

Treatment of a 0.01 M solution of meso-**11** in CH_2Cl_2 with 0.125 equiv of camphorsulfonic acid for 67 h, followed by reduction with sodium cyanoborohydride in methanol to freeze equilibration,[11] led to the isolation of a single meso bis-cyclam **14** in 55% yield (eq 5). The structure and stereochemistry was



confirmed by X-ray crystallography (see below). This corresponds to the meso homo dimer (Figure 1) in which azapenams

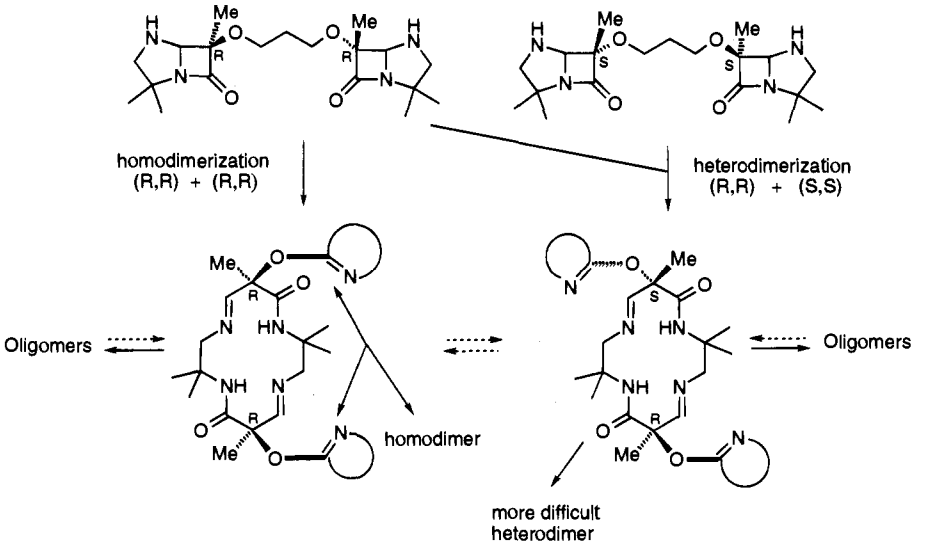
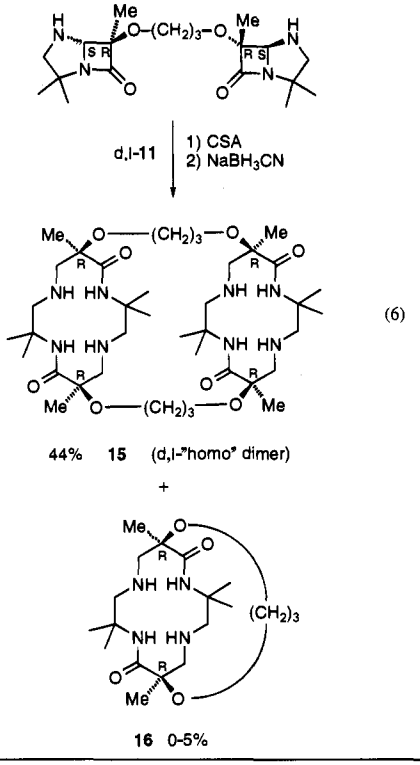


Figure 2.

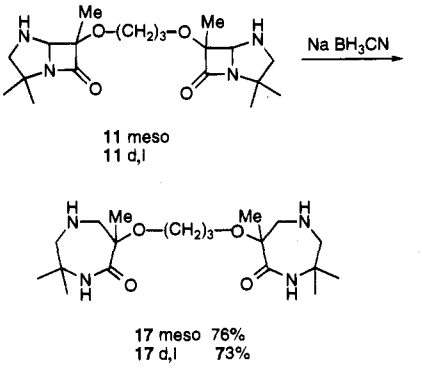
of *like* configuration combined ($S \rightarrow S$, $R \rightarrow R$), although the reaction was accompanied by unidentified byproducts.

In a similar manner, dimerization of *d,l*-**11** again produced the homo dimer as the major product (44% yield of *d,l* homo dimer **15**, eq 6). In addition, a very small amount of mono-



(6)

cyclam **16** was also obtained under some conditions, accompanied by other byproducts. To verify that **16** was indeed the mono-cyclam, both the meso and the *d,l* diastereoisomeric azapenams were independently reduced under acidic conditions to produce the corresponding bis-diazepinones **17**, which have the same molecular weight as **16** (eq 7). They were indeed



(7)

quite different as expected.

This selectivity for centers of like configuration to combine in this process, thus favoring the formation of homo bis-cyclams over hetero bis-cyclams, is likely due to the stepwise nature and the reversibility of the bis-cyclam-forming process.[11] Figure 2 shows the consequences of the first step of both homo- and heterodimerization of *d,l*-**11**. If the first cyclam ring forms between imines of like configuration (homo), the resulting compound has the remaining two imines ideally located to cyclize to form the homo dimer. In contrast, if the first cyclam ring forms between imines of opposite configuration (hetero), the resulting compound has the remaining two imines on opposite faces, ill-disposed to react with each other, making heterodimerization more difficult. Since cyclam formation is reversible,[11] this compound can equilibrate, presumably through the starting imine, over to the homo dimer precursor, or it can oligomerize. Indeed, bis-cyclam formation is quite sensitive to reaction conditions, and high concentrations of bis-azapenams, larger amounts of camphorsulfonic acid, prolonged reaction times, or higher temperatures decrease the yield of bis-cyclam, with a resulting increase in oligomeric byproducts. Even leaving the unreduced pure bis-cyclams standing in solution results in slow deposition of insoluble oligomeric material with concomitant loss of bis-cyclam, indicating the mobility of the unreduced

(11) Previous studies had shown that this dimerization was reversible and the diastereoisomers of the cyclams could interconvert (Hegedus, L. S.; Moser, W. H. *J. Org. Chem.* **1994**, *59*, 7779), complicating both separation and interpretation. Reduction of the imines prevented this. This reversible dimerization of seven-membered cyclic imines is general and has been used to make a number of different 14-member macrocyclic systems in addition to the N,N-systems reported herein. For the C–N system, see: (a) Goldman, I. M.; Larson, J. K.; Tretter, J. R.; Andrews, E. G. *J. Am. Chem. Soc.* **1969**, *91*, 4941. For the N–O system, see: (b) Kluiber, R. W.; Sasso, G. *Inorg. Chim. Acta* **1970**, *4*, 226. For the S–N system, see: (c) Martin, J. W. L.; Wainwright, K. P.; Weerasuria, K. D. V.; Wild, S. B. *Inorg. Chim. Acta* **1985**, *99*, L5. (d) Martin, J. W. L.; Organ, G. J.; Wainwright, K. P.; Weerasuria, K. D. V.; Willis, A. C.; Wild, S. B. *Inorg. Chem.* **1987**, *26*, 2963. For As–N, see: (e) Martin, J. W. L.; Stephens, F. S.; Weerasuria, K. D. V.; Wild, S. B. *J. Am. Chem. Soc.* **1988**, *110*, 4346. (f) Wild, S. B. *Pure Appl. Chem.* **1990**, *62*, 1139.

systems and the necessity for imine reduction to allow isolation and purification of the bis-cyclam ring system.

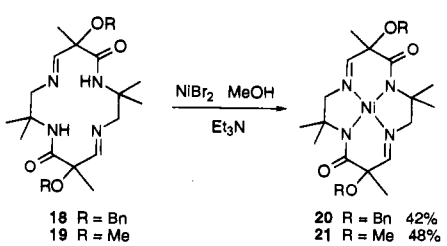
The diastereoisomers of the bis-azapenam **10** ($n = 2$) were also separable, although in this case, tedious chromatographic separation was required. Treatment of one of the separated diastereoisomers with camphorsulfonic acid followed by reduction gave a single bis-cyclam after reduction (40% yield), assigned as the homo *d,l* compound by comparison with the $n = 3$ series. Treatment of the other diastereoisomer of **10** with camphorsulfonic acid gave a 3:1 mixture of two bis-cyclams, assigned as the meso homo and the meso hetero compound, again by comparison with the $n = 3$ series. Treatment of the 1:1 mixture of diastereoisomers **10** with camphorsulfonic acid produced a 4:3:1 mixture (97% yield) of three diastereoisomeric bis-cyclams which could be separated by tedious, repetitive layer chromatography. These corresponded to the meso homo dimer, the *d,l* homo dimer, and the meso hetero dimer, respectively.

The desirability to separate the diastereoisomers of the bis-azapenams **10**–**13** before conversion to bis-cyclams was verified for compound **12** ($n = 4$), for which separation was not achieved. Treatment of the mixture of diastereoisomers of **12** under standard cyclam-forming conditions resulted in an intractable mixture of products which could be neither purified nor separated. NMR spectra of the crude reaction mixture clearly indicated that cyclam formation had occurred, but beyond that, little was learned. The unseparated mixture of diastereoisomers of **13** ($n = 10$) was subjected to dimerization and reduction. From the resulting mixture of bis-cyclams, two different diastereoisomers could be isolated in 42 and 28% yield, respectively. The stereochemistry of these could not be assigned from spectroscopic data alone.

These studies emphasize the desirability of synthesizing single diastereoisomers of bis-azapenams to utilize in the dimerization process. We have already shown[7] that by using enantiomerically pure, optically active imidazolines as substrates in eq 1, single enantiomerically pure azapenams and cyclams are obtained. Extension of this methodology to these bis-cyclams offers a solution to the stereochemical complexity encountered, and studies along these lines are in progress.

Metal Complexation Studies. Although papers dealing with metal complexes of cyclams and related tetraazamacrocycles are legion, to our knowledge, none have dealt with 5,12-dioxocyclams. Because ready access to this class of ligands as well as to bis-5,12-dioxocyclams was possible, studies to determine the complexing properties of these ligands commenced.

The mono-cyclams were studied first to provide base-line information for the bis-cyclams. Treatment of unsaturated dioxocyclams **18** and **19** (1:1 mixture of diastereoisomers) with anhydrous nickel bromide in methanol at reflux in the presence of triethylamine produced nickel complexes **20** and **21** in ≈40% isolated (unoptimized) yield as pink solids (eq 8). For complex



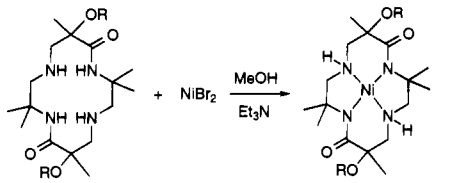
(8)

18 R = Bn
19 R = Me

20 R = Bn 42%
21 R = Me 48%

20, a single meso diastereoisomer was isolated, because of either selective crystallization or equilibration of the cyclam, whereas for **21**, a mixture of both meso and *d,l* diastereoisomers was isolated. (The meso isomer of **19** gave a single meso-nickel complex.)

Nickel complexes **24** and **25** were similarly prepared from the reduced ligands **22** and **23** (1:1 mixture of diastereoisomers, eq 9). A single meso complex was obtained in ≈40% yield



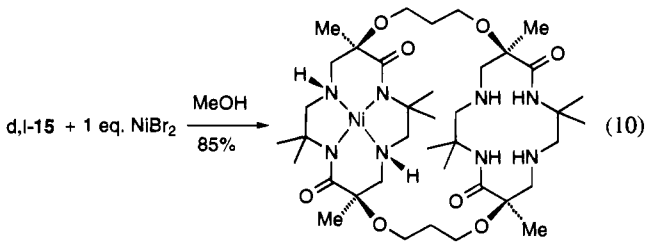
(9)

22 R = Bn
23 R = Me

24 R = Bn 45%
25 R = Me 43%

after crystallization. With data for the mono-cyclams in hand, attention was turned to the bis-cyclams.

Treatment of *d,l* homo dimer **15** with 1 equiv of anhydrous nickel bromide in methanol in the presence of potassium carbonate led to the isolation of two isomeric mono-nickel complexes, which could be separated chromatographically (eq 10). On standing in solvents such as $CHCl_3$ or CH_2Cl_2, the



(10)

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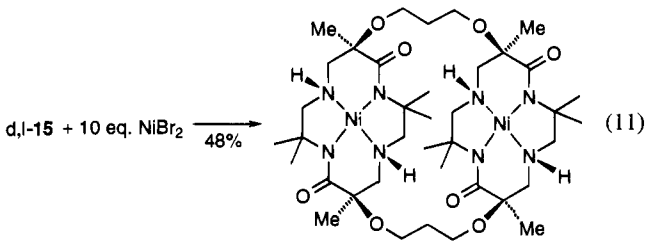
minor isomer rearranged to the major isomer, which was characterized by X-ray crystallography (see below). These two isomers were thought to differ only by the configuration at the complexed secondary amine nitrogen centers, which, because of complexation, cannot undergo facile inversion.[12] When the experiment was repeated using 10 equiv of nickel bromide, the bis-nickel complex **27** was obtained (eq 11), again as a mixture of isomers which could be separated but rearranged to a single isomer on standing in chloroform. The mono-**28** and bis-nickel



(11)

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complex **29** of meso-**14** were also prepared in 97 and 54% yield, respectively. Finally, the bis-nickel complexes of the two isolated diastereoisomers of bis-cyclam isomers $n = 10$ were prepared in 83 and 98% yield, respectively, and were characterized spectroscopically. Further studies with these complexes were not carried out.

Structural Studies. The X-ray crystal structures of the monomeric meso amide–imine nickel complex **20** and the

(12) Isomers arising from the asymmetry of the coordinated secondary amines are possible in these systems: (a) Wamer, L. G.; Rose, N. J.; Busch, D. H. *J. Am. Chem. Soc.* **1967**, *89*, 703. (b) Barefield, E. K.; Wagner, F.; Hodges, K. D. *Inorg. Chem.* **1976**, *15*, 1370.

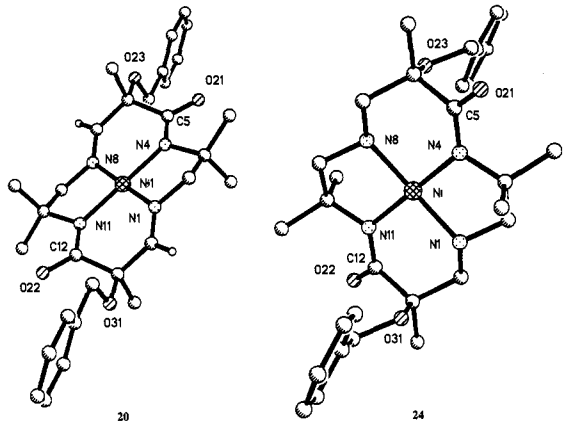

Figure 3. X-ray crystal structures of dioxocyclam nickel complexes.

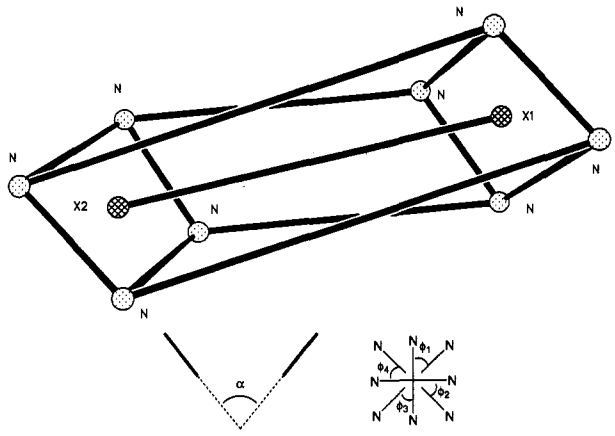

Figure 4. Schematic illustration of structural features of ligands and complexes.

amide−amine nickel complex **24** (Figure 3) were determined primarily for the purpose of comparison, both to related mono-cyclam nickel complexes and to the bis-nickel complexes reported herein. As expected, complexation of the free ligand somewhat flattens the relatively flexible 14-membered ring, and the nickel and four nitrogen atoms are strictly coplanar. In the amide−amine complex **24**, all four N−Ni bond lengths are roughly the same (1.915 Å for the amine, 1.911 Å for the amide), whereas in complex **20**, they differ slightly (1.857 Å for the imine, 1.900 Å for the amide), as previously observed for related[13] amine−imine complexes. A point of some consequence is that the hydrogen atoms on the amine sp^3 nitrogens in complex **24** are calculated to be *syn* to the nearest *O*-benzyl groups and thus *anti* to each other.

The structures of the bis-cyclams and their nickel complexes are considerably more interesting, in that the conformations and relative dispositions of the two rings are not independent but rather are a function of the configurations of the stereogenic centers and the torsional effects imposed by the five-atom chains bridging the two macrocyclic rings top and bottom. Three parameters are of particular interest in the context of complexation and ultimately catalysis. These features, schematically presented in Figure 4, are the distance between the two tetraaza centers of coordination, *d*, the dihedral angle of the planes of the two macrocyclic tetraaza coordination sites, α, and the torsional angle ϕ between the two tetraaza coordination sites. Because of the flexibility of the uncomplexed ring, the angles between adjacent nitrogens on the same ring are quite variable, ranging from 77.9 to 101.9°. Thus, the dihedral angle ϕ is different for each opposing pair of nitrogens on opposite rings (ϕ_1, ϕ_2, ϕ_3, ϕ_4; Figure 4). Because no single value accurately represents the true situation, the range of ϕ's is shown in Table 1, and the degree of skewing is presented visually with each structure in the form of a Fischer projection.

Table 1. Structural Parameters for Bis-Dioxocyclams and Their Nickel Complexes

compound	*d* (Å)	α (deg)	ϕ (deg)
15 (L_{dl})	7.448	75.4	8.7−19.5
26 ($L_{dl}Ni$)	6.758	2.1	1.3−8.4
27 ($L_{dl}Ni_2$)	7.544	65.1	16.8−20.3
14 (L_{meso})	6.284 (6.068)	0.0 (0.0)	0.1−0.6 (0.6−1.3)
29 ($L_{meso}Ni_2$)	7.068 (6.934)	0.0 (0.0)	0.2−0.5 (0.0−0.2)

Consider first the *d,l* bis-cyclam **15** and its mono- (**26**) and bis-nickel (**27**) complexes (Figure 5). In the free ligand **15** (L_{dl}, Table 1), the two centers of coordination are 7.448 Å apart, and the planes of the two tetraaza coordination sites are at an angle of 75.4° to each other, much like a partially opened book. In addition, the two tetraaza coordination sites are skewed substantially. Incorporation of nickel into one of the sites flattens that ring, and this change in geometry is transmitted to the other ring via the two five-atom bridges. In the mono-nickel *d,l* complex **26** ($L_{dl}Ni$), the two centers of coordination move slightly closer together (6.758 Å), the planes of the coordination sites become almost parallel (α = 2.1), and the torsional angle ϕ closes slightly. Upon introduction of nickel into the second ring of **27** ($L_{dl}Ni_2$), serious reorganization again occurs. The two centers of coordination (now the Ni−Ni distance) retreat to 7.544 Å, the planes of the coordination sites reopen to 65.1°, and the torsional angle opens substantially. Thus, the status of each ring affects the other, and they each adjust to accommodate the needs of the other.

The crystallographic situation for both the meso ligand **14** and its bis-nickel complex **29** (Figure 6) is somewhat more complex. Each unit cell contains two independent molecules which have slightly different dimensions, thus the double entries in Table 1. What is remarkable is the profound difference between the *d,l* system and the meso system. For the free meso ligand **14** (L_{meso}), the two centers of coordination are ≈6.3Å distant, and the planes of the two tetraaza coordination sites are virtually parallel (α = 0°) and eclipsed (ϕ < 2°). Thus, this ligand provides coordination sites which are "face-to-face", a ligand array highly sought for providing controlled coordination sites for the study of catalysis and electron transfer processes.[14] Although the meso mono-nickel complex **28** has not been crystallographically characterized, the meso bis-nickel complex **29** ($L_{meso}Ni_2$) maintains this strict face-to-face orientation, with the two nickel atoms held ≈7 Å apart in eclipsed, parallel coordination planes. To our knowledge, the only other face-to-face cyclam system is that of Ito,[3] which has two dimethyl cyclam rings bridged by a single *o*-xylene group. For comparison, the bis-nickel complex of this system has the two nickel atoms somewhat closer, 5.802 vs ≈7 Å, and, because this ligand is a tetraamine rather than a diamine−diamide, a bridging bromide resides between the two nickel atoms.

Summary

An efficient and direct synthesis of bis-dioxocyclam ligands which allows variation of both the degree of separation of the two macrocyclic ligands and the relative orientations of the two tetraaza coordination sites has been developed. Metals can be

(13) Bailey, M. F.; Maxwell, I. E. *J. Chem. Soc., Dalton Trans.* **1972**, 938.

(14) Most of these systems are porphyrins: Guilard, R.; Lopez, M. A.; Tabard, A.; Richard, P.; Lecomte, C.; Brandes, S.; Hutchinson, J. E.; Collman, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 9877 and references therein.

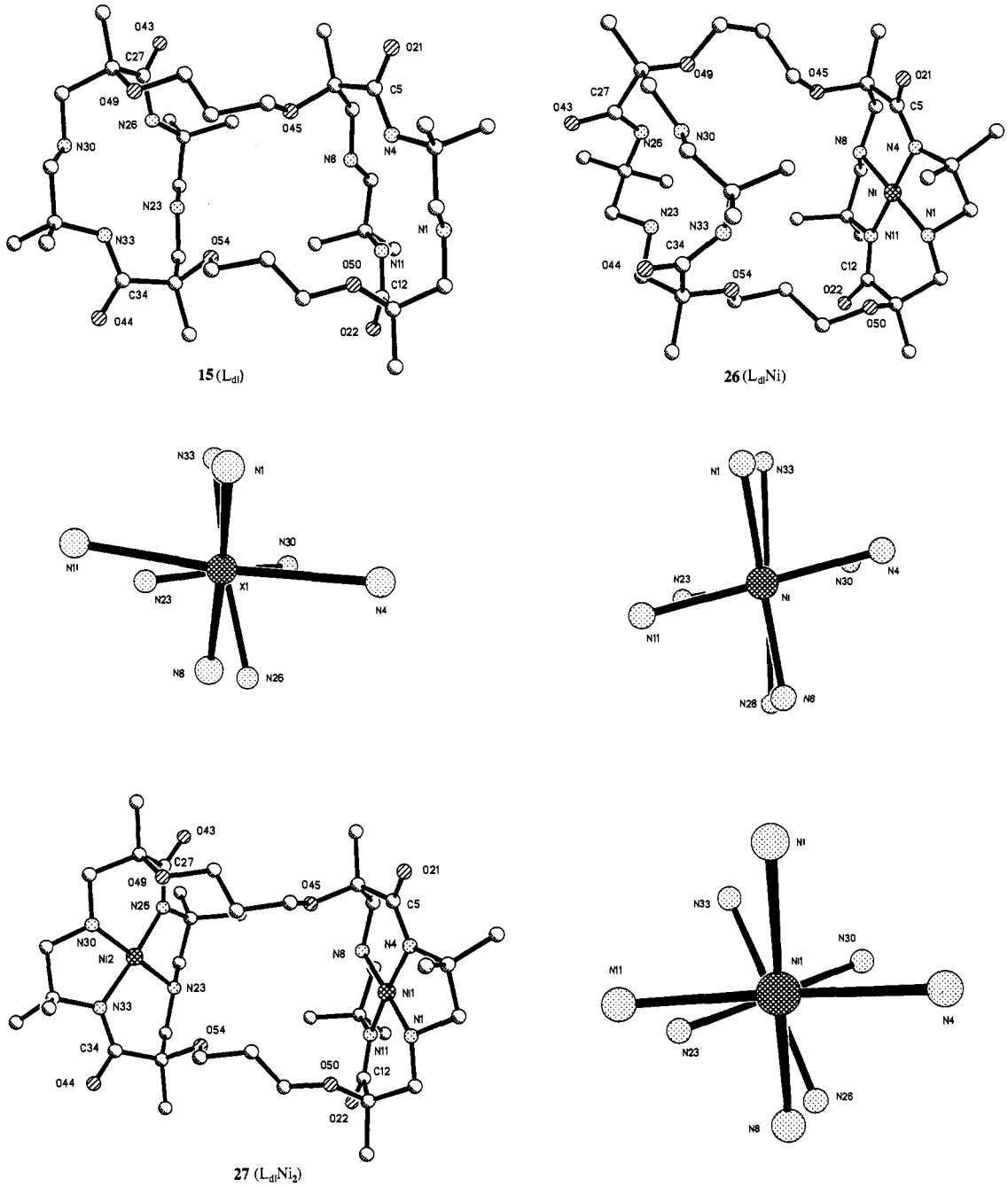

Figure 5. X-ray structures for *d,l* dioxocyclam **15** and complexes **26** and **27**.

incorporated stepwise into these ligands. Development of stereospecific syntheses of single diastereoisomers of their bis-dioxocyclams, as well as the synthesis and reactivity studies of mixed metal complexes of these ligands, is currently under investigation.

Experimental Section

General. If not otherwise stated, all NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^1H and 75.5 MHz for ^{13}C. Chemical shifts are given in δ ppm relative to Me_4Si (δ 0.00, ^1H) or $CDCl_3$ (δ 77.0, ^{13}C). UV spectra were recorded on Varian DMS 80 and HP8452A UV−vis spectrophotometers.

The following chemicals were prepared according to literature procedures: pentacarbonyl[(methyl){(tetramethylammonio)oxy}carbene]-chromium(0),[15] 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ^2-imidazoline (5),[7] (6*R**,13*S**)- and (6*S**,13*S**)-3,3,6,10,10,13-hexamethyl-6,13-bis(phenylmethoxy)-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione (**18**),[7] (6*R**,13*S**)- and (6*S**,13*S**)-3,3,6,10,10,13-hexamethyl-6,13-dimethoxy-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione (**19**),[7] (6*R**,13*S**)- and (6*S**,13*S**)-3,3,6,10,10,13-hexamethyl-6,13-bis(phenylmethoxy)-1,4,8,11-tetraazacyclotetradecane-5,12-dione (**24**),[7] and (6*R**,13*S**)- and (6*S**,13*S**)-3,3,6,10,10,13-hexamethyl-6,13-dimethoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione (**25**).[7]

Bis-Chromium Alkoxycarbene Complexes 1−4. $(CO)_5Cr{=}C(CH_3)(O(CH_2)_nO)(CH_3)C{=}Cr(CO)_5$. (a) Complex 1 ($n$ = 2) from 1,2-Ethanediol. Pentacarbonyl[(methyl){(tetramethylammonio)oxy}-carbene]chromium(0) (2.14 g, 6.9 mmol) and 1,2-ethanediol (0.17 g, 2.8 mmol) were dissolved in dry CH_2Cl_2 (50 mL) under an argon atmosphere, and the solution was cooled to −65 °C. Acetyl bromide (0.45 mL, 6.1 mmol) was added dropwise, and the resulting solution was stirred for 1 h at −65 °C. The temperature was allowed to rise to room temperature in 3 h. Silica gel was added to the yellow-orange solution, and the solvent was evaporated. Purification by chromatography on silica gel (hexane to hexane/EtOAc, 9:1) gave 0.81 g (1.5 mmol, 55%) of complex **1** as a yellow-orange solid: mp 77 °C; ^1H NMR δ 5.46 (br s, 4 H, OCH_2), 3.02 (s, 6 H, CH_3); ^{13}C NMR δ 361.6

(15) Fischer, E. O.; Maasböl, A. *Chem. Ber.* **1967**, *100*, 2445.

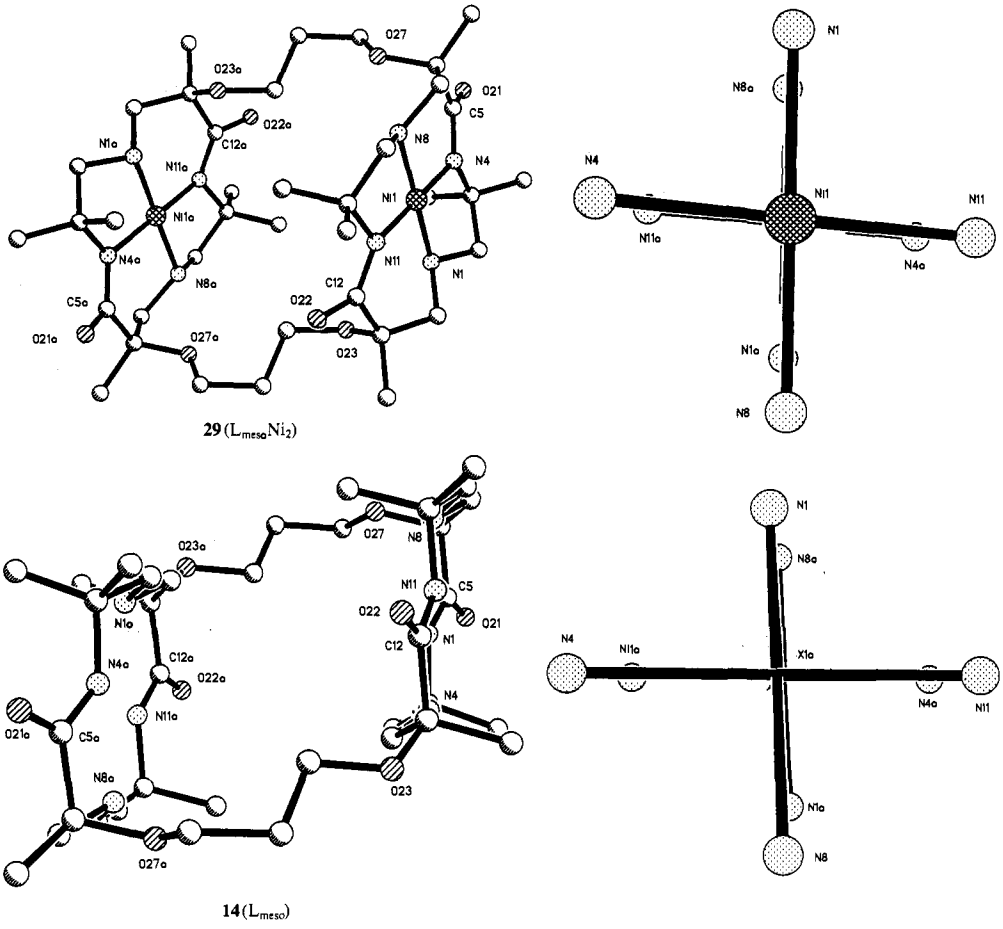

Figure 6. X-ray structures for meso dioxocyclam **14** and its bis-nickel complex **29**.

(Cr=C), 223.0 (CO trans), 216.0 (CO cis), the signals of carbene substituents (CH_2O, CH_3) were not detected; IR (KBr) ν 2065, 1948, 1920 (CO) cm^{-1}. Anal. Calcd for $C_{16}H_{10}Cr_2O_{12}$: C, 38.57; H, 2.02. Found: C, 38.29; H, 1.76.

(b) **Complex 2 (n = 3) from 1,3-Propanediol.** Pentacarbonyl-[(methyl){(tetramethylammonio)oxy}carbene]chromium(0) (1.59 g, 5.1 mmol), acetyl bromide (0.33 mL, 4.5 mmol), and 1,3-propanediol (0.16 g, 2.1 mmol) were allowed to react for 6 h according to the procedure described for **1** to give 0.93 g (1.7 mmol, 83%) of complex **2** as a yellow-orange oil: ^1H NMR δ 5.13 (br s, 4 H, OCH_2), 2.98 (s, 6 H, CH_3), 2.72 (5-line multiplet, 2 H, CH_2); ^{13}C NMR δ 360.3 (Cr=C), 223.2 (CO trans), 216.3 (CO cis), 29.3 (CH_2), the signals of carbene substituents (CH_2O, CH_3) were not detected; IR (neat) ν 2064, 1917 cm^{-1} (CO). Anal. Calcd for $C_{17}H_{12}Cr_2O_{12}$: C, 39.96; H, 2.36. Found: C, 39.86; H, 2.47.

(c) **Complex 3 (n = 4) from 1,4-Butanediol.** Pentacarbonyl-[(methyl){(tetramethylammonio)oxy}carbene]chromium(0) (5.52 g, 17.8 mmol) was dissolved in dry CH_2Cl_2 (175 mL) under an argon atmosphere, and the solution was cooled to −45 °C. Acetyl bromide (1.32 mL, 17.8 mmol) was added dropwise, and the solution was stirred at −45 °C for 1 h. 1,4-Butanediol (0.79 mL, 8.9 mmol) was added dropwise, and the solution was allowed to warm to room temperature in 19 h to give after chromatography on silica gel (hexane to hexane/EtOAc, 9:1) 3.10 g (5.6 mmol, 62%) of complex **3** as a yellow-orange solid: mp 81 °C; ^1H NMR δ 5.01 (br s, 4 H, OCH_2), 2.98 (br s, 6 H, CH_3), 2.26 (br s, 4 H, CH_2); ^{13}C NMR δ 359.0 (Cr=C), 223.2 (CO trans), 216.4 (CO cis), 26.11 ($[CH_2]_2$), the signals of carbene substituents (CH_2O, CH_3) were not detected; IR (KBr) ν 2065, 1983, 1936, 1904 (CO) cm^{-1}. This compound decomposed slowly, and acceptable elemental analysis was not obtained.

(d) **Complex 4 (n = 10) from 1,10-Decanediol.** Pentacarbonyl-[(methyl){(tetramethylammonio)oxy}carbene]chromium(0) (2.06 g, 6.7 mmol), acetyl bromide (0.43 mL, 5.9 mmol), and 1,10-decanediol (0.463 g, 2.7 mmol) were allowed to react according to the procedure described for **3** (for 7 h from −60 to 10 °C) to give 1.46 g (2.4 mmol, 90%) of complex **4** as a yellow-orange solid: mp 41−42 °C; ^1H NMR δ 4.91 (br s, 4 H, OCH_2), 2.94 (s, 6 H, CH_3), 1.99 (5-line multiplet, 4 H, $[CH_2]CH_2O$), 1.3−1.6 (m, 12 H, $[CH_2]_6CH_2CH_2O$); ^{13}C NMR δ 357.4 (Cr=C), 223.4 (CO trans), 216.5 (CO cis), 29.2 (CH_2), 29.0 (CH_2), 25.7 (CH_2), the signals of carbene substituents (CH_2O, CH_3) were not detected; IR (KBr) ν 2063, 1992, 1966 (br), 1893 (CO) cm^{-1}. Anal. Calcd for $C_{24}H_{26}Cr_2O_{12}$: C, 47.22; H, 4.29. Found: C, 47.00; H, 4.38.

General Procedure for the Photoreaction of Bis-Chromium Alkoxycarbene Complexes with Imidazoline 5 To Form Bis-Azapenams 6−9. The bis-chromium complex (1 equiv, 1 mmol) and imidazoline **5** (1 equiv, 2 mmol) were dissolved in CH_2Cl_2 (15−20 mL/mmol of **5**) under argon in a 45−200 mL Pyrex pressure tube equipped with a Matheson/Whitey Brand 600 psi pressure head and pressure release valve. The resulting dark-yellow solution was pressurized with CO to ≈90 psi and then irradiated (450-W Conrad-Hanovia 7825 medium-pressure mercury lamp, Pyrex well) under 85−100 psi of CO pressure. The reaction was followed by the fading of the color. After 24−48 h, the solvent was evaporated and the residue was triturated with MeOH (20 mL/mmol) and kept for a few hours at −20 °C. Filtration of chromium hexacarbonyl, evaporation of MeOH, and purification by chromatography on silica gel (EtOAc/hexane, 1:1) gave the bis-azapenam as a mixture of two diastereoisomers and rotamers.

1,2-Bis[[7-oxo-4-(benzyloxycarbonyl)-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]hept-6-yl]oxy]ethane (6). Bis-carbene complex **1** (1.72 g, 3.2 mmol) and imidazoline **5** (1.51 g, 6.5 mmol) were allowed to react according to the general procedure (irradiation for 30 h) to give 1.14 g (55%) of product **6** as a solid foam and as a 1:1 mixture of diastereoisomers and rotamers after flash chromatography (hexane/EtOAc, 1:1 to 1:2). **6**: ^1H NMR δ 7.36 (br s, 10 H, ArH), 5.0−5.3 (m, 6 H, CH_2Ph and CH), 3.4−3.9 (m, 6 H, CH_2O and CH_2N), 3.14 (d, J = 10.4 Hz, 2 H, CH_2N), 1.61 (br s, 6 H, C2Me$_2$), 1.30 and 1.18 (2 br s, 12 H, C6Me and C2Me$_2$); ^{13}C NMR δ 173.0 and 172.7 (CO lactam), 153.6 and 153.0 (CO carbamate), 135.8 and 135.4 (ipso Ar), 128.3, 128.2, 128.0, 127.9 and 127.6 (Ar), 89.7 (C6), 74.5 and 74.0 (C5), 67.2 and 67.1 (CH_2Ph), 64.6 (CH_2O), 60.8 and 60.3 (CMe_2), 60.4

(CH_2N), 25.5 (CH_3), 21.6 (CH_3), 13.7, 13.5 and 13.4 (CH_3); IR (neat) ν 1771 (CO lactam), 1712 (CO carbamate) cm^{-1}. Anal. Calcd for $C_{34}H_{42}N_4O_8$: C, 64.34; H, 6.67; N, 8.83. Found: C, 64.47; H, 6.65; N, 8.94.

1,3-Bis[[7-oxo-4-(benzyloxycarbonyl)-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]hept-6-yl]oxy]propane (7). Bis-carbene complex **2** (3.88 g, 7.1 mmol) and imidazoline **5** (3.30 g, 14.2 mmol) were allowed to react according to the general procedure (irradiation for 70 h) to give 3.22 g (5.0 mmol, 70%) of product **7** as a 1:1 mixture of diastereoisomers and rotamers partly contaminated with an impurity after chromatography (hexane/EtOAc, 1:1). Two crystallizations from methanol gave 1.18 g (1.8 mmol, 26%) of the *d,l* diastereoisomer. A second flash chromatography gave 1.38 g (2.1 mmol, 33%) of the meso diastereoisomer. *d,l*-**7** (as a mixture of rotamers): mp 132−134 °C (MeOH); ^1H NMR δ 7.35 (br s, 10 H, ArH), 5.05−5.35 (m, 6 H, CH_2-Ph and CH), 3.77 (d, J = 10.5 Hz) and 3.69 (d, J = 10.4 Hz, 2 H, CH_2N), 3.4−3.9 (m, 4 H, CH_2O), 3.14 (d, J = 10.5 Hz, 2 H, CH_2N), 1.65−1.95 (m, 2 H, CH_2), 1.61 (br s, 3 H, C2*Me*$_2$), 1.31, 1.30, 1.28, 1.20, 1.18 (5 br s, 18 H, C6Me and C2Me_2); ^{13}C NMR δ 173.8 and 173.3 (CO lactam), 153.8 and 153.3 (CO carbamate), 135.9 and 135.7 (ipso Ar), 128.5, 128.2, 128.0 and 127.8 (Ar), 90.0 and 89.9 (C6), 74.7 and 74.2 (C5), 67.4 (CH_2Ph), 62.0 (CH_2O), 61.0 and 60.5 (CMe_2), 60.3 (CH_2N), 30.2 (CH_2), 25.8 (CH_3), 21.8 (CH_3), 13.9 (CH_3). Anal. Calcd for $C_{35}H_{44}N_4O_8$: C, 64.80; H, 6.84; N, 8.64. Found: C, 65.00; H, 6.90; N, 8.62.

Meso-7 (as a mixture of rotamers partly contaminated with an impurity): mp 42−45 °C; ^1H NMR δ 7.35 (br s, 10 H, ArH), 5.0−5.35 (m, 6 H, CH_2Ph and CH), 3.77 (d, J = 10.4 Hz) and 3.69 (d, J = 10.3 Hz, 2 H, CH_2N), 3.4−3.85 (m, 4 H, CH_2O), 3.14 (d, J = 10.4 Hz, 2 H, CH_2N), 1.55−1.95 (m, 2 H, CH_2), 1.61 (br s, 6 H, C2Me_2), 1.29 and 1.18 (2 br s, 12 H, C6Me and C2Me_2); ^{13}C NMR δ 173.4 and 172.9 (CO lactam), 153.5 and 152.9 (CO carbamate), 135.8 and 135.5 (ipso Ar), 128.2, 127.9, 127.8 and 127.5 (Ar), 89.7 and 89.6 (C6), 74.4 and 73.9 (C5), 67.1 and 67.0 (CH_2Ph), 61.7 (CH_2O), 60.7 and 60.2 (CMe_2), 60.0 (CH_2N), 29.9 (CH_2), 25.5 (CH_3), 21.5 (CH_3), 13.6 (CH_3); IR (neat) ν 1770 (CO lactam), 1713 (CO carbamate) cm^{-1}. Anal. Calcd for $C_{35}H_{44}N_4O_8$: C, 64.80; H, 6.84; N, 8.64. Found: C, 64.87; H, 6.90; N, 8.51.

1,4-Bis[[7-oxo-4-(benzyloxycarbonyl)-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]hept-6-yl]oxy]butane (8). Bis-carbene complex **3** (2.58 g, 4.5 mmol) and imidazoline **5** (2.11 g, 9.1 mmol) were allowed to react according to the general procedure (irradiation for 29 h) to give 2.04 g (3.0 mmol, 68%) of product **8** as an oil and as a 1:1 mixture of diastereoisomers and rotamers after flash chromatography (hexane/EtOAc, 1:1 to 1:2). ***d,l*- and meso-8** (as a mixture of rotamers): ^1H NMR δ 7.36 (br s, 10 H, ArH), 5.0−5.3 (m, 6 H, CH_2Ph and CH), 3.78 (d, J = 10.4 Hz) and 3.71 (d, J = 10.3 Hz, 2 H, CH_2N), 3.3−3.8 (m, 4 H, CH_2O), 3.15 (d, J = 10.4 Hz, 2 H, CH_2N), 1.62 (br s, 6 H, C2Me_2), 1.5−1.75 (m, 6 H, CH_2), 1.30, 1.212, 1.209 and 1.19 (4 br s, 12 H, C6Me and C2Me_2); ^{13}C NMR δ 173.7 and 173.3 (CO lactam), 153.6 and 153.0 (CO carbamate), 135.8 and 135.4 (ipso Ar), 128.3, 128.2, 128.0, 127.95, 127.7 and 127.6 (Ar), 89.8 and 89.7 (C6), 74.5 and 74.0 (C5), 67.2 and 67.1 (CH_2Ph), 65.1 (CH_2O), 60.7 and 60.3 (CMe_2), 60.0 (CH_2N), 28.6 (CH_2), 26.1 and 25.6 (CH_3), 21.6 and 20.6 (CH_3), 14.0, 13.93, 13.88 and 13.6 (CH_3); IR (neat) ν 1772 (CO lactam), 1711 (CO carbamate) cm^{-1}. Anal. Calcd for $C_{36}H_{46}N_4O_8$: C, 65.24; H, 7.00; N, 8.45. Found: C, 65.06; H, 6.95; N, 8.58.

1,10-Bis[[7-oxo-4-(benzyloxycarbonyl)-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]hept-6-yl]oxy]decane (9). Bis-carbene complex **4** (1.24 g, 2.0 mmol) and imidazoline **5** (0.94 g, 4.0 mmol) were allowed to react according to the general procedure (irradiation for 62 h) to give 0.85 g (1.1 mmol, 56%) of product **9** as an oil and as a 1:1 mixture of diastereoisomers and rotamers after flash chromatography (hexane/EtOAc, 1:2). ***d,l*- and meso-9** (as a mixture of rotamers): ^1H NMR δ 7.34 (br s, 10 H, ArH), 5.08−5.30 (m, 6 H, CH_2Ph and CH), 3.35−3.8 (m, 6 H, CH_2N, CH_2O), 3.15 (d, J = 10.5 Hz, 2 H, CH_2N), 1.60 (s, 6 H, C2Me_2), 1.45−1.7 (m, 4 H, OCH_2CH_2), 1.10−1.45 (m, 24 H, $[CH_2]_6$, C2Me_2 and C6Me); ^{13}C NMR δ 173.7 and 173.3 (CO lactam), 153.5 and 152.9 (CO carbamate), 135.7 and 135.4 (ipso Ar), 128.2, 128.0, 127.9, 127.6 and 127.5 (Ar), 89.8 and 89.7 (C6), 74.5 and 74.0 (C5), 67.1 (CH_2Ph), 65.5 (CH_2O), 60.6 (CH_2N), 60.2 and 60.0 (CMe_2), 29.5 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 25.5 (CH_3), 21.5 (CH_3), 13.9 and 13.6 (CH_3); IR (neat) ν 1772 (CO lactam), 1714 (CO carbamate) cm^{-1}. Anal. Calcd for $C_{42}H_{58}N_4O_8$: C, 67.54; H, 7.83; N, 7.50. Found: C, 67.76; H, 7.61; N, 7.53.

General Procedure for the Deprotection of the *N*-(Benzyloxycarbonyl)-Bis-azapenams 6−9. The protected bis-azapenam was dissolved in methanol (10 mL/mmol), and triethylamine (0.2 mL/mmol) was added. Hydrogenation with 10% palladium on carbon (1 mg catalyst/2 mg substrate) at 45 psi of H_2 for 30 min, filtration through Celite, and evaporation of the solvent gave the product. Purification and/or separation of the two diastereoisomers was achieved by flash chromatography on silica gel. Because these decomposed and dimerized on standing, they were converted to bis-cyclams without further characterization.

1,2-Bis[[7-oxo-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]hept-6-yl]-oxy]ethane (10). Bis-azapenam **6** (as a 1:1 mixture of diastereoisomers, 0.215 g, 0.34 mmol) was deprotected according to the general procedure (stirred for 10 min) to give 0.110 g (0.30 mmol, 89%) of product **10** as a 1:1 mixture of diastereoisomers partly separated by radial chromatography on a 2 mm silica gel plate (EtOAc). Separation of 100 mg of a 1:1 mixture of two diastereoisomers gave 19 mg (15%) of *d,l*-**10**, 38 mg (31%) of a ≈1:1 mixture of *d,l*-**10**:meso-**10**, and 20 mg (16%) of a 16:84 mixture of *d,l*-**10**:meso-**10**.

Meso-10 (R_f = 0.17, EtOAc/MeOH, 95:5): ^1H NMR δ 4.78 (s, 2 H, CH), 3.85 (d, J = 6.8 Hz, 2 H, CH_2O), 3.72 (d, J = 6.8 Hz, 2 H, CH_2O), 3.06 (d, J = 11.2 Hz, 2 H, CH_2N), 2.62 (d, J = 11.2 Hz, 2 H, CH_2N), 2.1−2.5 (br, 2 H, NH), 1.56 (s, 6 H, CH_3), 1.33 (s, 6 H, CH_3), 1.10 (s, 6 H, CH_3); ^{13}C NMR δ 175.5 (CO), 89.6 (C6), 77.9 (C5), 65.3 (CH_2O), 62.0 (CH_2N), 60.9 (CMe_2), 24.9 (CH_3), 21.7 (CH_3), 14.8 (CH_3).

***d,l*-10** (R_f = 0.19, EtOAc/MeOH, 95:5): ^1H NMR δ 4.77 (s, 2 H, CH), 3.55−3.9 (m, 4 H, CH_2O), 3.06 (d, J = 11.2 Hz, 2 H, CH_2N), 2.62 (d, J = 11.2 Hz, 2 H, CH_2N), 2.1−2.45 (br, 2 H, NH), 1.56 (s, 6 H, CH_3), 1.34 (s, 6 H, CH_3), 1.10 (s, 6 H, CH_3); ^{13}C NMR δ 175.5 (CO), 89.5 (C6), 78.0 (C5), 65.1 (CH_2O), 62.0 (CH_2N), 60.9 (CMe_2), 24.9 (CH_3), 21.7 (CH_3), 14.6 (CH_3); IR (neat) ν 3353 (CONH, NH), 1747 (CO) cm^{-1}.

1,3-Bis[[7-oxo-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]hept-6-yl]-oxy]propane (11). Bis-azapenam **7** (as a single *d,l* diastereoisomer, 1.15 g, 1.8 mmol) was deprotected according to the general procedure (stirred for 30 min) to give 0.60 g (1.6 mmol, 89%) of product *d,l*-**11** after flash chromatography on silica gel (CH_2Cl_2/MeOH, 97.5:2.5). *d,l*-**11** (R_f = 0.43, CH_2Cl_2/MeOH, 95:5): ^1H NMR δ 4.75 (s, 2 H, CH), 3.76 (dt, J_1 = 9.1 Hz, J_2 = 6.4 Hz, 2 H, CH_2O), 3.62 (dt, J_1 = 9.0 Hz, J_2 = 5.9 Hz, 2 H, CH_2O), 3.06 (d, J = 11.2 Hz, 2 H, CH_2N), 2.62 (d, J = 11.3 Hz, 2 H, CH_2N), 2.32 (br s, 2 H, NH), 1.86 (quint, J = 6.2 Hz, 2 H, CH_2), 1.56 (s, 6 H, CH_3), 1.30 (s, 6 H, CH_3), 1.11 (s, 6 H, CH_3); ^{13}C NMR δ 175.9 (CO), 89.4 (C6), 77.5 (CH), 62.0 (CH_2O or CH_2N), 61.9 (CH_2O or CH_2N), 60.8 (CMe_2), 30.4 (CCH_2C), 24.9 (CH_3), 21.7 (CH_3), 15.1 (CH_3); IR (neat) ν 3493, 3348 (CONH, NH), 1748 (CO) cm^{-1}.

Bis-azapenam **7** (as a mixture of meso/*d,l* diastereoisomers contaminated with an impurity, 0.51 g, 0.78 mmol) was deprotected according to the general procedure (stirred for 30 min) to give 0.23 g (0.61 mmol, 78%) of products meso-**11** and *d,l*-**11** in a ratio of 9:1 after purification by flash chromatography (CH_2Cl_2/MeOH, 97.5:2.5). Purification of 0.143 g by radial chromatography (silica gel, 2 mm plate; Et_2O/MeOH, 95:5) gave 0.076 g (53%) of meso-**11**, 0.033 g (23%) of a 1:1 mixture of the two diastereoisomers, and 0.017 g (12%) of *d,l*-**11**.

Meso-11 (R_f = 0.38, CH_2Cl_2/MeOH, 95:5): ^1H NMR δ 4.79 (s, 2 H, CH), 3.76 (dt, J_1 = 9.1 Hz, J_2 = 6.0 Hz, 2 H, CH_2O), 3.63 (dt, J_1 = 9.2 Hz, J_2 = 6.0 Hz, 2 H, CH_2O), 3.07 (d, J = 11.2 Hz, 2 H, CH_2N), 2.62 (d, J = 11.3 Hz, 2 H, CH_2N), 2.33 (br s, 2 H, NH), 1.86 (5 line multiplet, 1 H, CH_2), 1.85 (5 line multiplet, 1 H, CH_2), 1.57 (s, 6 H, CH_3), 1.29 (s, 6 H, CH_3), 1.11 (s, 6 H, CH_3); ^{13}C NMR δ 175.9 (CO), 89.4 (C6), 77.5 (CH), 62.0 (CH_2O or CH_2N), 61.9 (CH_2O or CH_2N), 60.8 (CMe_2), 30.4 (CCH_2C), 24.9 (CH_3), 21.7 (CH_3), 15.1 (CH_3); IR (neat) ν 3354 (CONH, NH), 1748 (CO) cm^{-1}.

1,4-Bis[[7-oxo-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]hept-6-yl]-oxy]butane (12). Bis-azapenam **8** (as a 1:1 mixture of diastereoisomers, 2.05 g, 3.1 mmol) was deprotected according to the general procedure (stirred for 25 min) to give 0.92 g (2.3 mmol, 73%) of product **12** as a 1:1 mixture of diastereoisomers which could not be separated

by flash chromatography on silica gel (EtOAc/MeOH, 97.5:2.5). **12** (as a 1:1 mixture of meso and *d,l* diastereoisomers): ^{1}H NMR δ 4.73 (br s, 2 H, CH), 3.6–3.7 (m, 2 H, CH_2O), 3.5–3.6 (m, 2 H, CH_2O), 3.06 (d, J = 11.2 Hz, 2 H, CH_2N), 2.62 (d, J = 11.2 Hz, 2 H, CH_2N), 2.25 (br s, 2 H, NH), 1.67 (m, 4 H, OCH_2CH_2), 1.56 (s, 6 H, CH_3), 1.30 (s, 6 H, CH_3), 1.11 (s, 6 H, CH_3); ^{13}C NMR δ 176.0 (CO), 89.4 (C6), 77.9 (C5), 65.5 (CH_2O or CH_2N), 62.0 (CH_2O or CH_2N), 60.8 (CMe_2), 26.6 ($[CH_2]_2$), 24.9 (CH_3), 21.7 (CH_3), 14.9 (CH_3); IR (neat) ν 3350 (NH), 1748 (CO) cm^{-1}.

1,10-Bis[[7-oxo-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]hept-6-yl]-oxy]decane (13). Bis-azapenam **9** (as a 1:1 mixture of diastereoisomers, 0.90 g, 1.1 mmol) was deprotected according to the general procedure (stirred for 20 min) to give 0.44 g (0.83 mmol, 74%) of product **13** as a 1:1 mixture of diastereoisomers which could not be separated by flash chromatography (EtOAc/MeOH, 97.5:2.5): ^{1}H NMR δ 4.73 (s, 2 H, CH), 3.76 (dt, J_1 = 8.4 Hz, J_2 =6.8 Hz, 2 H, CH_2O), 3.62 (dt, J_1 = 8.5 Hz, J_2 = 6.8 Hz, 2 H, CH_2O), 3.06 (d, J = 11.2 Hz, 2 H, CH_2N), 2.63 (d, J = 11.2 Hz, 2 H, CH_2N), 2.10–2.45 (br s, 2 H, NH), 1.50–1.70 (m, 4 H, OCH_2CH_2), 1.57 (s, 6 H, CH_3), 1.31 (s, 6 H, CH_3), 1.20–1.40 (m, 12 H, $[CH_2]_6$), 1.11 (s, 6 H, CH_3); ^{13}C NMR δ 175.9 (CO), 89.2 (C6), 77.6 (CH), 65.7 (CH_2O), 61.8 (CH_2N), 60.6 (CMe_2), 29.8 (CH_2CH_2O), 29.2 (CH_2), 29.1 (CH_2), 25.8 (CH_2), 24.7 (CH_3), 21.5 (CH_3), 14.7 (CH_3); IR (neat) ν 3352 (NH), 1747 (CO) cm^{-1}.

General Procedure for the Dimerization/Reduction of Bis-Azapenams 10–13 to Produce Bis-Dioxocyclams. The bis-azapenam (as a single diastereoisomer or mixture of diastereoisomers, 1 mmol) and a catalytic amount (0.125 equiv, 0.25 mmol]) of racemic camphorsulfonic acid in CH_2Cl_2 (100 mL/mmol of bis-azapenam) were stirred at room temperature for the specified time. The solution was washed with aqueous 5% $NaHCO_3$ and dried over Na_2SO_4. The crude bis-dioxocyclam (imine), $NaBH_3CN$ (2 equiv), and a small amount of bromocresol green were dissolved in 1:1 MeOH/CH_2Cl_2. HCl/MeOH (1 N) was added dropwise via a syringe to the cooled (0 °C) blue solution until the yellow-green color remained, and the resulting solution was stirred and warmed to room temperature overnight. Excess $NaBH_3CN$ was neutralized with 1 N HCl/MeOH. Aqueous NaOH (5%) was added to adjust the pH to ≈9–10, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over K_2CO_3 and was evaporated to give a white solid which was chromatographed on silica gel.

Bis-Cyclam Meso Homo Dimer 14 (n = 3). Bis-azapenam meso-**11** (176 mg, 0.46 mmol) was allowed to react according to the general procedures of dimerization (for 67 h) and reduction to give 97 mg (0.13 mmol, 55%) of product meso homo dimer **14** after purification by flash chromatography (CH_2Cl_2/MeOH, 95:5): mp >260 °C (MeOH); ^{1}H NMR δ 8.19 (s, 4 H, CONH), 3.55 (m, 4 H, CH_2O), 3.42 (dt, J_1 = 7.1 Hz, J_2 = 9.3 Hz, 4 H, CH_2O), 2.89 (d, J = 11.5 Hz, 4 H, CH_2N), 2.77 (s, 8 H, CH_2N), 2.34 (d, J = 11.5 Hz, 4 H, CH_2N), 1.82 (quint, J = 11.5 Hz, 4 H, CH_2CH_2O), 1.5–2.0 (br s, 4 H, NH), 1.41 (s, 12 H, CH_3), 1.30 (s, 12 H, CH_3), 1.27 (s, 12 H, CH_3); ^{13}C NMR δ 171.9 (CO), 79.1 (C6), 60.4 (CH_2N), 59.4 (CH_2N), 56.4 (CH_2O), 52.6 (CMe_2), 32.3 (CCH_2C), 25.2 (CH_3), 24.8 (CH_3), 19.8 (CH_3); IR (KBr) ν 3412, 3243 (CONH, NH), 1671 (CO), 1542 cm^{-1}. Anal. Calcd for $C_{38}H_{72}N_8O_8$:C, 59.35; H, 9.44; N, 14.57. Found: C, 59.47; H, 9.28; N, 14.72.

The structure of meso homo dimer **14** was determined by an X-ray analysis, and the results of this study are presented in the supplementary material.

Bis-Cyclam *d,l* Homo Dimer 15 (n = 3). Bis-azapenam *d,l*-**11** (252 mg, 0.66 mmol) was allowed to react according to the general procedures of dimerization (for 4 days) and reduction to give 112 mg (0.15 mmol, 44%) of product *d,l* homo dimer **15** after purification by flash chromatography (CH_2Cl_2/MeOH, 95:5): mp >260 °C (CH_3CN); ^{1}H NMR δ 9.10 (s, 4 H, CONH), 3.40 (t, J = 6.8 Hz, 8 H, CH_2O), 2.78 (d, J = 12.6 Hz, 4 H, CH_2N), 2.68 (d, J = 12.6 Hz, 4 H, CH_2N), 2.60 (d, J = 11.2 Hz, 4 H, CH_2N), 2.51 (d, J = 11.2 Hz, 4 H, CH_2N), 1.76 (quint, J = 6.8 Hz, 4 H, CH_2CH_2O), 1.55 (s, 4 H, NH), 1.44 (s, 12 H, CH_3), 1.34 (s, 12 H, CH_3), 1.24 (s, 12 H, CH_3); ^{13}C NMR δ 171.7 (CO), 78.5 (C6), 61.3 (CH_2N), 61.1 (CH_2N), 56.7 (CH_2O), 52.2 (CMe_2), 31.4 (CCH_2C), 25.0 (CH_3), 24.2 (CH_3), 19.2 (CH_3); IR (KBr) ν 3413, 3335, 3255 (br, NH and CONH), 1670 (CO), 1539 cm^{-1}; UV (CH_2Cl_2) λ 229.8 nm (ϵ = 745); MS (CsI/glycerol, HR FAB) m/z 769.6 $(M + H)^+$; MW calculated for $C_{38}H_{73}N_8O_8$ 769.5551, found 769.5544 (Δ = −0.96 ppm). Anal. Calcd for $C_{38}H_{72}N_8O_8$: C, 59.35; H, 9.44. Found: C, 59.37; H, 9.18.

The structure of *d,l* homo dimer **14** was determined by an X-ray analysis, and the results of this study are presented in the supplementary material.

Mono-Cyclam 16. Bis-azapenam *d,l*-**11** *d,l* (75 mg, 0.20 mmol) and racemic camphorsulfonic acid (23 mg, 0.10 mmol, 0.25 equiv) were dissolved in CH_2Cl_2 (20 mL) and stirred for 26 h at room temperature. The crude mixture was concentrated to ≈5 mL and reduced according to the general procedure to give after chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) 3.8 mg (0.010 mmol, 5%) of mono-cyclam **16** (R_f = 0.32), 15 mg (0.019 mmol, 20%) of *d,l* homo dimer **15** (R_f = 0.26), and 5.5 mg (0.007 mmol, 6%) of the *d,l* hetero dimer (R_f = 0.19). The structure of the *d,l* hetero dimer was determined by comparison with the centrosymmetrical monocyclam.[7] **16**: mp >190 °C dec; ^{1}H NMR δ 8.21 (s, 2 H, CONH), 3.64 (m, 4 H, CH_2O), 3.30 (d, J = 14.3 Hz, 2 H, CH_2N), 2.98 (d, J = 12.5 Hz, 2 H, CH_2N), 2.51 (d, J = 14.3 Hz, 2 H, CH_2N), 2.32 (d, J = 12.5 Hz, 2 H, CH_2N), 1.91 (5-line multiplet, 2 H, CH_2CH_2O), 1.5–1.7 (br s, 2 H, NH), 1.35 (s, 6 H, CH_3), 1.27 (s, 6 H, CH_3), 1.26 (s, 6 H, CH_3); ^{13}C NMR δ 172.5 (CO), 82.9 (C6), 63.4 (CH_2N), 60.6 (CH_2N), 57.9 (CH_2O), 53.4 (CMe_2), 29.0 (CCH_2C), 24.6 (CH_3), 22.2 (CH_3), 18.1 (CH_3); IR (neat) ν 3356 (NH, CONH), 1651 (CO), 1528 cm^{-1}; MS (EI) m/z 384.3 (M^+).

***d,l* hetero dimer**: mp >260 °C; ^{1}H NMR δ 7.39 (s, 4 H, CONH), 3.48–3.63 (m, 8 H, CH_2O), 3.00 (d, J = 12.2 Hz, 4 H, CH_2N), 2.79 (d, J = 12.1 Hz, 4 H, CH_2N), 2.73 (d, J = 12.1 Hz, 4 H, CH_2N), 2.56 (d, J = 12.0 Hz, 4 H, CH_2N), 1.93 (5-line multiplet, 2 H, CCH_2C), 1.34 (s, 12 H, CH_3), 1.33 (s, 12 H, CH_3), 1.32 (s, 12 H, CH_3); ^{13}C NMR δ 173.2 (CO), 80.4 (C6), 61.2 (CH_2N), 59.1 (CH_2N), 55.8 (CMe_2), 53.3 (CH_2O), 32.7 (CCH_2C), 25.5 (CH_3), 24.7 (CH_3), 20.8 (CH_3); IR (KBr) ν 3399 (br, NH and CONH), 1667 (CO), 1516; MS (EI) m/z 768.5.

Bis-Cyclam Diastereoisomers Derived from Bis-Azapenam 10 (n = 2). Bis-azapenam **10** (n = 2, 138 mg, 0.38 mmol) was allowed to react according to the general procedures of dimerization (for 87 h) and reduction to give after a first chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) 136 mg (0.38 mmol, 97%) of product as a mixture of three diastereoisomers (meso homo dimer:*d,l* homo dimer:*d,l* hetero dimer = 6.0:4.8:2.2) which were partly separated after further radial chromatography (silica gel, 2 mm plate, CH_2Cl_2/MeOH, 95:5) to give 50 mg of *d,l* homo dimer (0.067 mmol, 36%, R_f = 0.20), 15 mg of *d,l* hetero dimer *d,l* (0.020 mmol, 11%, R_f = 0.15), and 32 mg of meso homo dimer (0.043 mmol, 23%, R_f = 0.27).

The structures of the three diastereoisomers (n = 2) were determined by ^{1}H NMR. The homo dimers (meso and *d,l*) were compared with the bis-cyclams **14** and **15** (n = 3), and the *d,l* hetero dimer was compared with the centrosymmetrical mono-dioxocyclam[7] and the traces of *d,l* hetero dimer (n = 3).

Bis-cyclam meso homo dimer (n = 2): mp >260 °C; ^{1}H NMR δ 7.32 (s, 4 H, CONH), 3.69 (d, J = 8.0 Hz, 4 H, CH_2O), 3.55 (d, J = 8.2 Hz, 4 H, CH_2O), 2.99 (d, J = 12.4 Hz, 4 H, CH_2N), 2.81 (AB system, J = 12.7 Hz, 8 H, CH_2N), 2.30 (d, J = 12.4 Hz, 4 H, CH_2N), 1.39 (s, 12 H, CH_3), 1.33 (s, 12 H, CH_3), 1.30 (s, 12 H, CH_3); ^{13}C NMR δ 171.7 (CO), 80.6 (C6,13), 63.6 (C7,14), 58.8 (C2,9), 57.9 (CH_2O), 53.5 (CMe_2), 26.5 (CH_3), 24.3 (CH_3), 19.2 (CH_3); IR (KBr) ν 3466, 3406 (br, NH, CONH), 1671 (CO), 1527 cm^{-1}; MS (HR FAB) MW calculated for $C_{36}H_{69}N_8O_8$ 741.523 837, found 741.520 859 ± 0.0014 (Δ = −2.0 ppm).

Bis-cyclam *d,l* homo dimer (n = 2): mp >260 °C; ^{1}H NMR δ 7.38 (s, 4 H, CONH), 3.60 (s, 8 H, CH_2O), 2.96 (d, J = 12.5 Hz, 4 H, CH_2N), 2.87 (d, J = 12.0 Hz, 4 H, CH_2N), 2.74 (d, J = 12.0 Hz, 4 H, CH_2N), 2.48 (d, J = 12.5 Hz, 4 H, CH_2N), 1.8–2.3 (br s, 4 H, NH), 1.35 (s, 12 H, CH_3), 1.32 (s, 12 H, CH_3), 1.31 (s, 12 H, CH_3); ^{13}C NMR δ 172.0 (CO), 80.2 (C6,13), 63.3 (C7,14), 58.0 (C2,9), 56.9 (CH_2O), 53.8 (CMe_2), 26.2 (CH_3), 25.1 (CH_3), 19.5 (CH_3); IR (KBr) ν 3396 (br, NH and CONH), 1676 (CO), 1529 cm^{-1}; MS (HR FAB) MW calculated for $C_{36}H_{69}N_8O_8$ 741.523 837, found 741.522 492 ± 0.0007 (Δ = 1.8 ppm).

Bis-cyclam meso hetero dimer (n = 2): mp 198 °C dec; ^{1}H NMR δ 7.41 (s, 4 H, CONH), 3.6−3.8 (m, 8 H, CH_2O), 3.05 (d, J = 12.5 Hz, 4 H, CH_2N), 2.80 (d, J = 12.5 Hz, 4 H, CH_2N), 2.73 (d, J = 12.5 Hz, 4 H, CH_2N), 2.52 (d, J = 12.5 Hz, 4 H, CH_2N), 1.41 (s, 12 H, CH_3), 1.31 (s, 12 H, CH_3), 1.30 (s, 12 H, CH_3); ^{13}C NMR δ 172.7 (CO), 81.0 (C6,13), 64.1 (C7,14), 59.4 (C2,9), 56.5 (CH_2O), 53.4 (CMe_2), 25.6 (CH_3), 25.1 (CH_3), 22.0 (CH_3); IR (KBr) ν 3389 (br, NH and CONH), 1666 (CO), 1522 cm^{-1}; MS (HR FAB) MW calculated for $C_{36}H_{69}N_8O_8$ 741.523 837, found 741.5233 ± 0.0013 (Δ = 2.8 ppm).

Bis-Cyclam Diastereoisomers Derived from Bis-Azapenam 12 (n = 4). Bis-azapenam (n = 4, as mixture of diastereoisomers, 0.184 g, 0.45 mmol) and camphorsulfonic acid (0.055 g, 0.24 mmol, 0.25 equiv) were allowed to react according to the general procedure of dimerization for 73 h. The crude dimerization mixture was dissoved in MeOH (10 mL), and sodium borohydride (0.164 g, 4.34 mmol) was added portionwise over a 2.5 h period. The resulting mixture was stirred for 24 h at room temperature. The solvent was evaporated in vacuo, and the residue was washed with 0.5 N NaOH (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4, and evaporation of the solvent gave 0.146 g of a mixture which could not be separated by chromatography on silica gel. Trituration in acetone of this crude mixture gave 13 mg (0.03 mmol, 7%) of a ≈1:1 mixture of two bis-cyclam diastereoisomers. Spectroscopic data of this experiment are presented in the supplementary material.

Bis-Cyclam Diastereoisomers Derived from Bis-Azapenam 13 (n = 10). Bis-azapenam (n = 10, as mixture of diastereoisomers, 0.43 g, 0.81 mmol) was allowed to react according to the general procedure to give after separation by flash chromatography on silica gel (CH_2Cl_2/MeOH, 97.5:2.5 to 95:5) 0.18 g (0.17 mmol, 42%) of diastereoisomer **I** and 0.12 g (0.11 mmol, 28%) of diastereoisomer **II**.

Diastereoisomer I (R_f = 0.29, CH_2Cl_2/MeOH, 95:5): mp 174−176 °C; ^{1}H NMR δ 7.56 (s, 4 H, CONH), 3.4−3.55 (m, 8 H, CH_2O), 3.24 (d, J = 11.3 Hz, 4 H, CH_2N), 2.84 (d, J = 12.0 Hz, 4 H, CH_2N), 2.68 (d, J = 12.0 Hz, 4 H, CH_2N), 2.15 (d, J = 11.3 Hz, 4 H, CH_2N), 1.5−1.6 (m, 8 H, CH_2CH_2O and NH), 1.43 (s, 12 H, CH_3), 1.35 (br s, 24 H, $[CH_2]_8$), 1.28 (s, 12 H, CH_3), 1.27 (s, 12 H, CH_3); ^{13}C NMR δ 172.2 (CO), 79.0 (C6), 62.2 (CH_2N), 57.5 (CH_2N), 55.9 (CH_2O), 52.4 (CMe_2), 29.6, 29.2, 28.9 and 27.3 ($[CH_2]_8$), 26.2 (CH_3), 25.1 (CH_3), 19.4 (CH_3); IR (neat) ν 3415, 3274 (CONH, NH), 1679 (CO), 1521 (C−N) cm^{-1}; MS (HR FAB) m/z 965.77 (M + H)$^+$, 966.78 ($^{13}C_1{}^{12}C_{51}H_{101}N_8O_8)^+$; MW calculated for $C_{52}H_{101}N_8O_8$ 965.774 238, found 965.774 231 (Δ = −0.7 ppm); Sm (DF, 2 × 2) 483.5 ($^{13}C_1{}^{12}C_{51}H_{10}N_8O_8$ + 2H)$^{2+}$.

Diastereoisomer II (R_f = 0.25, CH_2Cl_2/MeOH, 95:5): mp 130−131 °C; ^{1}H NMR δ 7.13 (br s, 4 H, CONH), 3.42−3.52 (m, 4 H, CH_2O), 3.3−3.4 (m, 8 H, CH_2O and CH_2N), 2.82 (d, J = 12.0 Hz, 4 H, CH_2N), 2.62 (d, J = 12.0 Hz, 4 H, CH_2N), 2.11 (d, J = 11.3 Hz, 4 H, CH_2N), 1.5−1.65 (m, 8 H, CH_2CH_2O), 1.43 (s, 12 H, CH_3), 1.2−1.4 (br s, 24 H, $[CH_2]_6$), 1.28 (s, 12 H, CH_3), 1.23 (s, 12 H, CH_3); ^{13}C NMR δ 172.3 (CO), 79.3 (C6), 62.4 (CH_2N), 56.8 (CH_2N), 55.9 (CH_2O), 52.5 (CMe_2), 30.2, 29.7 and 26.9 ($[CH_2]_8$), 26.5 (CH_3), 25.1 (CH_3), 19.2 (CH_3); IR (KBr) ν 3536, 3477, 3412, 3276 (CONH, NH), 1674 (CO), 1524 (CN) cm^{-1}; MS (HR FAB) m/z 965.77 (M + H)$^+$, 966.78 ($^{13}C_1{}^{12}C_{51}H_{101}N_8O_8)^+$; MW calculated for $C_{52}H_{101}N_8O_8$ 965.774 238, found 965.774 632 (Δ = −0.4 ppm); Sm (DF, 2 × 2) 483.6 (M + 2H)$^+$.

1,3-Bis[[hexahydro-5-oxo-3,3,6-trimethyl-5*H*-1,4-diazepin-6-yl]-oxy]propane (Meso- and *d,l*-17). meso-17. Bis-azapenam meso-**11** (141 mg, 0.37 mmol), sodium cyanoborohydride (70 mg, 1.11 mmol), and a small amount of bromocresol green were dissolved in 6 mL of a 1:1 mixture of CH_2Cl_2/MeOH. To the blue solution, cooled to 0 °C, was added dropwise HCl/MeOH ≈ 1 N to maintain pH ≈ 4 (yellow-green). The green solution were stirred at room temperature for 24 h, and unreacted sodium cyanoborohydride was destroyed with an excess HCl/MeOH. NaOH (10%) was added (pH ≈ 9−10), and the aqueous layer was extracted with 4 × 20 mL of CH_2Cl_2, dried over K_2CO_3, and concentated in vacuo to give 150 mg of a white solid. Purification on silica gel (CH_2Cl_2/MeOH, 9:1 to 4:1) gave 108 mg (0.28 mmol, 76%) of product meso-**17** as a white solid: mp 195 °C; ^{1}H NMR δ 5.84 (br s, 2 H, CONH), 3.63 (dt, J_1 = 8.9 Hz, J_2 = 7.2 Hz, 2 H, CH_2O), 3.33 (dt, J_1 = 9.1, J_2 = 6.4 Hz, 2 H, CH_2O), 3.06 (br d, J = 15.0 Hz, 2 H, CH_2N), 2.88 (br d, J = 14.6 Hz, 2 H, CH_2N), 2.79 (d, J = 14.7 Hz, 2 H, CH_2N), 2.75 (br d, J = 14.4 Hz, 2 H, CH_2N), 2.49 (br s, 2 H, NH), 1.90 (m, 2 H, CH_2CH_2O), 1.46 (s, 6 H, CH_3), 1.24 (s, 6 H, CH_3), 1.15 (s, 6 H, CH_3); ^{13}C NMR δ 173.9 (CO), 80.3 (C6), 60.7 (CH_2N), 60.2 (CH_2O), 56.0 (CH_2N), 54.4 (CMe_2), 30.7 (CCH_2C), 30.0 (CH_3), 25.3 (CH_3), 20.3 (CH_3); IR (KBr) ν 3432, 3277, 3210 (CONH, NH), 1646 (CO) cm^{-1}. Anal. Calcd for $C_{19}H_{36}N_4O_4$: C, 59.35; H, 9.44; N, 14.57. Found: C, 59.18; H, 9.19; N, 14.48.

***d,l*-17.** Bis-azapenam *d,l*-**11** (88 mg, 0.23 mmol) and sodium cyanoborohydride (44 mg, 0.69 mmol) were allowed to react following the procedure described above (for 8 h) to give after purification by chromatography on silica gel 65 mg (0.17 mmol, 73%) of bis-diazapinone *d,l*-**17**: mp 167 °C ($CHCl_3$/hexane); ^{1}H NMR δ 5.67 (br s, 2 H, CONH), 3.63 (dt, J_1 = 7.4 Hz, J_2 = 6.8 Hz, 2 H, CH_2O), 3.33 (dt, J_1 = 9.0 Hz, J_2 = 5.7 Hz, 2 H, CH_2O), 3.06 (br d, J = 15.0 Hz, 2 H, CH_2N), 2.88 (br d, J = 14.6 Hz, 2 H, CH_2N), 2.79 (d, J = 14.6 Hz, 2 H, CH_2N), 2.75 (br d, J = 14.5 Hz, 2 H, CH_2N), 2.47 (br s, 2 H, NH), 1.89 (m, 2 H, CH_2CH_2O), 1.46 (s, 6 H, CH_3), 1.24 (s, 6 H, CH_3), 1.15 (s, 6 H, CH_3); ^{13}C NMR δ 173.9 (CO), 80.3 (C6), 60.3 (CH_2N, CH_2O), 56.0 (CH_2N), 54.4 (CMe_2), 30.4 (CH_2CH_2O), 30.0 (CH_3), 25.2 (CH_3), 20.4 (CH_3); IR (KBr) ν 3444, 3364, 3279, 3223 (CONH, NH), 1644 (CO) cm^{-1}. Anal. Calcd for $C_{19}H_{36}N_4O_4$: C, 59.35; H, 9.44; N, 14.57. Found: C, 59.15; H, 9.22; N, 14.34.

General Procedure for the Synthesis of Nickel Complexes of Dioxocyclams (Imine or Amine). The mono- or bis-dioxocyclam was dissolved in methanol (40 mL/mmol) with nickel bromide (10 equiv) and triethylamine or potassium carbonate (10 equiv). The resulting solution was heated in a sealed tube at 80−90 °C for the specified time. The crude mixture was filtered through Celite and the solvent evaporated. The crude mixture was dissolved in dichloromethane, washed with water, and dried over sodium carbonate. Purification and/or separation of the two diastereoisomers was achieved by flash chromatography on silica gel.

[(6*R,13*S**)-3,3,6,10,10,13-Hexamethyl-6,13-bis(phenylmethoxy)-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione]nickel (II) (20).** Dioxocyclam **18** (0.235 g, 0.53 mmol) as a mixture of two diastereoisomers, triethylamine (a few drops), and nickel bromide (0.174 g, 0.80 mmol) were allowed to react according to the general procedure for 36 h in MeOH at reflux to give after chromatography on silica gel (Et_2O/MeOH, 8:1) 0.127 g (0.22 mmol, 42%) of product **20** as a pink solid: ^{1}H NMR δ 7.24−7.41 (m, 12 H, ArH, CH=N), 4.80 (d, J = 11.2 Hz, 2 H, CH_2Ph), 4.81 (d, J = 11.2 Hz, 2 H, CH_2Ph), 3.24 (d, J = 12.1Hz, 2 H, CH_2N), 3.05 (d, J = 12.1 Hz, 2 H, CH_2N), 1.65 (s, 6 H, CH_3), 1.43 (s, 6 H, CH_3), 1.35 (s, 6 H, CH_3); ^{13}C NMR δ 175.8 (CO), 170.8 (C=N), 138.0, 128.5, 128.3, 128.0 (Ph), 81.2 (CH_2N), 76.8 (CMe_2), 69.0 (CH_2Ph), 60.6 (C6,13), 26.6 (CH_3), 24.1 (CH_3), 23.3 (CH_3); IR (KBr) ν 1597 (CO) cm^{-1}; UV−vis (CH_2Cl_2) 507 (ϵ = 174), 385 (ϵ = 1164) nm. Anal. Calcd for $C_{30}H_{38}N_4NiO_4$: C, 62.41; H, 6.63; N, 9.70. Found: C, 62.21; H, 6.62; N, 9.68. The structure of **20** was determined by X-ray analysis, and the results of this study are presented in the supplementary material.

[(6*R,13*S**)-3,3,6,10,10,13-Hexamethyl-6,13-dimethoxy-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione]nickel(II) (21).** Dioxocyclam **19** (0.100 g, 0.27 mmol) as a mixture of two diastereoisomers, triethylamine (a few drops), and nickel bromide (0.089 g, 0.41 mmol) were allowed to react according to the general procedure for 36 h in MeOH at reflux to give after chromatography on silica gel (Et_2O/MeOH, 4:1) 0.055 g (0.13 mmol, 48%) of product **21** as a pink solid and as a 1.75:1 mixture of two diastereoisomers.

Diastereoisomer I: ^{1}H NMR δ 7.43 (s, 2 H, CH=N), 3.40 (d, J = 12.1 Hz, 2 H, CH_2N), 3.37 (s, 6 H, OCH_3), 3.20 (d, J = 12.1 Hz, 2 H, CH_2N), 1.58 (s, 6 H, CH_3), 1.42 (s, 6 H, CH_3), 1.36 (s, 6 H, CH_3); ^{13}C NMR δ 175.5 (CO), 170.5 (C=N), 81.3 (CH_2N), 76.8 (CMe_2), 60.6 (C6,13), 54.3 (OCH_3), 26.2 (CH_3), 23.9 (CH_3), 23.0 (CH_3).

Diastereoisomer II: ^{1}H NMR δ 7.53 (s, 2 H, CH=N), 3.80 (d, J = 12.1 Hz, 2 H, CH_2N), 3.48 (s, 6 H, OCH_3), 2.95 (d, J = 12.1 Hz, 2 H, CH_2N), 1.68 (s, 6 H, CH_3), 1.49 (s, 6 H, CH_3), 1.21 (s, 6 H, CH_3); ^{13}C NMR δ 176.1 (CO), 170.2 (C=N), 82.1 (CH_2N), 76.2 (CMe_2), 61.2 (C6,13), 54.5 (OCH_3), 26.9 (CH_3), 24.3 (CH_3), 22.3 (CH_3); IR (KBr) ν 1590 (CO) cm^{-1}; UV−vis (CH_2Cl_2) 502 (ϵ = 106), 372 (ϵ = 682) nm.

[(6*R,13*S**)-3,3,6,10,10,13-Hexamethyl-6,13-bis(phenylmethoxy)-1,4,8,11-tetraazacyclotetradeca-5,12-dione]nickel(II) (24).** Dioxocyclam **22** (0.129 g, 0.29 mmol), triethylamine (a few drops), and nickel

bromide (0.157 g, 0.72 mmol) were allowed to react according to the general procedure for 24 h in refluxing MeOH to give after chromatography on silica gel (Et_2O/MeOH, 8:1) 0.076 g (0.13 mmol, 45%) of product **24** as a pink solid: ^{1}H NMR δ 7.24−7.40 (m, 10 H, ArH), 4.46 (t, J = 11.2 Hz, 4 H, CH_2Ph), 3.23 (br t, J = 12.4 Hz, 2 H, NH), 2.93 (t, J = 11.7 Hz, 2 H, CH_2N), 2.35 (m, 4 H, CH_2N), 1.78 (dd, J_1 = 10.8 Hz, J_2 = 3.9 Hz, 2 H, CH_2N), 1.36 (s, 6 H, CH_3), 1.31 (s, 6 H, CH_3); ^{13}C NMR δ 173.6 (CO), 139.0, 128.5, 127.7, 127.6 (Ph), 77.3 (C6,13), 66.7 (CH_2Ph), 65.9 (CH_2N), 59.8 (CH_2N), 59.3 (CMe_2), 24.7 (CH_3), 23.8 (CH_3), 20.0 (CH_3); IR (KBr) ν 1586 (CO) cm^{-1}; UV−vis (CH_2Cl_2) 535 (ϵ = 116), 430 (ϵ = 80) nm. Anal. Calcd for $C_{30}H_{42}N_4NiO_4$: C, 61.98; H, 7.28; N, 9.63. Found: C, 62.11; H, 7.53; N, 9.80. The structure of **24** was determined by X-ray analysis, and the results of this study are presented in the supplementary material.

[(6*R,13*S**)-3,3,6,10,10,13-Hexamethyl-6,13-dimethoxy-1,4,8,11-tetraazacyclotetradeca-5,12-dione]nickel(II) (25).** Dioxocyclam **23** (as a mixture of diastereoisomers, 0.084 g, 0.23 mmol), triethylamine (a few drops), and nickel bromide (0.075 g, 0.35 mmol) were allowed to react according to the general procedure for 36 h in MeOH at reflux to give after chromatography on silica gel (Et_2O/MeOH, 8:1) 0.042 g (0.10 mmol, 43%) of product **25** as a pink solid and as a mixture of two diastereoisomers: ^{1}H NMR δ 3.44 (s, 6 H, OCH_3), 2.88 (m br, 2 H, NH), 2.72 (dd, J_1 = 13.7 Hz, J_2 = 10.5 Hz, 2 H, CH_2N), 2.54 (t, J = 11.6 Hz, 2 H, CH_2N), 2.11 (dd, J_1 = 11.5 Hz, J_2 = 2.2 Hz, 2 H, CH_2N), 1.82 (dd, J_1 = 10.5 Hz, J_2 = 2.9 Hz, 2 H, CH_2N), 1.37 (s, 6 H, CH_3), 1.29 (s, 6 H, CH_3), 1.17 (s, 3 H, CH_3); ^{13}C NMR δ 172.7 (CO), 77.3 (C6,13), 65.9 (CH_2N), 58.6 (CH_2N), 57.2 (CMe_2), 52.0 (CH_3O), 25.0 (CH_3), 23.0 (CH_3), 19.6 (CH_3); IR (KBr) ν 1577 (CO) cm^{-1}; UV−vis (CH_2Cl_2) 531 (ϵ=159), 430 (ϵ=95) nm.

Mono-Nickel Complexes of *d,l* Homo Dimer 15 (26). Bis-cyclam *d,l* homo dimer **15** (52.5 mg, 0.068 mmol), nickel bromide (15 mg, 0.068 mmol) and potassium carbonate (9.4 mg, 0.068 mmol) were allowed to react according to the general procedure for 71 h to give 47.7 mg (0.058 mmol, 85%) of product **26** as a mixture of two bis-nickel complex isomers [(33.1 mg, 0.040 mmol, 59%, R_f = 0.69, CH_2Cl_2/MeOH, 9:1) and (14.6 mg, 0.018 mmol, 26%, R_f = 0.43, CH_2Cl_2/MeOH, 9:1)] after separation by flash chromatography (CH_2Cl_2/MeOH, 95:5 to 9:1). The more polar complex isomerized on standing in CH_2Cl_2 or $CDCl_3$ solutions at room temperature to the more stable isomer for which the structure was determined by X-ray analysis (R_f = 0.69, CH_2Cl_2/MeOH, 9:1): mp >260 °C (CH_2Cl_2); ^{1}H NMR δ 9.29 (s, 2 H, CONH), 3.78 (dt, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 2 H, CH_2O), 3.42−3.62 (m, 6 H, CH_2O), 2.86−3.02 (m, 4 H, CH_2N), 2.80 (d, J = 12.8 Hz, 2 H, CH_2N), 2.71 (d, J = 12.8 Hz, 2 H, CH_2N), 2.62 (d, J = 11.2 Hz, 2 H, CH_2N), 2.56 (d, J = 11.1 Hz, 2 H, CH_2N), 2.20−2.39 (m, 4 H, CH_2CH_2O), 1.99−2.14 (m, 2 H, NH), 1.82−1.92 (m, 2 H, NH [Ni]), 1.46 (s, 6 H, CH_3), 1.44 (s, 6 H, CH_3), 1.36 (s, 6 H, CH_3), 1.26 (s, 6 H, CH_3), 1.25 (s, 6 H, CH_3), 1.18 (s, 6 H, CH_3); ^{13}C NMR δ 172.9 (CO [Ni]), 171.8 (CO), 78.5 (C6,13), 77.2 (C6,13 [Ni]), 65.0 (CH_2N [Ni]), 62.3 (CH_2N [Ni]), 61.7 (CH_2N), 60.5 (CH_2N), 58.3 (CMe_2 [Ni]), 56.6 (CH_2O [Ni]), 56.0 (CH_2O), 52.1 (CMe_2), 31.6 (CH_2CH_2O), 25.3 (CH_3), 24.8 (CH_3 [Ni]), 24.1 (CH_3), 23.2 (CH_3 [Ni]), 20.0 (CH_3 [Ni]), 19.0 (CH_3); IR (KBr) ν 3430, 3265 (CONH, NH), 1667 (CO), 1584 cm^{-1}; UV−vis (CH_2Cl_2) 520 (ϵ = 63), 428 (ϵ = 48) nm; MS (HR FAB) m/z 825.47 $(M + H)^+$; MW calcd for $C_{38}H_{71}N_8O_8{}^{58}Ni_1$ 825.474 834, found 825.473 510 (Δ = 1.3 mDa).

Bis-Nickel Complexes of *d,l* Homo Dimer 15 (27). Bis-cyclam *d,l* homo dimer **15** (26.2 mg, 0.034 mmol), nickel bromide (148 mg, 0.68 mmol), and potassium carbonate (14.1 mg, 0.10 mmol) were allowed to react according to the general procedure for 6 days to give 14.4 mg (0.016 mmol, 48%) of product **27** as a mixture of two bis-nickel complex isomers [(7.6 mg, 0.009 mmol, 25%, R_f = 0.15, CH_2Cl_2/MeOH, 95:5) and (6.8 mg, 0.008 mmol, 23%, R_f = 0.03, CH_2Cl_2/MeOH, 95/5)] after separation by flash chromatography (CH_2Cl_2/MeOH, 95:5 to 9:1). The more polar complex isomerized on standing in CH_2Cl_2 or $CDCl_3$ solutions at room temperature to the more stable isomer for which the structure was determined by X-ray analysis. The results of this study are presented in the supplementary material. *d,l*-**27** (R_f = 0.15): mp >260 °C (CH_2Cl_2/EtOAc); ^{1}H NMR δ 3.90 (dt, J_1 = 9.0 Hz, J_2 = 6.1 Hz, 4 H, CH_2N), 3.63 (m, 4 H, CH_2O), 2.97 (m, 8 H, CH_2O), 2.67 (m, 4 H, CH_2N), 2.28−2.38 (m, 4 H, CH_2), 2.10 (d, J = 10.6 Hz, 4 H), 1.83−2.02 (m, 4 H, CH_2CH_2O), 1.47 (s, 12 H, CH_3), 1.25 (s, 12 H, CH_3), 1.21 (s, 12 H, CH_3); ^{13}C NMR δ 173.0 (CO), 77.3 (C6,13), 64.9 (CH_2N), 62.5 (CH_2N), 58.3 (CMe_2), 55.9 (CH_2O), 32.1 (CH_2CH_2O), 25.2 (CH_3), 23.4 (CH_3), 19.8 (CH_3); IR (KBr) ν 3459, 3263 (NH), 1581 (CO) cm^{-1}; UV−vis (CH_2Cl_2) 518 (ϵ = 117), 424 (ϵ = 111) nm.

Mono-Nickel Complexes of Meso Homo Dimer 14 (28). Bis-cyclam meso homo dimer **14** (25 mg, 0.033 mmol), nickel bromide (7.1 mg, 0.033 mmol), and potassium carbonate (6.5 mg, 0.05 mmol; 1.5 mg after 24 h and 5 mg after 48 h) were allowed to react according to the general procedure for 52 h to give 26.1 mg (0.032 mmol, 97%) of product **28** as a mixture of two mono-nickel complex isomers [(17.0 mg, 0.021 mmol, 63%, R_f = 0.21, CH_2Cl_2/MeOH, 95:5) and (9.1 mg, 0.011 mmol, 34%, R_f = 0.07, CH_2Cl_2/MeOH, 95:5)] after separation by flash chromatography (CH_2Cl_2/MeOH, 95:5 to 9:1). The more polar complex isomerized on standing in CH_2Cl_2 or $CDCl_3$ solutions at room temperature to the more stable isomer for which the structure was determined by X-ray analysis. The results of this study are presented in the supplementary material. **28** (R_f = 0.21, CH_2Cl_2/MeOH, 95:5): mp >260 °C (CH_2Cl_2); ^{1}H NMR δ 7.85 (s, 2 H, CONH), 3.81 (dt, J_1 = 9.3 Hz, J_2 = 5.6 Hz, 2 H, CH_2O), 3.55−3.72 (m, 4 H, CH_2O), 3.37−3.47 (m, 2 H, CH_2O), 3.07 (d, J = 12.0 Hz, 2 H, CH_2N), 3.0 (br d, J = 12.0 Hz, 2 H, NH), 2.88 (d, J = 13.6 Hz, 2 H, CH_2N), 2.85 (d, J = 12.0 Hz, 2 H, CH_2N), 2.74 (d, J = 12.4 Hz, 2 H, CH_2N), 2.54 (t, J = 11.5 Hz, 2 H, CH_2N), 2.34 (d, J = 11.3 Hz, 2 H, CH_2N), 2.16−2.24 and 2.12 (m + dd, J_1 = 11.2 Hz, J_2 = 2.2 Hz, 4 H, CH_2N, CH_2CH_2O), 1.9−2.3 (m, 2 H, CH_2CH_2O), 1.88 (dd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, 2 H, CH_2N), 1.42 (s, 6 H, CH_3), 1.41 (s, 6 H, CH_3), 1.31 (s, 6 H, CH_3), 1.29 (s, 6 H, CH_3), 1.28 (s, 6 H, CH_3), 1.21 (s, 6 H, CH_3); ^{13}C NMR δ 172.9 (CO [Ni]), 172.1 (CO), 79.8 (C6,13), 77.0 (C6,13 [Ni]), 65.3 (CH_2N [Ni]), 61.7 (CH_2N [Ni]), 60.2 (CH_2N), 58.8 (CH_2N), 58.4 (CMe_2 [Ni]), 56.2 (CH_2O [Ni]), 55.5 (CH_2O), 52.6 (CMe_2), 32.7 (CH_2CH_2O), 25.8 (CH_3), 24.8 (CH_3 [Ni]), 24.6 (CH_3), 23.1 (CH_3 [Ni]), 20.5 (CH_3 [Ni]), 19.4 (CH_3); IR (KBr) ν 3421, 3248 (CONH, NH), 1666 (CO), 1580 cm^{-1}; UV−vis (CH_2Cl_2) 522 (ϵ = 118), 426 (ϵ = 81) nm.

Bis-Nickel Complexes of Meso Homo Dimer 14 (29). Bis-cyclam meso homo dimer **14** (32.5 mg, 0.042 mmol), nickel bromide (179 mg, 0.82 mmol), and potassium carbonate (11.3 mg, 0.05 mmol) were allowed to react according to the general procedure for 57 h to give after chromatography (CH_2Cl_2/MeOH, 95:5 to 5:1) 4.6 mg (0.005 mmol, 13%) of mono-nickel complex **28** and 20.2 mg (0.023 mmol, 54%) of product **31** as a mixture of two bis-nickel complex isomers [(18.2 mg, 0.021 mmol, 49%, R_f = 0.33, CH_2Cl_2/MeOH, 9:1) and (2.0 mg, 0.002 mmol, 5%, R_f = 0.12, CH_2Cl_2/MeOH, 9:1)]. On standing in CH_2Cl_2 or $CDCl_3$ solutions at room temperature, the more polar complex isomerized to the other isomer for which the structure was determined by X-ray analysis. The results of this study are presented in the supplementary material. **29** (R_f = 0.33): mp >260 °C (CH_2Cl_2); ^{1}H NMR δ 3.83 (dt, J_1 = 9.4 Hz, J_2 = 5.2 Hz, 4 H, CH_2O), 3.67 (dt, J_1 = 9.3 Hz, J_2 = 6.6 Hz, 4 H, CH_2O), 2.9−3.12 (m, 8 H, CH_2N, NH), 2.66−2.84 (m, 2 H, CH_2CH_2O), 2.35−2.52 (m + t, J = 11.3 Hz, 6 H, CH_2CH_2O and CH_2N), 2.15 (dd, J_1 = 11.3 Hz, J_2 = 2.4 Hz, 4 H, CH_2N), 1.93 (d, J = 8.4 Hz, 4 H, CH_2), 1.46 (s, 12 H, CH_3), 1.30 (s, 12 H, CH_3), 1.22 (s, 12 H, CH_3); ^{13}C NMR δ 172.8 (CO), 76.2 (C6,-13), 65.1 (CH_2N), 61.4 (CH_2N), 58.4 (CMe_2), 56.2 (CH_2O), 33.0 (CH_2CH_2O), 25.2 (CH_3), 23.0 (CH_3), 20.0 (CH_3); IR (KBr) ν 3415, 3242 (NH), 1579 (CO) cm^{-1}; UV−vis (CH_2Cl_2) 519 (ϵ=160), 428 (ϵ=119) nm.

Bis-Nickel Complexes of the Bis-Cyclam Diastereoisomers Derived from Bis-Azapenam 13 (*n* = 10). Bis-cyclam diastereoisomer **I** (n = 10, R_f = 0.29, 30 mg, 0.031 mmol), nickel bromide (136 mg, 0.62 mmol), and K_2CO_3 (26 mg, 0.18 mmol) in 2 mL of MeOH were heated at 100 °C in a pressure tube for 3 h. The excess nickel bromide was filtered and the solvent evaporated (note that only one isomer of the bis-nickel complex was detected in the crude mixture by TLC). The residue dissolved in CH_2Cl_2 (15 mL) was washed with 5% aqueous $NaHCO_3$ (2 × 5 mL) and dried over K_2CO_3. Evaporation of the solvent gave a pink solid which was chromatographed on silica gel (CH_2Cl_2/MeOH, 97.5:2.5 to 95:5) to give 32.7 mg (0.030 mmol, 98%) of bis-nickel complex: mp >260 °C (CH_2Cl_2); ^{1}H NMR δ 3.55−3.65 (m, 8 H, CH_2O), 3.10 (br t, J = 13.0 Hz, 4 H, NH), 2.72 (dd, J_1 = 10.7 Hz, J_2 = 13.7 Hz, 4 H, CH_2N), 2.65 (t, J = 11.4 Hz, 4 H, CH_2N), 2.14 (dd, J_1 = 1.6 Hz, J_2 = 11.2 Hz, 4 H, CH_2N), 1.85 (dd, J_1 = 3.2 Hz, J_2

= 10.6 Hz, 4 H, CH_2N), 1.4−1.8 (m, 32 H, $[CH_2]_4CH_2O$), 1.40 (s, 12 H, CH_3), 1.30 (s, 12 H, CH_3), 1.22 (s, 12 H, CH_3); ^{13}C NMR δ 172.9 (CO), 76.1 (C6), 65.8 (CH_2O), 63.2 (C3), 58.6 (CMe_2), 57.6 (C5), 29.0, 27.4, 26.9 and 24.87 ($[CH_2]_8$), 24.90 (CH_3), 22.8 (CH_3), 20.3 (CH_3); IR (KBr) ν 3421, 3247 (NH), 1578 (CO) cm^{-1}; UV−vis (CH_2Cl_2) 530 (ϵ = 324), 429 (ϵ = 159) nm; MS (HR FAB) MW calcd for $C_{52}H_{97}N_8O_8{}^{58}Ni_2$ 1077.613 632, found 1077.613 570 (Δ = 0.1 mDa).

Bis-Cyclam Diastereoisomer II (n = 10, R_f = 0.25). Bis-cyclam (n = 10, R_f = 0.25, 30 mg, 0.031 mmol), nickel bromide (136 mg, 0.62 mmol, 10 equiv), and K_2CO_3 (26 mg, 0.18 mmol) were allowed to react according to the procedure described above (for 3 h) to give after purification by chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 to 9:1) 27.7 mg (0.026 mmol, 83%) of product as a ≈1:1 mixture of two isomers [(14.8 mg, 0.018 mmol, 44%, R_f = 0.20, CH_2Cl_2/MeOH, 95:5) and (12.9 mg, 0.012 mmol, 39%, R_f = 0.06, CH_2Cl_2/MeOH, 95:5)]. On standing in CH_2Cl_2, the more polar complex (R_f = 0.06) totally isomerized to the stable isomer: mp 250 °C (CH_2Cl_2); ^1H NMR δ 3.62 (t, J = 6.7 Hz, 8 H, CH_2O), 3.08 (m, 4 H, NH), 2.83 (dd, J_1 = 10.6 Hz, J_2 = 13.9 Hz, 4 H, CH_2N), 2.49 (t, J = 11.6 Hz, 4 H, CH_2N), 2.13 (dd, J_1 = 2.3 Hz, J_2 = 11.3 Hz, 4 H, CH_2N), 1.87 (d, J = 9.7 Hz, 4 H, CH_2N), 1.7−1.85 (m, 8 H, $[CH_2]_2CH_2O$), 1.43 (s, 12 H, CH_3), 1.5−1.65 (m, 8 H, $[CH_2]_2[CH_2]_3O$), 1.29 (s, 12 H, CH_3), 1.21 (s, 12 H, CH_3); ^{13}C NMR δ 173.1 (CO), 76.6 (C6), 65.5 (CH_2O), 64.0 (C3), 58.4 (CMe_2), 56.9 (C5), 30.7, 29.82, 29.77 and 26.5 ($[CH_2]_8$), 25.1 (CH_3), 22.9 (CH_3), 20.3 (CH_3); IR (KBr) ν 3431, 3252 (NH), 1580 (CO) cm^{-1}; UV−vis (CH_2Cl_2) 527 (ϵ = 190), 428 (ϵ = 121) nm; MS (HR FAB) MW calcd for $C_{52}H_{97}N_8O_8{}^{58}Ni_2$ 1077.613 632, found 1077.613 736 (Δ = −0.1 mDa).

Acknowledgment. Support for this research under Grant No. GM26178 from the National Institutes of General Medical Sciences (Public Health Service) is gratefully acknowledged. Mass spectra were obtained on instruments supported by the National Institutes of Health shared instrumentation Grant GM49631. E.L. thanks the Spanish MEC and the Fullbright Foundation for support in the form of a fellowship.

Supplementary Material Available: ^1H NMR spectra of bis-cyclams derived from **12** (n = 4) and the full X-ray crystal structure data for compounds **14**, **15**, **20**, **24**, **26**, **27**, and **29** (79 pages); tables of observed and calculated structure factors (65 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA943420V