Synthesis and Exchange Reactions of 1,4,8,11-Tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-diones

Louis S. Hegedus* and William H. Moser

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received August 16, 1994®

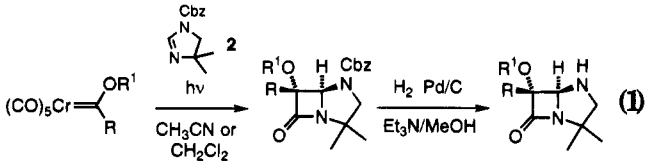
A number of functionalized, unsaturated 5,12-dioxo cyclams were synthesized by acid-catalyzed dimerization of appropriately functionalized azapenams. Although easily isolated and purified, these unsaturated tetraaza macrocycles underwent acid-catalyzed exchange reactions of the monomer unit to give mixed systems. Even a simple dihydrobenzazepine participated in this exchange process to give a "hybrid" macrocycle.

Introduction

Fourteen-membered 1,4,8,11-tetraaza macrocycles (cyclams)[1] and their 5,7-diones (dioxo cyclams)[2] have been the recent focus of substantial research activity, and both their metal complexation chemistry and catalysis by these metal complexes have been extensively studied. A remarkable synthesis of the related 1,4,8,11-tetraaza 5,-12-diones involving the acid-catalyzed cleavage/dimerization of azapenams produced by the photolytic reaction between N-protected imidazolines and chromium alkoxycarbene complexes has recently been reported from these laboratories.[3] Herein we report the synthesis of a range of differently substituted macrocycles of this latter type, along with an unusual macrocycle scrambling reaction.

Results and Discussion

Synthesis of Azapenams. Photolysis of chromium alkoxycarbene complexes **1a–g** with imidazoline **2** produced azapenams **3a–g** in varying yields. Removal of the *N*-Cbz protecting group produced free azapenams **4a–g** (eq 1). Two features of this process warrant comment.

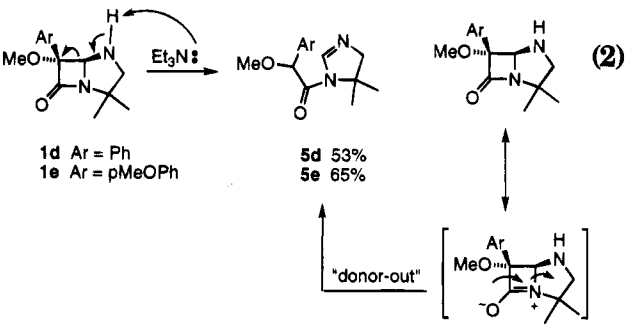


1a	R = $nC_{16}H_{33}$; R^1 = Me	**3a**	71%	**4a**	94%
1b	R =  ; R^1 = Me	**3b**	52%	**4b**	99%
1c	R = iPr; R^1 = Et	**3c**	77%	**4c**	99%
1d	R = Ph; R^1 = Me	**3d**	48%	**4d**	83%*
1e	R = pMeOPh; R^1 = Me	**3e**	39%	**4e**	89%*
1f	R = cHex; R^1 = Me	**3f**	37%	**4f**	96%
1g	R = tBu; R^1 = Et	**3g**	20%	**4g**	99%

* based on ^{1}H NMR spectra of crude reaction mixture

The relative stereochemistry of the azapenams (large R group *cis* to large NCbz group) is *exactly opposite* that anticipated from the conventional view of ketene–imine cycloaddition reactions which are thought to involve attack of the ketene by the imine from the face opposite the large R group, followed by conrotatory ring closure.[4] Indeed these, and all other β-lactams derived from chromium alkoxycarbene complexes, appear to result from attack over the *large* (R) group of the ketene, the stereoselectivity being controlled by *electronic* factors in the ring closure step rather than by steric factors in the attack step.[5] As the steric bulk of the R group increased, the rates and the yields of the β-lactam-forming reaction decreased, but the less sterically hindered isomer was never observed.

Hydrogenolytic removal of the *N*-Cbz group, in the presence of triethylamine to prevent acid-catalyzed processes (see below) proceeded in virtually quantitative yield for the azapenams having alkyl side chains (**1a–c**, **1f,g**), but deprotection of aryl azapenams **1d,e** resulted in substantial amounts of ring cleaved products[6] **5d,e** (eq 2) in addition to the desired azapenam. Extended exposure to triethylamine, as well as attempted chromatographic purification on silica gel, resulted in further cleavage of the azapenam, either by an ionic or concerted[5] ring opening process.



1d Ar = Ph
1e Ar = pMeOPh

5d 53%
5e 65%

Synthesis of Tetraaza Macrocycles. Treatment of azapenams **4a–f** with 0.25 equiv of camphorsulfonic acid in methylene chloride resulted in their clean conversion

® Abstract published in *Advance ACS Abstracts*, November 15, 1994.

(1) For general reviews see: (a) Busch, D. H. *Acc. Chem. Res.* **1978**, *11*, 392. (b) Bhallacharya, S.; Mukhejee, R.; Chakraworthy, A. *Inorg. Chem.* **1986**, *25*, 3448 and references therein. (c) Ito, T.; Kato, M.; Yamashita, M.; Ito, H. *J. Coord. Chem.* **1986**, *15*, 29.

(2) For example Machida, R.; Kimura, E.; Kushi, Y. *Inorg. Chem.* **1986**, *25*, 3461 and references therein.

(3) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010.

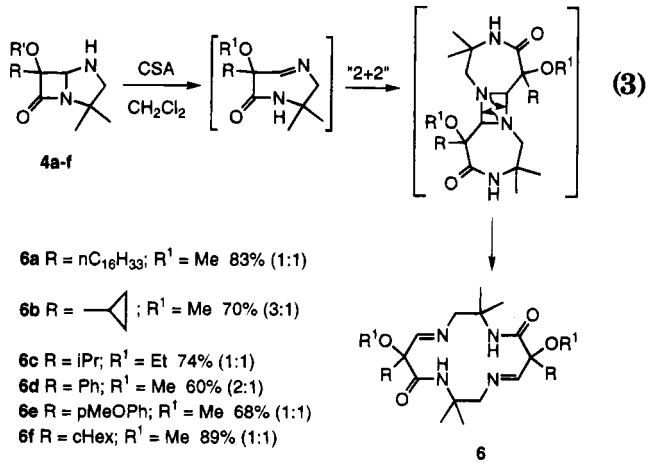
(4) Georg, G. I.; Ravikumar, V. T. Stereocontrolled Ketene-Imine Cycloaddition Reactions. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1993; pp 295–368.

(5) Dumas, S.; Hegedus, L. S. *J. Org. Chem.* **1994**, *59*, 4967–4971. Based on the arguments of Lopez *et al.* Lopez, R.; Sordo, T. L.; Sordo, J. A.; Gonzalez, J. *J. Org. Chem.* **1993**, *58*, 7036. Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995.

(6) A similar instability of amino azapenams has been noted: Ronan, B.; Hegedus, L. S. *Tetrahedron* **1993**, *49*, 5549.

0022-3263/94/1959-7779$04.50/0

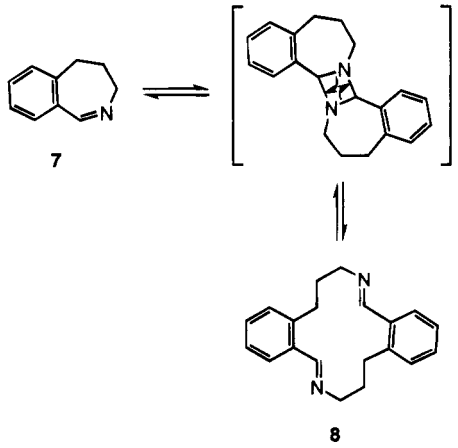
to tetraaza macrocycles **6a–f** in good yield (eq 3). Since racemic azapenams were used and since macrocycles **6** now contain two chiral centers, these materials were obtained as mixtures of diastereoisomers in the proportions shown.



(3)

A point of confusion in the original disclosure[3] of this dimerization resulted from the observation that although 1:1 mixtures of isomers were initially obtained, upon crystallization yields of a *single meso* isomer exceeding 80% of the *total* amount of macrocycle formed were obtained. Since the two chiral centers were quaternary and nonepimerizable, no reasonable pathway for interconversion of diastereoisomers was conceived, and the diastereoisomers were misassigned as rotational isomers (conformers). Subsequent experimental observations in conjunction with a related literature precedent[7] has resolved this confusion.

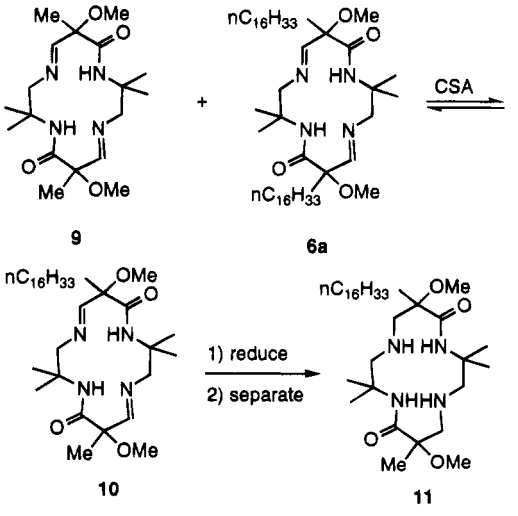
In 1969, Goldman *et al.*[7] reported that 3,4-dihydro-5*H*-2-benzazepine (**7**) dimerized to diazamacrocycle **8** upon standing and that this dimerization was *reversible* under acidic conditions (eq 4). Should compounds **6** be formed *reversibly*, or should they equilibrate through the proposed seven-membered imine, a route for interconversion of diastereoisomers becomes available.



(4)

It had already been assumed that the conversion of **4** to **6** proceeded through a seven-membered imine since reduction of **4** under acidic conditions produced the corresponding saturated diazepinone.[3] However, the imine intermediate could not be detected when the acid-catalyzed dimerization reaction was monitored by ^1H NMR spectroscopy. To probe for equilibration of macrocycles **6** *via* seven-membered imines under acidic conditions, the parent compound **6** (R = R^1 = Me) was exposed to hydrogen gas under acidic conditions in the presence of Pd/C catalysts in an attempt to trap the seven-membered imine by reduction to the diazepinone. This failed, and only reduced macrocycle was isolated.

If the diastereoisomers of **6** are indeed interconverting *via* the monomer, a crossing experiment should detect this, in spite of the inability to detect or trap the monomer. To test this a 1:1 mixture of the methyl (**9**) (1:1 mixture of diastereoisomers) and the hexadecyl (**6a**) macrocycle (1:1 mixture of diastereoisomers) were equilibrated for 24 h in methylene chloride in the presence of 0.25 equiv of camphorsulfonic acid. A crude ^1H NMR spectrum of the resulting mixture showed an approximate 1:1:1 mixture of the two starting macrocycles (each of which was a 1:1 mixture of diastereoisomers), as well as a new set of peaks due to the two diastereoisomers of the mixed macrocycle. Reduction of this mixture to freeze this equilibration, followed by tedious chromatographic separation of the six diastereoisomers of the three macrocycles allowed the isolation and full characterization of the "hybrid" macrocycle **11**, providing experimental verification that macrocycles **6** are indeed in a mobile equilibrium under conditions of their formation. This, then, explains the isolation of *only* the *R,S*-diastereoisomer of **9**, in >80% yield, when a 1:1 mixture of both diastereoisomers was allowed to crystallize. The *R,S* isomer selectively crystallized, and equilibration in solution allowed the entire 1:1 mixture to be converted to a single diastereoisomer in the solid state.

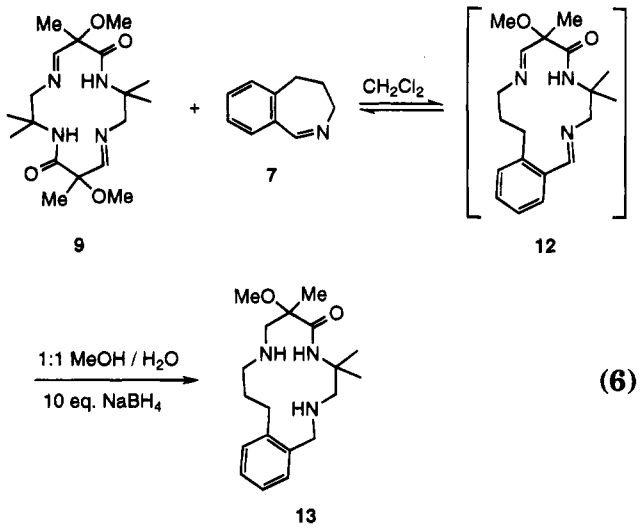


(5)

Hybridization experiments between **9** and five- and six-membered cyclic imines prone to cyclotrimerization resulted in no cross reaction. However, equilibrating **9** with monomer **7** in methylene chloride for 72 h, followed by reduction with sodium borohydride to freeze equilibration, led to the isolation of the hybrid macrocycle **13** (eq 6) in 12% overall yield, assuming complete conversion to the hybrid. (Before reduction, the ^1H NMR spectrum showed approximately a 2:1 ratio of cyclam **9** and hybrid **12**, making the *theoretical* yield of **13** to be only 33%.) Although not particularly efficient, this "hybridization"

(7) Goldman, I. M.; Larson, J. K.; Tretter, J. R.; Anderson, E. G. *J. Am. Chem. Soc.* **1969**, *91*, 4941.

procedure offers ready access to unusual macrocyclic systems, and studies to produce other ring sizes continue.



(6)

The details of this exchange are both interesting and obscure. In contrast to the benzazepine systems in eq 4, the seven-membered imine from macrocycles such as **9** has never been detected, so equilibration via this species is undemonstrated. Direct, bimolecular exchange between **7** and **9** without intervention of the monomer of **9** is quite conceivable and at least easily written. However, direct bimolecular exchange of **9** and **6a**, as in eq 5, is somewhat more difficult to envisage and the details of this process await further study.

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp apparatus and are uncorrected. 300-MHz ^{1}H NMR and 75.5-MHz ^{13}C NMR were obtained on a Bruker ACE-300 spectrometer. Chemical shifts are given in ppm relative to $(CH_3)_4Si$ (0 ppm, ^{1}H) or $CDCl_3$ (77.0 ppm, ^{13}C) unless otherwise noted. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All reactions were performed under an atmosphere of argon except as specified. The crude reaction mixtures were purified by column chromatography with silica gel (ICN Biomedicals Silitech 32–63 μm).

Et_2O (Mallinckrodt) was distilled from sodium/benzophenone under an atmosphere of nitrogen. CH_2Cl_2 (tech grade) and Et_3N (Mallinckrodt) were distilled from CaH_2. Hexanes (Mallinckrodt, tech grade) for chromatographic purposes were distilled at ambient pressure. Ethyl acetate (Mallinckrodt) for chromatographic purposes was used without further purification. Aluminum oxide (activated, basic, Brockman I) was purchased from Aldrich.

The following chemicals were prepared according to literature procedures: [(methoxy)(hexadecyl)carbene]pentacarbonylchromium(0) (**1a**),[8] [(methoxy)(cyclopropyl)carbene]pentacarbonylchromium(0) (**1b**),[9] [(methoxy)(phenyl)carbene]pentacarbonylchromium(0) (**1d**),[10] [(methoxy)(*p*-methoxyphenyl)carbene]pentacarbonylchromium(0) (**1e**),[11] [(ethoxy)(*tert*-butyl)carbene]pentacarbonylchromium(0) (**1g**),[12] 4,4-dimethyl-Δ^2-imidazoline,[3] 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ^2-imidazoline (**2**),[3] and 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one.[13]

[(Ethoxy)(isopropyl)carbene]pentacarbonylchromium-(0) (1c). An airless flask containing $K_2Cr(CO)_5$[14] (10 mmol) in THF (20 mL) was cooled to −78 °C. Isobutyryl chloride (1.05 mL, 10.0 mmol) was added under argon into the flask. The green-black mixture was stirred at −78 °C for 15 min. The mixture was warmed to 25 °C over 2 h, and the solvent was removed under reduced pressure. The green-black residue was taken up in chilled, degassed H_2O (150 mL), and $Et_3O^+BF_4^-$ (1.90 g, 10.0 mmol) was added at 25 °C. The resulting yellow mixture was stirred at 25 °C (15 min). After filtration through Celite, the aqueous layer was extracted with hexanes (4 × 15 mL). The combined hexane layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via flash chromatography (SiO_2, hexanes) gave 816 mg (28%) of **1c** as an orange solid, whose purity was established by ^{1}H and ^{13}C NMR spectral data. ^{1}H NMR: δ 5.06 (q, J = 7.0 Hz, 2H), 4.12 (sept, J = 6.5 Hz, 1H), 1.59 (t, J = 7.0 Hz, 3H), 0.96 (d, J = 6.5 Hz, 6H); ^{13}C NMR: δ 364.1, 223.3, 216.4, 77.9, 59.9, 18.1, 14.7; IR (neat) ν 2061, 1915 cm^{-1}.

[(Methoxy)(cyclohexyl)carbene]pentacarbonylchromium(0) (1f). A flame-dried 250 mL round-bottom flask equipped with a stir bar was charged with $Cr(CO)_6$ (1.0 g, 4.5 mmol) and freshly distilled Et_2O (50 mL), flushed with argon, and sealed with a rubber septum. Cyclohexyllithium[15] (4.94 mmol, 38 mL of a 0.13 M solution in hexanes) was added via syringe at 25 °C. The resulting solution was allowed to stir for 4 h at 25 °C, and the solvent was removed under reduced pressure. The residue was taken up in chilled, degassed H_2O (50 mL), and $Me_3O^+BF_4^-$ (666 mg, 4.50 mmol) was added at 25 °C. After filtration through Celite, the aqueous layer was extracted with hexanes (4 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via flash chromatography (SiO_2, hexanes) gave 1.19 g (83%) of **1f** as an orange oil, whose purity was established by ^{1}H and ^{13}C NMR spectral data. ^{1}H NMR: δ 4.74 (s, 3H), 3.86 (m, 1H), 1.95–1.56 + 1.33–0.87 (m); ^{13}C NMR: δ 366.2, 216.5, 211.5, 71.9, 43.5, 30.2, 28.6, 26.9, 25.9, 25.6; IR (neat) ν 2061, 1922 cm^{-1}.

General Procedure for the Photolysis of Chromium Carbene Complexes with Imidazoline to Produce Azapenams. Procedure A. The chromium carbene complex (1 equiv) and imidazoline **2** (1 equiv) were taken up in acetonitrile in a Pyrex test tube. The tube was sealed with a rubber septum, evacuated, purged with argon (three cycles) and irradiated at 25 °C for the specified time period. The solvent was removed under reduced pressure and the residue was dissolved in a 5/1 mixture of hexanes/EtOAc and air-oxidized in either sunlight or a light box (6 × 20 W Vitalite fluorescent bulbs). Filtration through Celite and removal of the solvent under reduced pressure gave the crude azapenam which was purified via flash or radial chromatography. Purity of these compounds was established by ^{1}H and ^{13}C NMR spectral data. The compounds were then deprotected to afford free azapenams, for which acceptable elemental analyses were obtained.

Procedure B. The chromium carbene complex (1.0–1.1 equiv) and imidazoline **2** (1 equiv) were taken up in CH_2Cl_2 in an airless flask equipped with sidearm. The resultant solution was degassed (freeze-thaw degassing using liquid N_2, three cycles) and transferred to an Ace pressure tube. The pressure tube was charged to 60–90 psi CO (three cycles) and irradiated at 25 °C for the specified time period. The solvent was removed under reduced pressure and $Cr(CO)_6$ was recovered via sublimation (50 °C, 0.1 mmHg). The residue was dissolved in a 5/1 mixture of hexanes/EtOAc and air-oxidized in either sunlight or a light box (6 × 20 W Vitalite fluorescent bulbs). Filtration through Celite and removal of the solvent under reduced pressure gave the crude azapenam which was purified via flash or radial chromatography. Purity of these

(8) Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779.
(9) Conner, J. A.; Jones, E. M. *J. Chem. Soc., Dalton Trans.* **1973**, 2119.
(10) Fischer, E. O.; Aumann, R. *Chem. Ber.* **1968**, *101*, 954.
(11) Fischer, E. O.; Kreiter, C. G.; Kollmeier, J.; Müller, J.; Fischer, R. D. *J. Organomet. Chem.* **1971**, *28*, 237.
(12) Hafner, A.; Hegedus, L. S.; deWeck, G.; Hawkins, B.; Dötz, K. H. *J. Am. Chem. Soc.* **1988**, *110*, 8413.
(13) Meyers, A. I.; Hutchings, R. H. *Tetrahedron* **1993**, *49*, 1807.
(14) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814.
(15) Johnson, O. H.; Nebergall, W. H. *J. Am. Chem. Soc.* **1949**, *71*, 1720.

compounds was established by ^1H and ^{13}C NMR spectral data. The compounds were then deprotected to afford free azapenams, for which acceptable elemental analyses were obtained.

(5*R,6*R**)-4-(Benzyloxycarbonyl)-6-hexadecyl-6-methoxy-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (3a).** [(Methoxy)(hexadecyl)carbene]pentacarbonylchromium(0) (**1a**) (341 mg, 0.741 mmol) and imidazoline **2** (172 mg, 0.741 mmol) in acetonitrile (70 mL) were allowed to react according to general procedure A (30 h). Purification via flash chromatography (SiO_2, 3/1 hexanes/EtOAc) gave 279 mg (71%) of **3a** as a white solid, mp = 52–53 °C: ^1H NMR (two rotamers, a/b 3/2) δ 7.33 (m, 5H), 5.26–5.07 (m, 3H), 3.79(a) (d, J = 10.5 Hz)/3.72(b) (d, J = 10.3 Hz)(1H), 3.45(a)/3.33(b) (s, 3H), 3.09-(a+b) (d, J = 10.6 Hz, 1H), 1.59 (s, 3H), 1.50–1.38 (m, 4H), 1.23 (br s, 26H), 1.14 (s, 3H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 173.3(b)/172.7(a) 153.9(b)/153.5(a) 136.0(b)/135.8(a) 128.5, 128.3, 128.2, 127.8, 92.9(b)/92.8(a) 74.2(b)/73.7(a) 67.5(a)/67.4-(b) 60.7(b)/60.3(a) 60.5, 53.3, 31.8, 29.9, 29.6, 29.5, 29.5, 29.3, 28.3, 28.1, 25.7, 22.6, 22.2, 21.8, 14.0; IR (neat) ν 1772, 1713 cm^{-1}.

(5*R,6*R**)-4-(Benzyloxycarbonyl)-6-cyclopropyl-6-methoxy-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (3b).** [(Methoxy)(cyclopropyl)carbene]pentacarbonylchromium(0) (**1b**) (540 mg, 1.96 mmol) and imidazoline **2** (454 mg, 1.96 mmol) in acetonitrile (70 mL) were allowed to react according to general procedure A (20 h). Purification via flash chromatography (SiO_2, 2/1 hexanes/EtOAc) gave 353 mg (52%) of **3b** as a clear, colorless oil: ^1H NMR (two rotamers, a/b 3/2) δ 7.33–7.25 (m, 5H), 5.24–5.06 (m, 3H), 3.73(a) (d, J = 10.3 Hz)/3.66-(b) (d, J = 10.2 Hz)(1H), 3.50(b)/3.36(a) (s, 3H), 3.18(a+b) (d, J = 10.3 Hz, 1H), 1.56(a)/1.54(b) (s, 3H), 1.14 (s, 3H), 0.85 (m, 1H), 0.7–0.6+0.5–0.3 (m, 4H); ^{13}C NMR δ 170.8(b)/170.6(a) 153.5(b)/153.0(a) 135.9(b)/135.6(a) 128.2, 128.0, 127.9, 127.6, 93.7(b)/93.3(a) 73.9(b)/73.5(a) 67.1(a)/66.9(b) 61.1(b)/60.5(a) 60.3(a)/60.2(b) 53.12(a)/53.06(b) 25.6(b)/25.5(a) 21.8, 8.5(a)/8.2-(b) 1.7(b)/1.4(a), −0.6; IR (neat) ν 1769, 1710 cm^{-1}.

(5*R,6*R**)-4-(Benzyloxycarbonyl)-6-ethoxy-6-isopropyl-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (3c).** [(Ethoxy)(isopropyl)carbene]pentacarbonylchromium(0) (**1c**) (116 mg, 0.397 mmol) and imidazoline **2** (92 mg, 0.397 mmol) in degassed acetonitrile (50 mL) were allowed to react according to general procedure A (45 h). Purification via flash chromatography (SiO_2, 2/1 hexanes/EtOAc) gave 110 mg (77%) of **3c** as a white solid, mp = 95–96 °C: ^1H NMR (two rotamers a/b 1/1) δ 7.30 (m, 5H), 5.32–5.12 (m, 3H), 3.92(a) (d, J = 10.8 Hz)/3.82(b) (d, J = 10.9 Hz) (1H), 3.73 (m, 1H), 3.58 (dq, J_1 = 8.7 Hz, J_2 = 7.0 Hz, 1H), 3.04 (a+b) (d, J = 10.9 Hz, 1H), 1.81 (m, 1H), 1.58 (s, 3H), 1.21 (t, J = 6.9 Hz, 3H), 1.04 (m, 6H), 0.90 (m, 3H); ^{13}C NMR δ 174.2(a)/173.4(b) 154.5(a)/154.3(b) 136.0(a)/135.8(b) 128.4, 128.1, 127.8, 95.7, 75.4(a)/75.0(b) 67.5, 61.8, 60.8, 60.1(a)/59.7(b) 29.5(a)/29.3(b), 25.3, 21.5, 16.6, 16.4, 16.3, 15.3; IR (neat) ν 1763, 1703 cm^{-1}.

(5*R,6*R**)-4-(Benzyloxycarbonyl)-6-methoxy-2,2-dimethyl-6-phenyl-1,4-diazabicyclo[3.2.0]heptan-7-one (3d).** [(Methoxy)(phenyl)carbene]pentacarbonylchromium(0) (**1d**) (418 mg, 1.34 mmol) and imidazoline **2** (283 mg, 1.22 mmol) in CH_2Cl_2 (15 mL) were allowed to react according to general procedure B (75 h). Purification via flash chromatography (SiO_2, 3/1 hexanes/EtOAc) gave 222 mg (48%) of **3d** as a white solid, mp = 54.5–56 °C: ^1H NMR (two rotamers, a/b 5/3) δ 7.5–7.0 (m, 10H), 5.41(b)/5.23(a) (s, 1H), 5.06(b) (d, J = 12.5 Hz)/5.01(a) (d, J = 12.4 Hz) (1H), 4.95(a) (d, J = 12.3 Hz)/4.88(b) (d, J = 12.5 Hz) (1H), 3.61(a) (d, J = 10.5 Hz)/3.50(b) (d, J = 10.4 Hz) (1H), 3.40(b)/3.37(a) (s, 3H), 2.86(a) (d, J = 10.5 Hz)/2.75(b) (d, J = 10.4 Hz) (1H), 1.69(a)/1.64(b) (s, 3H), 1.15(a)/1.14(b) (s, 3H); ^{13}C NMR δ 173.3(b)/172.9(a) 153.5(b)/153.2(a) 136.1(b)/135.8(a) 132.0(b)/131.9(a) 129.1, 129.0, 128.5, 128.4, 128.3, 128.24, 128.20, 128.0, 127.50, 127.45, 95.0, 76.1, 67.2(a)/67.0(b) 61.6(b)/61.2(a) 60.8(a)/60.5(b) 54.5(a)/54.4(b) 25.6, 21.8(a)/21.7(b); IR (neat) ν 1768, 1711 cm^{-1}.

(5*R,6*R**)-4-(Benzyloxycarbonyl)-6-methoxy-6-(*p*-methoxyphenyl)-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (3e).** [(Methoxy)(*p*-methoxyphenyl)carbene]pentacarbonylchromium(0) (**1e**) (450 mg, 1.315 mmol) and imidazoline **2** (305 mg, 1.315 mmol) in CH_2Cl_2 (10 mL) were allowed to react according to general procedure B (20 h). Purification via flash chromatography (SiO_2, 3/1 hexanes/EtOAc) gave 210 mg (39%) of **3e** as a white solid, mp = 93–94 °C: ^1H NMR (two rotamers, a/b 3/2) δ 7.41(b)/7.19(a) (d, J = 8.6 Hz, 2H), 6.81(b)/6.65(a) (d, J = 8.6 Hz, 2H), 7.4–7.0 (m, 5H), 5.38(b)/5.26(a) (s, 1H), 5.12(b) (d, J = 12.5 Hz)/5.06(a) (d, J = 12.2 Hz) (1H), 4.99(a) (d, J = 12.2 Hz)/4.88(b) (d, J = 12.5 Hz) (1H), 3.75(b)/3.73(a) (s, 3H), 3.60(a) (d, J = 10.5 Hz)/3.51(b) (d, J = 10.4 Hz) (1H), 3.35(b)/3.32(a) (s, 3H), 2.79(a) (d, J = 10.5 Hz)/2.71(b) (d, J = 10.4 Hz) (1H), 1.65(a)/1.61(b) (s, 3H), 1.13 (s, 3H); ^{13}C NMR δ 173.3(b)/173.1(a) 160.0, 153.5(b)/153.2(a) 136.1(b)/135.8(a) 129.4, 128.9, 128.5, 128.4, 128.3, 128.2, 127.9, 127.4, 123.8(b)/123.5(a) 113.61(a)/113.58(b) 94.64(b)/94.56(a) 76.1, 67.2(a)/66.8(b) 61.4(b)/61.0(a) 60.6(a)/60.4(b) 55.0, 54.2-(a)/54.1(b) 25.5, 21.7(a)/21.6(b); IR (neat) ν 1766, 1711 cm^{-1}.

(5*R,6*R**)-4-(Benzyloxycarbonyl)-6-cyclohexyl-6-methoxy-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (3f).** [(Methoxy)(cyclohexyl)carbene]pentacarbonylchromium(0) (**1f**) (310 mg, 0.974 mmol) and imidazoline **2** (226 mg, 0.974 mmol) in CH_2Cl_2 (20 mL) were allowed to react according to general procedure B (33 h). Purification via flash chromatography (SiO_2, 3/1 hexanes/EtOAc) gave 140 mg (37%) of **3f** as a white solid, mp = 114–115 °C: ^1H NMR (two rotamers, a/b 1/1) δ 7.28 (m, 5H), 5.34–5.05 (m, 3H), 3.93(a) (d, J = 10.9 Hz)/3.82-(b) (d, J = 10.6 Hz) (1H), 3.45 (s, 3H), 3.06(a+b) (d, J = 10.9 Hz, 1H), 1.59 (s, 3H), 1.08 (s, 3H), 1.91 (m, 1H), 1.69–1.42 and 1.29–1.08 (m, 10H); ^{13}C NMR δ 173.4(a)/172.7(b) 154.4 136.1(a)/135.7(b) 128.5, 128.2, 127.8, 96.0, 74.6(a)/74.4(b) 67.5-(a)/67.3(b) 60.8, 60.1(a)/59.7(b) 53.8, 39.7(a)/39.3(b) 26.2, 26.1, 25.9, 25.2, 21.4; IR (neat) ν 1765, 1708 cm^{-1}.

(5*R,6*R**)-4-(Benzyloxycarbonyl)-6-*tert*-butyl-6-ethoxy-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (3g).** [(Ethoxy)(*tert*-butyl)carbene]pentacarbonylchromium(0) (**1g**) (290 mg, 0.947 mmol) and imidazoline **2** (208 mg, 0.895 mmol) in CH_2Cl_2 (20 mL) were allowed to react according to general procedure B (20 h). Purification via flash chromatography (SiO_2, 3/1 hexanes/EtOAc) gave 68 mg (20%) of **3g** as a clear, colorless oil: ^1H NMR (50 °C) δ 7.32 (m, 5H), 5.20–5.13 (m, 3H), 3.86–3.70 (m, 2H), 3.60 (dq, J_1 = 8.8 Hz, J_2 = 7.0 Hz, 1H), 3.17 (d, J = 10.7 Hz, 1H), 1.63 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.11 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (50 °C) δ 171.6, 154.3, 136.2, 128.5, 128.2, 127.9, 98.9, 76.8, 67.6, 62.1, 61.6, 60.0, 35.6, 26.1, 25.5, 22.0, 15.5; IR (neat) ν 1766, 1713 cm^{-1}.

General Procedure for the Deprotection of the *N*-Benzyloxycarbonyl Azapenams. The azapenam was taken up in methanol in an Ace pressure tube. 10% Pd/C catalyst and a small amount (1–2 drops) of triethylamine were added, and the pressure tube was charged to 45 psi H_2 (three cycles). Hydrogenation for the specified time period, followed by filtration through Celite and removal of solvent under reduced pressure gave the crude product which was purified, if necessary, via flash or radial chromatography.

(5*S,6*R**)-6-Hexadecyl-6-methoxy-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (4a).** Azapenam **3a** (230 mg, 0.435 mmol) and 57 mg 10% Pd/C were allowed to react according to the general procedure (12 min). Purification via flash chromatography (SiO_2, 3/1 hexanes/EtOAc) gave 161 mg (94%) of **4a** as a white solid, mp = 51.5–52.5 °C: ^1H NMR δ 4.66 (s, 1H), 3.40 (s, 3H), 3.01 (d, J = 11.1 Hz, 1H), 2.78 (br s, 1H), 2.62 (d, J = 11.0 Hz, 1H), 1.62–1.55 (m, 2H), 1.52 (s, 3H), 1.44 (m, 2H), 1.20 (br s, 26H), 1.06 (s, 3H), 0.83 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 175.1, 91.9, 77.2, 62.1, 60.7, 53.3, 31.9, 30.0, 29.6, 29.53, 29.47, 29.3, 28.4, 25.0, 22.6, 22.5, 21.8, 14.1; IR (neat) ν 3357, 1749 cm^{-1}. Anal. Calcd for $C_{24}H_{46}N_2O_2$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.21; H, 11.59; N, 7.07.

(5*S,6*R**)-6-Cyclopropyl-6-methoxy-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (4b).** Azapenam **3b** (255 mg, 0.740 mmol) and 64 mg 10% Pd/C were allowed to react according to the general procedure (10 min). Purification via flash chromatography (SiO_2, 9/1 EtOAc/MeOH) gave 153 mg (99%) of **4b** as a clear, colorless oil: ^1H NMR δ 4.68 (s, 1H), 3.41(s, 3H), 3.01 (d, J = 11.2 Hz, 1H), 2.73 (d, J = 11.3 Hz, 1H), 2.42 (br s, 1H), 1.49 (s, 3H), 1.12–1.08 (m, 1H), 1.06 (s, 3H), 0.65–0.41 (m, 4H); ^{13}C NMR δ 172.8, 92.3, 77.0, 62.3, 61.0, 53.2, 24.9, 21.9, 9.6, 2.0, −0.3; IR (neat) ν 3353, 1747 cm^{-1}. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.85; H, 8.79; N, 13.13.

(5*S,6*R**)-6-Ethoxy-6-isopropyl-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (4c).** Azapenam **3c** (88 mg, 0.244 mmol) and 10 mg 10% Pd/C were allowed to react according to the general procedure (5 min) to give 54 mg (99%) of **4c** as a clear colorless oil: ^{1}H NMR δ 4.69 (s, 1H), 3.68 (dq, J_1 = 8.9 Hz, J_2 = 7.0 Hz, 1H), 3.57 (dq, J_1 = 8.9 Hz, J_2 = 7.0 Hz, 1H), 3.02 (d, J = 11.1 Hz, 1H), 2.65 (d, J = 11.1 Hz, 1H), 2.11 (br s, 1H), 1.95 (sept, J = 6.8 Hz, 1H), 1.55 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.08 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 175.3, 94.0, 77.8, 62.3, 61.6, 60.5, 29.0, 25.1, 21.9, 16.7, 15.9, 15.5; IR (neat) ν 3354, 1744 cm^{-1}. Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.48; H, 9.76; N, 12.58.

(5*S,6*R**)-6-Methoxy-2,2-dimethyl-6-phenyl-1,4-diazabicyclo[3.2.0]-heptan-7-one (4d).** To a solution of azapenam **3d** (50 mg, 0.131 mmol) in methanol (10 mL) were added triethylamine (2 drops) and 13 mg 10% Pd/C. A hydrogen filled balloon was used to carry out the hydrogenation (5 min), giving 30 mg of a clear, colorless oil as an 8/1 mixture of **4d** and **5d** (approximately an 83% yield of **4d**). Because **4d** was found to be unstable to chromatography (silica or alumina), no further purification was carried out; the compound was directly converted to either **5d** or **6d**, for which acceptable elemental analyses were obtained: ^{1}H NMR δ 7.46–7.20 (m, 5H), 4.78 (s, 1H), 3.34 (s, 3H), 2.81 (d, J = 11.2 Hz, 1H), 2.48 (d, J = 11.1 Hz, 1H), 1.53 (s, 3H), 1.12 (s, 3H); ^{13}C NMR δ 173.7, 133.2, 128.9, 128.4, 128.0, 93.1, 79.5, 62.8, 62.3, 54.1, 25.5, 22.3; IR (neat) ν 3355, 1751 cm^{-1}.

(5*S,6*R**)-6-Methoxy-6-(*p*-methoxyphenyl)-2,2-diazabicyclo[3.2.0]heptan-7-one (4e).** To a solution of azapenam **3e** (147 mg, 0.358 mmol) in methanol (10 mL) were added triethylamine (1 drop) and 37 mg of 10% Pd/C. A hydrogen filled balloon was used to carry out the hydrogenation (5 min), giving 97 mg of a clear, colorless oil as a 10/1 mixture of **4e** and **5e** (approximately an 89% yield of **4e**). Because **4e** was found to be unstable to chromatography (silica or alumina), no further purification was carried out; the compound was directly converted to either **5e** or **6e**, for which acceptable elemental analyses were obtained: ^{1}H NMR δ 7.35 (dd, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 2H), 6.85 (dd, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 2H), 4.73 (s, 1H), 3.73 (s, 3H), 3.27 (s, 3H), 2.78 (d, J = 11.1 Hz, 1H), 2.42 (d, J = 11.2 Hz, 1H), 2.0 (br s, 1H), 1.47 (s, 3H), 1.09 (s, 3H); ^{13}C NMR δ 173.8, 159.8, 129.4, 127.2, 124.8, 113.8, 92.5, 79.3, 62.7, 62.1, 55.0, 53.7, 25.4, 22.2; IR (neat) ν 3354, 1750 cm^{-1}.

(5*S,6*R**)-6-Cyclohexyl-6-methoxy-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (4f).** Azapenam **3f** (112 mg, 0.289 mmol) and 25 mg of 10% Pd/C were allowed to react according to the general procedure (10 min). Purification via flash chromatography (SiO_2, 9/1 EtOAc/MeOH) gave 71 mg (96%) of **4f** as a white solid, mp = 128–129 °C: ^{1}H NMR δ 4.69 (s, 1H), 3.40 (s, 3H), 3.01 (d, J = 11.0 Hz, 1H), 2.67 (d, J = 11.1 Hz, 1H), 2.33 (br s, 1H), 1.89 (m, 1H), 1.74–1.55 (m, 5H), 1.54 (s, 3H), 1.32–1.15 (m, 5H), 1.07 (s, 3H); ^{13}C NMR δ 174.6, 94.2, 76.8, 62.3, 60.5, 53.6, 38.9, 26.6, 26.4, 26.3, 26.1, 25.7, 25.1, 21.9; IR (neat) ν 3355, 1733 cm^{-1}. Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.76; H, 9.41; N, 11.16.

(5*S,6*R**)-6-*tert*-Butyl-6-ethoxy-2,2-dimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one (4g).** Azapenam **3g** (42 mg, 0.112 mmol) and 17 mg of 10% Pd/C were allowed to react according to the general procedure (10 min) to give 26 mg (99% yield) of **4g** as a white solid, mp 118–120 °C: ^{1}H NMR δ 4.65 (s, 1H), 3.67 (dq, J_1 = 7.0 Hz, J_2 = 8.8 Hz, 1H), 3.57 (dq, J_1 = 7.0 Hz, J_2 = 8.8 Hz, 1H), 3.02 (d, J = 10.8 Hz, 1H), 2.74 (d, J = 10.8 Hz, 1H), 1.57 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.08 (s, 3H), 1.07 (s, 9H); ^{13}C NMR δ 172.7, 96.4, 80.0, 62.0, 61.6, 60.1, 35.3, 25.6, 24.9, 22.1, 15.5; IR (neat) ν 3357, 1745 cm^{-1}. Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.96; H, 10.06; N, 11.66. Found: C, 65.16; H, 9.97; N, 11.86.

Conversion of 4d to 5d. The 8/1 mixture of **4d** and **5d** (30 mg, 0.122 mmol) was taken up in a solution of methanol (5 mL) and triethylamine (5 drops) and stirred at room temperature (5 h). Purification via flash chromatography (SiO_2, 1/1 hexane EtOAc) gave 17 mg (53%) of **5d** as a clear, colorless oil: ^{1}H NMR δ 7.74 (s, 1H), 7.34–7.30 (m, 5H), 4.96 (s, 1H), 3.58 (dd, J_1 = J_2 = 2.2 Hz, 2H), 3.46 (s, 3H), 1.50 (s, 3H), 1.43 (s, 3H); ^{13}C NMR δ 167.9, 147.3, 135.4, 128.8, 128.4, 125.6, 85.6, 69.6, 61.8, 57.6, 25.33, 25.27; IR (neat) ν 1677, 1621 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.38. Found: C, 68.12; H, 7.45; N, 11.42.

Conversion of 4e to 5e. The 10/1 mixture of **4e** and **5e** (97 mg, 0.351 mmol) was taken up in a solution of methanol (5 mL) and triethylamine (8 drops) and stirred at room temperature overnight. Purification via radial chromatography (SiO_2, EtOAc) gave 35 mg (65%) of **5e** as a clear, colorless oil: ^{1}H NMR δ 7.67 (s, 1H), 7.26 (dd, J_1 = 8.6 Hz, J_2 = 1.7 Hz, 2H), 6.85 (dd, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 2H), 4.89 (s, 1H), 3.75 (s, 3H), 3.57 (app s, 2H), 3.42 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3H); ^{13}C NMR δ 168.0, 160.0, 147.1, 127.5, 127.2, 114.2, 85.0, 70.1, 61.7, 57.4, 55.2, 25.4; IR (neat) ν 1674, 1620 cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.29; N, 10.14. Found: C, 65.31; H, 7.12; N, 10.19.

General Procedure for the Dimerization of Azapenams to Tetraaza Macrocycles. The azapenam and racemic camphorsulfonic acid (5–10 mg) were taken up in CH_2Cl_2 and stirred at room temperature for the specified time period. The solution was washed with aqueous 5% $NaHCO_3$ and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Crude products were purified, if necessary, by recrystallization from hexanes/EtOAc.

6,13-Dihexadecyl-6,13-dimethoxy-3,3,10,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione (6a). Azapenam **4a** (135 mg, 0.342 mmol) was allowed to react according to the general procedure (45 h) to give 112 mg (83%) of **6a** as a white solid, mp = 98–99 °C, as a racemic mixture of diastereoisomers: ^{1}H NMR isomer a: δ 8.04 (s, 1H), 7.55 (s, 1H), 3.85 (d, J = 12.0 Hz, 1H), 3.28 (d, J = 10.9 Hz, 1H), 3.28 (s, 3H), 1.81 (m, 2H), 1.42 (s, 3H), 1.34 (s, 3H), 1.22 (br s, 28H), 0.84 (t, J = 6.9Hz, 3H); isomer b: δ 7.93 (s, 1H), 7.55 (s, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.47 (d, J = 10.9 Hz, 1H), 3.23 (s, 3H), 1.81 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H), 1.22 (br s, 28H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 168.8(a)/168.4-(b) 168.2(b)167.7(a) 83.5(b)/83.4(a) 68.8(a)/68.0(b) 54.1(b)/53.8-(a) 52.9(a)/52.7(b) 35.1(a)/34.7(b), 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 26.1(b)/25.7(a) 25.3(b)/24.9(a), 22.9, 22.7, 22.6(a+b), 14.1; IR (neat) ν 1674 cm^{-1}. Anal. Calcd for $C_{48}H_{92}N_4O_4$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.83; H, 11.94; N, 6.95.

6,13-Dicyclopropyl-6,13-dimethoxy-3,3,10,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,-12-dione (6b). Azapenam **4b** (200 mg, 0.951 mmol) was allowed to react according to the general procedure (37 h) to give 140 mg (70%) of **6b** as a white solid, mp = 191–193 °C, as a 3/1 mixture of diastereoisomers: ^{1}H NMR isomer a: δ 9.19 (s, 1H), 7.60 (s, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.26 (s, 3H), 3.10 (d, J = 12.0 Hz, 1H), 1.47 (s, 3H), 1.21 (s, 3H), 1.15 (m, 1H), 0.6–0.4 (m, 4H); isomer b: δ 8.83 (s, 1H), 7.56 (s, 1H), 3.53 (d, J = 12.3 Hz, 1H), 3.41 (d, J = 12.3 Hz, 1H), 3.28 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.15 (m, 1H), 0.6–0.4 (m, 4H); ^{13}C NMR δ 168.5(a)/167.8(b) 168.2(a+b), 81.2(a+b), 70.9-(a)/69.3(b) 53.8(b)/53.5(a) 53.7(a)/53.5(b) 25.1(b) 25.0(b) 24.8-(a) 24.0(a) 18.6(a)/17.9(b) 1.0(b)/0.9(a)/0.8(a); IR (neat) ν 1677 cm^{-1}. Anal. Calcd for $C_{22}H_{36}N_4O_4$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.01; H, 8.39; N, 13.22.

6,13-Diethoxy-6,13-diisopropyl-3,3,10,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione (6c). Azapenam **4c** (54 mg, 0.238 mmol) was allowed to react according to the general procedure (45 h) to give 40 mg (74%) of **6c** as a white solid, mp = 149–150 °C, as a racemic mixture of diastereoisomers: ^{1}H NMR isomer a: δ 9.69 (s, 1H), 7.69 (s, 1H), 3.63–3.47+3.23–3.13 (m, 4H), 3.41 (s, 2H), 2.16 (sept, J = 7.0 Hz, 1H), 1.44 (s, 3H), 1.28 (s, 3H), 1.18 (t, J = 6.9 Hz), 0.96 (d, J = 7.0, 3H), 0.89 (d, J = 6.9 Hz, 3H); isomer b: δ 9.62 (s, 1H), 7.70 (s, 1H), 3.63–3.47+3.23–3.13 (m, 4H), 3.41 (s, 2H), 2.27 (sept, J = 6.9 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 1.18 (t, J = 6.9 Hz, 3H), 0.96 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 170.1(b)/169.2(a) 168.5(b)/168.3-(a) 84.6(b)/84.1(a) 71.4(b)/71.0(a) 61.7(a)/61.5(b), 53.6(b)/53.5-(a), 37.4(b)/36.4(a) 24.7, 24.5, 24.3, 24.1(a+b), 17.0, 16.91, 16.86, 16.7(a+b), 15.71, 15.66(a+b); IR (neat) ν 1671 cm^{-1}. Anal. Calcd for $C_{24}H_{44}N_4O_4$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.48; H, 9.81; N, 12.20.

6,13-Dimethoxy-6,13-diphenyl-3,3,10,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione (6d). Azapenam **4d** (32 mg, 0.131 mmol) was allowed to react according to the general procedure (15 h) to give 24 mg (75%) of **6d** as a white solid, mp = 199–201 °C, as a 3/1 mixture of diastereoisomers: ^{1}H NMR isomer a: δ 9.34 (s, 1H), 7.80 (s, 1H), 7.6–7.2 (m, 5H), 3.95 (d, J = 11.1 Hz, 1H), 3.39 (s, 3H), 3.25 (d, J = 12.2 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H); isomer b: δ 9.72 (s, 1H), 7.75 (s, 1H), 7.6–7.2 (m, 5H), 3.65 (d, J = 12.3 Hz, 1H), 3.44 (s, 3H), 3.42 (d, J = 11.1 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 167.7(b)/167.4(a), 167.8-(b)/167.6(a), 138.1(b)/138.0(a), 128.50, 128.47, 128.3, 126.4, 126.2 (a+b), 83.8(a)/83.7(b), 70.1(a)/69.9(b), 54.2(a)/53.9(b), 53.8(a)/53.6(b), 25.2(b), 25.0(a), 24.6(a), 24.4(b); IR (neat) ν 1681 cm^{-1}. Anal. Calcd for $C_{28}H_{36}N_4O_4$: C, 68.27; H, 7.37; N, 11.38. Found: C, 68.05; H, 7.37; N, 11.16.

6,13-Dimethoxy-6,13-bis(*p*-methoxyphenyl)-3,3,10,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione (6e). Azapenam **4e** (97 mg, 0.351 mmol) was allowed to react according to the general procedure (22 h) to give 66 mg (68%) of **6e** as a white solid, mp = 194–196 °C, as a 3/2 mixture of diastereoisomers: ^{1}H NMR isomer a: δ 9.19 (s, 1H), 7.78 (s, 1H), 7.38 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.96 (d, J = 12.0 Hz, 1H), 3.78 (s, 3H), 3.35 (s, 3H), 3.24 (d, J = 12.0 Hz, 1H), 1.44 (s, 3H), 1.38 (s, 3H); isomer b: δ 9.54 (s, 1H), 7.74 (s, 1H), 7.38 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 3.64 (d, J = 12.0 Hz, 1H), 3.45 (d, J = 12.0 Hz, 1H), 3.41 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H); ^{13}C NMR δ 168.1(a)/167.8(b), 167.9(a)/167.3(b), 159.5-(a+b), 130.2(a)/130.1(b), 127.9,127.6, 113.9 (a+b), 83.6(b)/83.5-(a), 69.8(a)/69.7(b), 55.3(a+b), 54.1(a)/53.9(b), 53.7(b)/53.6(a), 25.3, 25.2, 24.7, 24.6(a+b); IR (neat) ν 1681 cm^{-1}. Anal. Calcd for $C_{30}H_{40}N_4O_6$: C, 65.20; H, 7.29; N, 10.14. Found: C, 64.96; H, 7.49; N, 10.57.

6,13-Dicyclohexyl-6,13-dimethoxy-3,3,10,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione (6f). Azapenam **4f** (74 mg, 0.289 mmol) was allowed to react according to the general procedure (43 h) to give 66 mg (89%) of **6f** as a white solid, mp = 143–144 °C, as a 3/1 mixture of diastereoisomers: ^{1}H NMR isomer a: δ 9.71 (s, 1H), 7.71 (s, 1H), 3.65 (J = 12.0 Hz, 1H), 3.24 (s, 3H), 3.22 (m, 1H), 1.91–1.84, 1.72–1.57, 1.20–0.95 (m, 11H), 1.47 (s, 3H), 1.28 (s, 3H); isomer b: δ 9.67 (s, 1H), 7.71 (s, 1H), 3.44 (m, 2H), 3.24 (s, 3H), 1.91–1.84, 1.72–1.57, 1.20–0.95 (m, 11H), 1.44 (s, 3H), 1.36 (s, 3H); ^{13}C NMR δ 170.2(a)/169.7(b), 168.4(b)/167.7(a), 85.4(a)/84.9(b), 72.0(a)/71.2(b), 54.2(a)/54.1(b), 53.9(a)/53.6(b), 47.2(a)/46.8(b), 29.8, 29.3, 27.2, 26.5, 27.0, 26.4, 26.2, 25.7, 25.2-(a+b), 24.8, 24.5, 24.1; IR (neat) ν 1677, 1655 cm^{-1}. Anal. Calcd for $C_{28}H_{48}N_4O_4$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.80; H, 9.75; N, 11.28.

6-Hexadecyl-6,13-dimethoxy-3,3,10,10,13-pentamethyl-1,4,8,11-tetraazacyclotetradecane-5,12-dione (11). 6a (144 mg, 0.182 mmol), **9** (67 mg, 0.182 mmol), and racemic camphorsulfonic acid (11 mg, 0.047 mmol) were taken up in CH_2Cl_2 (10 mL) and allowed to stir at room temperature (53 h). The solution was then washed with aqueous 5% $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Without further purification, the crude macrocyclic products were taken up in a 4/1 solution of MeOH/CH_2Cl_2 (10 mL) in an Ace pressure tube equipped with stirbar. 49 mg 10% Pd/C catalyst was added, the pressure tube was charged to 45 psi of H_2 (three cycles) and the solution was allowed to stir at room temperature (64 h). Filtration through Celite and removal of the solvent under reduced pressure afforded the crude dioxo cyclam products. Flash chromatography (SiO_2, 95/5 CH_2Cl_2/MeOH) allowed for the isolation of 14 mg of a single diastereomer of **11** as a white solid, for which purity was established by ^{1}H and ^{13}C NMR spectral data: ^{1}H NMR (C_6D_6) δ 7.50 (s, 1H), 7.41 (s, 1H), 3.42 (d, J = 12.1 Hz, 1H), 3.29 (d, J = 12.3 Hz, 1H), 2.99 (s, 3H), 2.96 (s, 3H), 2.87 (d, J = 11.9 Hz, 1H), 2.83 (d, J = 12.3 Hz, 1H), 2.63 (d, J = 12.3 Hz, 1H), 2.59 (d, J = 12.7 Hz, 1H), 2.06 (d, J = 12.4 Hz, 1H), 2.04 (d, J = 12.1 Hz, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.33 (br s, 30H), 1.29 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H), 0.91 (m, 3H); ^{13}C NMR (C_6D_6) δ 172.0, 171.4, 83.1, 81.3, 58.5, 58.3, 57.1, 54.3, 53.8, 53.7, 50.6, 49.8, 32.3, 31.4, 30.4, 30.2, 30.10, 30.06, 29.8, 27.24, 27.20, 24.2, 24.1, 23.4, 23.1, 18.7, 14.3; IR (neat) ν 3415, 1673 cm^{-1}; MS 583 (M+); HRMS calcd for $C_{33}H_{66}N_4O_4$ 582.5084, found 582.5082.

3,4-Dihydro-5*H*-2-benzazepine (7). 2,3,4,5-Tetrahydro-1*H*-2-benzazepin-1-one[13] (600 mg, 4.08 mmol) was dissolved in Et_2O (10 mL) and cooled to 0 °C. *tert*-Butyl hypochlorite (487 mg, 4.48 mmol) and $NaHCO_3$ (160 mg) were then added, and the solution was allowed to warm to room temperature and stirred for 45 min. The resultant *N*-chloroimidate was sequentially washed with H_2O (20 mL), 1.5 M H_2SO_4 (15 mL), and H_2O (20 mL) and then dried over $MgSO_4$. The organics were then added dropwise to a 0 °C stirring solution of KOH (229 mg, 4.08 mmol) in absolute ethanol (15 mL). The resultant solution was warmed to room temperature and stirred for 19 h. Solvents were removed under reduced pressure, and the residue was dissolved in H_2O and extracted with CH_2Cl_2 (4 × 20 mL). The combined organics were dried over $MgSO_4$ and concentrated to yield 589 mg (99%) of **7** as a viscous orange oil. Upon standing for approximately 20 min, dimerization to **8** occurred. Spectral data for **7** and **8** were identical to that reported in the literature.[7]

12,13-Benzo-6-methoxy-3,3,6-trimethyl-1,4,8-triazacyclotetradec-12-en-5-one (13). 9 (176 mg, 0.479 mmol) and **7** (278 mg, 0.958 mmol) were taken up in CH_2Cl_2 (10 mL) and allowed to stir at room temperature (72 h). The solvent was then removed under reduced pressure and without further purification the crude macrocyclic products were taken up in a 1/1 solution of MeOH/H_2O (20 mL) and cooled to 0 °C. $NaBH_4$ (544 mg, 14.37 mmol) was added in small portions over 1 h, and the resultant solution was allowed to stir at 0 °C for 2 h and at room temperature overnight. The MeOH was removed under reduced pressure and the remaining aqueous phase was washed with aqueous 5% $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over $MgSO_4$ and concentrated to afford the crude mixture of products as an orange oil. Separation of the products via flash chromatography (SiO_2 washed in 96/4 EtOAc/Et_3N, 95/5 CH_2Cl_2/MeOH as eluent) and further purification via a second flash chromatography (activated basic Al_2O_3, 95/5 EtOAc/MeOH) afforded 19 mg of **13** as a clear, orange oil, for which purity was established by ^{1}H and ^{13}C NMR spectral data: ^{1}H NMR δ 7.2–7.0 (m, 4H), 6.75 (s, 1H), 3.80 (d, J = 11.0 Hz, 1H), 3.67 (d, J = 11.4 Hz, 1H), 3.46 (d, J = 11.1 Hz, 1H), 3.19 (s, 3H), 3.0–2.8 (m, 2H), 2.86 (d, J = 11.7 Hz, 1H), 2.7–2.5 (m, 2H), 2.48 (d, J = 11.7 Hz, 1H), 2.34 (d, J = 11.4 Hz, 1H), 2.05 (br s, 2H), 1.81 (m, 2H), 1.41 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR δ 172.4, 139.8, 138.3, 130.9, 127.64, 127.58, 125.7, 80.4, 57.2, 53.8, 53.4, 53.1, 50.2, 45.4, 27.5, 25.8, 25.4, 25.0, 18.4; IR (neat) ν 3415, 1673 cm^{-1}; HRMS calcd for $C_{19}H_{31}N_3O_2$ 333.2416, found 333.2417.

Acknowledgment. Support for this research under Grant No. CHE-9224489 from the National Science Foundation is gratefully acknowledged. Mass spectra were obtained on instruments supported by the National Institutes of Health shared instrumentation grant GM49631. W.M. would also like to thank the U.S. Department of Education for fellowship support under the Graduate Assistance in Areas of National Need Program (Grant No. P200A10210).

Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **1c,f**, **3a–g**, **4d,e**, **11**, and **13** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.