Synthesis of Optically Active Imidazolines, Azapenams, Dioxocyclams, and Bis-dioxocyclams

Yi Hsiao and Louis S. Hegedus*

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

Received December 13, 1996[⊗]

Optically active 4-methyl-4-carbomethoxy-Δ^2-imidazoline was efficiently synthesized on a multigram scale. Photolysis with (methoxymethylcarbene)chromium complex produced the optically active azapenam in good yield and with high stereoselectivity. Acid-catalyzed dimerization followed by reduction produced the corresponding optically active dioxocyclam in good yield. Using a bis-carbene complex, an optically active bis-dioxocyclam was produced in excellent yield.

Introduction

Cyclams constitute a class of 14-membered tetraazamacrocycles that form very stable, kinetically inert complexes with a range of metals, particularly first-row transition metals, with the potential for wide-ranging biological activity,[1] including proton and metal ion transport, oxygen complexation and activation,[2] and superoxide dismutase activity.[3] Dioxocyclams are a subgroup of this class, structurally intermediate between oligopeptides and polyamines, which have also been extensively studied.[4] Nickel complexes of dioxocyclams catalyze olefin epoxidation,[4,5] while closely related nickel macrocycles effect selective oxidative cleavage of exposed guanine residues in nucleic acids.[6] Nickel(II) complexes of bis-tetraazamacrocycles containing rigid spacers catalyzed phosphate ester hydrolysis more effectively than mononuclear nickel(II) complexes.[7] This process has potential application for the nonoxidative cleavage of the phosphate diester backbone of DNA.[8] Cyclams and dioxocyclams are exceptional ligands for technecium-99m, and these complexes provide a new class of renal imaging agents,[9] while cyclam tetraacetates form lanthanide complexes of use in magnetic resonance imaging.[10] Finally, bis-cyclams[11] and related bis-nickel complexes[12] have potent anti-HIV activity, inhibiting replication and interrupting the viral uncoating event. Little is known about the mechanism of this process, and less about the structural requirements of the various cyclam agents for anti-HIV activity.

Optically active cyclams or dioxocyclams, bearing chirality on the carbon skeleton, are considerably less common and have only recently been synthesized, although in low (7−12%) yield.[4] Recently, novel approaches to optically active nonracemic dioxocyclams via optically active imidazolines[13] and racemic bis-dioxocyclams via achiral imidazolines[14] have been reported from these laboratories. For a number of planned biological applications, from the above list, it became important to be able to stereospecifically synthesize single enantiomers of optically active mono- and bis-dioxocyclams having peripheral functionality to provide the desired selectivity and solubility for the planned studies. The results of efforts addressing this problem are presented below.

Results and Discussion

Initial studies centered on the synthesis of optically active dioxocyclams from monosubstituted imidazolines, prepared from optically active amino acids as shown in Scheme 1. This route, used to prepare isopropyl **6a** and its corresponding dioxocyclam in the original work,[5] was extended to the methyl (**6b**) and phenyl (**6c**) analogs, from (*S*)-alanine and (*S*)-phenylglycine respectively. The results for the *gem*-dimethyl analog **6d**, from commercially available diamine **3d**, are shown for purposes of comparison. This reaction sequence was reasonably efficient in all four cases up to the unprotected imidazolines **4**, all of which were quite stable and easily purified by distillation. Surprisingly, monoalkylimidazolines **4a**−**c** underwent protection in poor yield, and the protected heterocycles **5a** and **5b** were quite thermally unstable, decomposing on standing over the course of a few days. This was in marked contrast to *gem*-dimethylimidazoline (**4d**), which underwent protection in good yield and produced a quite stable **5d**. The photochemical cycloaddition (**5a**−**c** → **6a**−**c**) also went in poor yield, probably because of thermal decomposition of the imidazolines, and produced azapenams **6** contaminated with many

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1997.

(1) For reviews see: (a) Kimura, E. *Tetrahedron* **1992**, *48*, 6175−6217. (b) Kimura, E. *J. Coord. Chem.* **1986**, *15*, 1−28. (c) Busch, D. H. *Acct. Chem. Res.* **1978**, *11*, 392−400. (d) Parker, D. Tailoring Macrocycles for Medical Applications. In *Crown Compounds Towards Future Applications*; Copper, S. R., Ed.; VCH: New York, 1992; pp 51−67.

(2) Busch, D. H.; Alcock, N. W. *Chem. Rev.* **1994**, *94*, 585−623.

(3) Kimura, E.; Sakonaka, A.; Nakamoto, M. *Biochim. Biophys. Acta* **1981**, *678*, 172−179.

(4) Wagler, T. R.; Fang, Y.; Burrows, C. J. *J. Org. Chem.* **1989**, *54*, 1584−1589 and references therein.

(5) Nam, W.; Ho, R.; Valentine, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 7052−7054.

(6) Burrows, C. J.; Rokita, S. E. *Acc. Chem. Res.* **1994**, *27*, 295−301.

(7) Crane, C. G.; Burrows, C. J. *J. Inorg. Biochem.* **1991**, *43*, 661. For a comprehensive review see: Halcrow, M. A.; Christou, G. *Chem. Rev.* **1994**, *94*, 2421−2482.

(8) (a) For an example using Ce(III) see: Takasaki, B. K.; Chin, J. *J. Am. Chem. Soc.* **1994**, *116*, 1121−1122. (b) For a recent example of bimetallic catalysis see: Tsubouchi, A.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 11614−11615.

(9) (a) Herzog, K. M.; Deutsch, E.; Deutsch, K.; Silberstein, E. B.; Saragarajan, R.; Cacini, W. *J. Nucl. Med.* **1992**, *33*, 2190−2195. (b) Riche, F.; Pasqualini, R.; Duatte, A.; Vidal, M. *Appl. Radiat. Isot.* **1992**, *43*, 437−442.

(10) (a) Dischino, D. D.; Delany, E. J.; Emswiler, J. E.; Gaughan, G. T.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991**, *30*, 1265−1269. (b) Kodama, M.; Koike, T.; Mahatma, A. B.; Kimura, E. *Inorg. Chem.* **1991**, *30*, 1270−1273.

(11) DeClerq, 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*, 5286−5290.

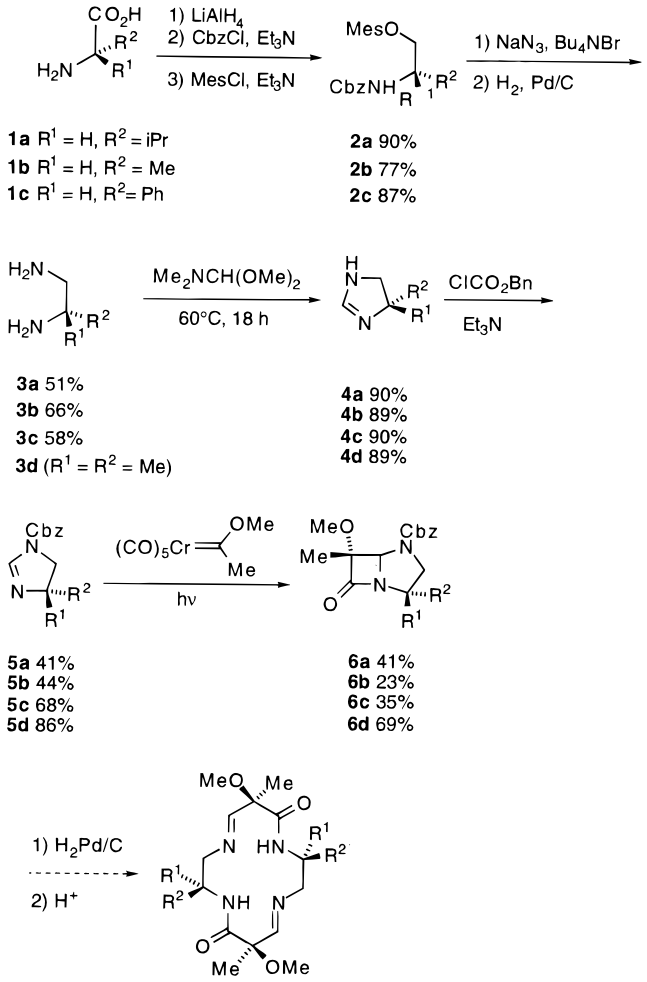
(12) Inoue, Y.; Kanamori, T.; Yoshida, T.; Bu, X.; Shionoya, M.; Koike, T.; Kimura, E. *Biol. Pharm. Bull.* **1994**, *17*, 243−250.

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

(14) Dumas, S.; Lastra, E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3368.

S0022-3263(96)02343-2 CCC: $14.00

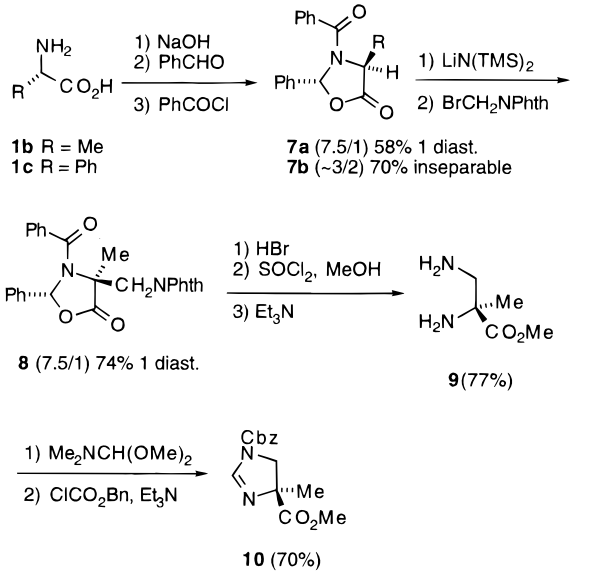
Scheme 1



unidentified byproducts, again in contrast to the disubstituted case **5d** → **6d**. With yields in the 8−21% range over the last two steps, and the expectation that these low-yield problems would only be amplified when applied to bis-dioxocyclam synthesis, these monosubstituted, optically active imidazolines were deemed unsuitable for further study.

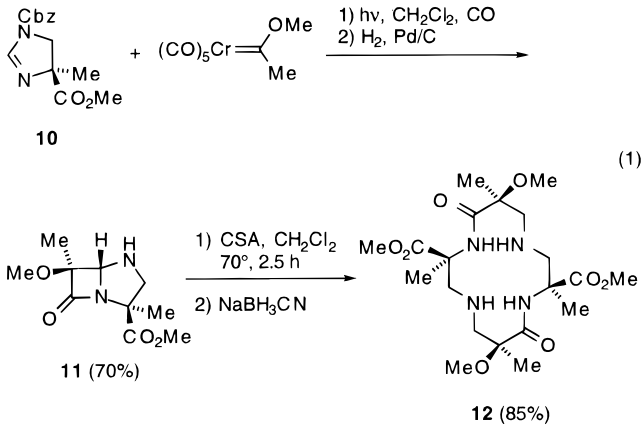
The observation that *gem*-disubstituted imidazoline **5d** suffered neither from protection problems nor low yields in the photochemical step, along with a desire to introduce additional functionality into the ultimate macrocycles led to the choice of imidazoline **10** as the next target. This was efficiently synthesized on a large scale in good yield with high optical purity using oxazolidinone chemistry developed by Seebach and Fadel,[15] to produce the desired diamine by the procedures of Jones[16] and Gilbert[17] (Scheme 2). Initially, both (*S*)-alanine and (*S*)-phenylglycine were used as sources of the chiral center. However, the oxazolidinone from phenylglycine produced an inseparable mixture of diastereoisomers **7b**, while that from alanine gave a 58% yield of optically pure **7a** on a 20−50 g scale after only two recrystallizations. Alkylation of **7a** with *N*-(bromomethyl)phthalimide produced **8** in 74% yield as a single diastereoisomer, after one recrystallization. Hydrolysis to the diamine **9** followed

Scheme 2



by conversion to the desired protected imidazoline **10** proceeded uneventfully, completing the synthesis. (A related method of Davies[18] was briefly examined but proved less convenient in this particular instance.)

Photolysis of imidazoline **10** with the (methoxymethylcarbene)chromium complex under standard conditions (500 W Hanovia medium pressure Hg lamp, 30 °C, Pyrex) gave variable, low yields of the desired azapenam **11** with the chromium pentacarbonyl imidazoline complex from decomposition of the carbene complex as the major byproduct. Optimum photochemical conditions were found to require the use of four 500 W quartz/halogen lamps as the light source and control of the reaction temperature to 70 °C. Under these conditions reproducibly good yields of a single diastereoisomer of the β-lactam on multigram scales were readily obtained (eq 1).

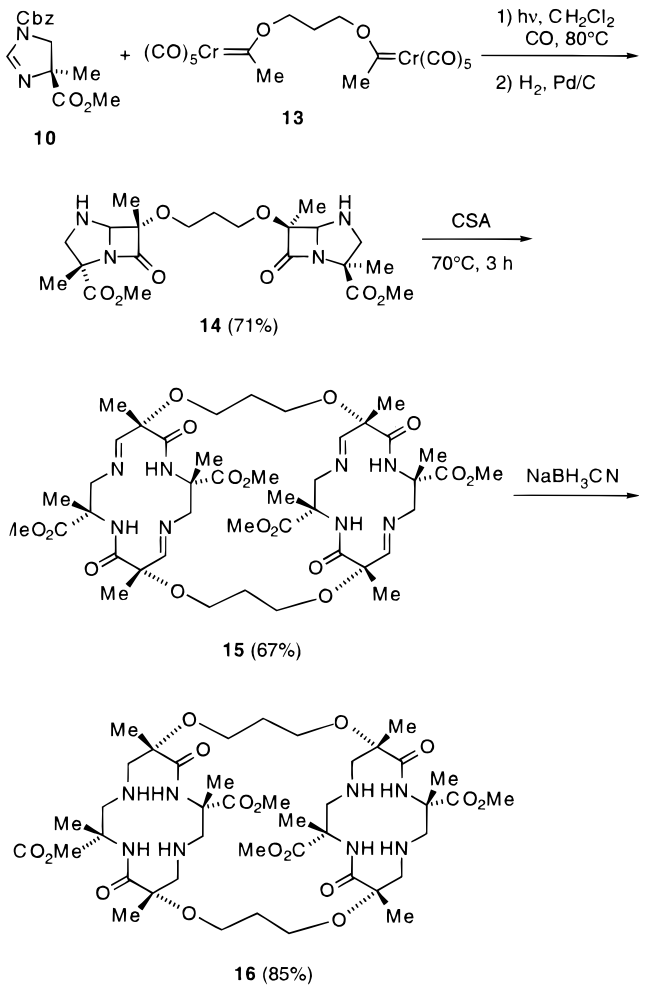


(1)

The absolute configuration of azapenam **11** was determined by X-ray crystallography[19] and is as shown. The stereochemical outcome of the photocyclization to form **11** was not easily predicted. Previous studies[20] of reactions between alkoxycarbene complexes and imines suggested that the stereochemical outcome of these reactions was contrasteric, arising from the sterically more crowded transition state, and being driven by electronic effects

(15) (a) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243. (b) Fadel, A.; Salaun, J. *Tetrahedron Lett.* **1987**, *28*, 2243.
(16) Jones, R. C. F.; Crockett, A. K.; Rees, D. C.; Gilbert, I. H. *Tetrahedron: Asymmetry* **1994**, *5*, 1661.
(17) Gilbert, I. H.; Rees, D. C.; Crockett, A. K.; Jones, C. F. *Tetrahedron* **1995**, *51*, 6315.
(18) Alonso, F.; Davies, S. G. *Tetrahedron: Asymmetry* **1995**, *6*, 353.
(19) We thank Melissa Hellman for carrying out the X-ray diffraction studies.
(20) Dumas, S.; Hegedus, L. S. *J. Org. Chem.* **1994**, *59*, 4967.

Scheme 3



that dramatically lowered the barrier for cyclization from this less stable transition state. Those arguments predicted that the larger group on the imidazoline (the methyl group) should end up on the same face of the β-lactam as the methoxy group. This was *not* the case with **11**, and the ester group must exert some as yet unexplained electronic bias on the stereochemical outcome of the reaction. The important point is that the reaction is highly stereoselective.

The acid-catalyzed dimerization of azapenam **11** produced, after reduction of the imine moieties, dioxocyclam **12** in excellent yield and, as expected, as a single diastereoisomer. (Note that dimerization of racemic **11** produced *two* diastereoisomers of **12**, so any lack of stereoselectivity during the reaction sequence in Scheme 2 would have been easily detected by ^{1}H NMR spectroscopy at this stage.) An X-ray crystal structure[19] again confirmed the assigned stereochemistry and indicated that the ester groups and methoxy groups were on the same face of the macrocycle.

The use of optically active imidazoline **10**, having a quaternary chiral center, allowed at least a 4-fold increase in yield (from the diamine) over those having a tertiary chiral center (Scheme 1), making optically active dioxocyclams more easily accessible. More importantly, this efficiency was also observed in the synthesis of bis-dioxocyclams (Scheme 3), for which imidazolines **5a**−**c** had proven unacceptably inefficient. Photolysis of imidazoline **10** with bis-carbene complex **13** followed by deprotection gave optically active bis-azapenam **14** in good yield and as a single diastereoisomer. Acid-catalyzed dimerization to give **15** followed by reduction gave optically active bis-dioxocyclam **16** in very good yield (40% overall from **10** and 31% overall from diamine **9**).

The structure and absolute stereochemistry of bis-dioxocyclam **16** was again confirmed by X-ray crystallography. Despite the fact that the bis-azapenam precursor **14** had an $[\alpha]_D$ of −177° and the monocyclam analog **12** had an $[\alpha]_D$ of +25°, bis-dioxocyclam **15** had an $[\alpha]_D$ of just −0.4°, notwithstanding the presence of eight chiral centers of *S* configuration! Only modest rotation was observed at shorter wavelengths with a maximum $[\alpha]_{436}$ of −5.4° (*c* 4.0 CH_2Cl_2) in spite of the fact that the compound is optically pure. The chiroptical properties of this unusual macrocycle and nickel complexes thereof are under current study.

In summary, an efficient synthesis of optically active mono- and bis-dioxocyclams having peripheral ester groups suitable for appending additional functional groups has been developed, making this class of compounds accessible for the study of biological properties. The chemistry developed should be suitable for alkyl groups other than methyl at the quaternary carbon in imidazoline **10** (Scheme 2) since oxazolidinones **8** having *n*-butyl,[16,17] isopropyl,[15b] benzyl,[15b] and $CH_3SCH_2CH_2$−[15b] groups have been synthesized in good yield and high optical purity. Its use in the development of biologically active dioxocyclams is under current study.

Experimental Section

General Methods. If not otherwise stated, melting points were taken on a MelTemp apparatus and are uncorrected. All NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C. Chemical shifts are given in δ ppm relative to $(CH_3)_4Si$ (δ 0.00, ^{1}H) or $CDCl_3$ (δ 77.0, ^{13}C). IR spectra were recorded on a Perkin-Elmer 1600 series FTIR.

Ether and THF was distilled from sodium/benzophenone under an atomosphere of nitrogen. CH_2Cl_2 and triethylamine were distilled from CaH_2.

The following chemicals were prepared according to literature procedures: pentacarbonyl(methoxymethylcarbene)-chromium,[21] bis-chromium alkoxycarbene complex (**13**),[14] oxazolidinone (**7a**).[15b]

(*S*)-2-[(Benzyloxycarbonyl)amino]propan-1-yl Mesyl Ester (2b). Lithium aluminum hydride (17.0 g, 0.43 mol) was suspended in 600 mL of THF at 0 °C. (*S*)-alanine (20.0 g, 0.22 mol) was added slowly in small portions. The reaction mixture was heated at reflux overnight and then cooled to room temperature. Saturated K_2CO_3 was added slowly. Filtration and evaporation of solvent gave a colorless oil. Distillation (76−78 °C/~20 mmHg) of the crude oil gave (*S*)-2-aminopropan-1-ol as a light yellowish oil (15.9 g, 95%): ^{1}H NMR δ 0.99 (d, J = 6.2 Hz, 3H), 2.51 (brs, 3H), 2.92−3.01 (m, 1H), 3.18 (dd, J = 7.7, 10.7 Hz), 3.48 (dd, J = 3.5, 10.2 Hz).

(*S*)-2-Aminopropan-1-ol was dissolved in dichloromethane (350 mL) and 5% $NaHCO_3$ (350 mL). Benzyl chloroformate (42.0 g, 234 mmol) was then added. The reaction mixture was stirred at 20 °C for 16 h. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with dichloromethane (150 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The residue was recrystallized from hexane and ethyl acetate (3:1) to give a white solid (37.3 g, 84%): ^{1}H NMR δ 1.15 (d, J = 6.7 Hz, 3H), 2.08 (brs, 1H), 3.51 (dd, J = 5.9, 11.0 Hz, 1H), 3.65 (dd, J = 3.5, 10.8 Hz, 1H), 3.82 (brs, 1H), 4.86 (brs, 1H), 5.08 (s, 2H), 7.29−7.35 (m, 5H).

(21) Bao, J.; Wulff, W. D.; Doming, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S-i.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.

(*S*)-2-[(Benzyloxycarbonyl)amino]propan-1-ol (37.0 g, 177 mmol) was dissolved in dichloromethane (300 mL) and triethylamine (20 g, 198 mmol). This solution was cooled to 0 °C, and then mesyl chloride (15 mL, 195 mmol) was added. After 20 min of stirring at 20 °C, the solution was washed with 1 N HCl (100 mL), 5% Na_2CO_3 (100 mL), and brine (100 mL), and then it was dried over Na_2SO_4. After evaporation of the solvent, recrystallization of the residue from ethyl acetate and hexane (1:5) gave white crystals of (*S*)-2-[(benzyloxycarbonyl)amino]propan-1-yl mesyl ester (49.3 g, 97%): mp 101−103 °C; $[\alpha]^{21}_D$ −20.9° (*c* 1.05, CH_2Cl_2); ^{1}H NMR δ 1.22 (d, J = 6.9 Hz, 3H), 2.93 (s, 3H), 4.01 (m, 1H), 4.12 (m, 1H), 4.18 (m, 1H), 4.98 (brs, 1H), 5.07 (s, 2H), 7.28−7.34 (m, 5H); ^{13}C NMR δ 17.0, 37.2, 46.0, 66.8, 71.7, 128.1, 128.2, 128.5, 136.2, 155.5; IR (KBr plate) ν 3372, 3035, 1693, 1524, 1459, 1345 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_5S$: C, 50.16; H, 5.96; N, 4.87. Found: C, 50.40; H, 6.17; N, 4.90.

(*S*)-*N*-(Benzyloxycarbonyl)-α-phenylglycinol Mesyl Ester (2c). Lithium aluminum hydride (11.0 g, 257 mmol) was suspended in 500 mL of THF at 0 °C. (*S*)-Phenylglycine (20.0 g, 132 mmol) was added slowly in small portions. The reaction mixture was then heated at reflux overnight and then cooled to room temperature. Saturated K_2CO_3 was added slowly. Filtration and evaporation of solvent gave a yellow solid. The residue was recrystallized from hexanes and ethyl acetate (3:1) to give (*S*)-α-phenylglycinol as a yellow solid (17.7 g, 97%): ^{1}H NMR δ 2.33 (brs, 3H), 3.53 (dd, J = 8.3, 10.8 Hz, 1H), 3.71 (dd, J = 4.4, 10.8 Hz, 1H), 4.02 (dd, J = 4.3, 8.3 Hz, 1H), 7.2−7.4 (m, 5H).

(*S*)-α-Phenylglycinol (15.0 g, 0.11 mol) was dissolved in dichloromethane (170 mL) and 5% $NaHCO_3$ (200 mL). Benzyl chloroformate (21.6g, 0.12 mol) was then added. The reaction mixture was stirred at 20 °C overnight. The layers were separated, and the aqueous layer was extracted with dichloromethane (150 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The residue was recrystallized from hexane and ethyl acetate (~3:1) to give white needles of (*S*)-*N*-(benzyloxycarbonyl)-α-phenylglycinol (26.8 g, 90%): ^{1}H NMR δ 1.24 (brs, 1H), 3.85 (brm, 2H), 4.83 (brm, 1H), 5.08 (m, 2H), 5.48 (brs, 1H), 7.26−7.37 (m, 5H).

(*S*)-*N*-(Benzyloxycarbonyl)-2-phenylglycinol (20.0 g, 73.7 mmol) was dissolved in dichloromethane (250 mL) and triethylamine (11.7 mL, 84 mmol). This solution was cooled to 0 °C, and then mesyl chloride (6.3 mL, 81 mmol) was added. After 20 min of stirring at 20 °C, the solution was washed with 1 N HCl (100 mL), 5% Na_2CO_3 (100 mL), and brine (100 mL), and then it was dried over Na_2SO_4. After evaporation of the solvent, recrystallization of the residue from ethyl acetate and hexane (~1:3) gave white crystals of (*S*)-*N*-(benzyloxycarbonyl)-α-phenylglycinol mesyl ester (25.7 g, 98%): mp 132−134 °C; $[\alpha]^{21}_D$ +17.7° (*c* 1.42, CH_2Cl_2); ^{1}H NMR δ 2.82 (s, 3H), 4.4−4.5 (m, 1H), 5.0−5.1 (m, 3H), 5.42 (brs, 1H), 7.30−7.39 (m, 10H); ^{13}C NMR δ 37.3, 54.1, 67.1, 70.8, 126.6, 128.2, 128.5, 128.9, 136.0, 155.7; IR (KBr plate) ν 3337, 1690, 1542, 1342, 1285, 1254 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.66; H, 5.43; N, 3.96.

(*S*)-1,2-Propanediamine (3b). (*S*)-2-[(Benzyloxycarbonyl)amino]propan-1-yl mesyl ester (22.5 g, 78.3 mmol) was dissolved in toluene (150 mL) and water (200 mL). Sodium azide (40.7 g, 626 mmol) and (^{n}Bu)$_4$NBr (2.8 g) were added. The reaction mixture was then heated overnight at 85−90 °C. After the reaction mixture was cooled to room temperature, the aqueous layer was separated, and the organic layer was washed with phosphate buffer (pH ~5.4, 0.5 M, 60 mL × 2) and brine (60 mL) and dried over $MgSO_4$. Evaporation of the solvent gave (*S*)-2-[(benzyloxycarbonyl)amino]propan-1-yl azide as a yellowish oil (16.2 g, 88%). This azide was used for the next step without further purification: ^{1}H NMR δ 1.19 (d, J = 6.8 Hz, 3H), 3.29−3.50 (m, 2H), 3.91 (brs, 1H), 4.78 (brs, 1H), 5.09 (brs, 2H), 7.29−7.35 (m, 5H); ^{13}C NMR δ 18.1, 46.6, 55.8, 66.7, 128.0, 128.1, 128.4, 136.3, 155.5.

The azide (16.2 g, 69.2 mmol) was hydrogenated using MeOH−HCl (~3 M, 300 mL) as solvent and Pd/C (10%, 4.0 g) as catalyst under 90 psi of hydrogen. After the mixture was stirred at room temperature for 24 h, the catalyst was removed by filtration and the solvent was evaporated. Recrystallization (MeOH:ether 1:5) of the residue gave yellowish crystals of (*S*)-1,2-propanediamine·2HCl (8.1 g, 55.1 mmol, 79%). To these dried crystals, a powder of sodium hydroxide (18.0 g, 450 mmol) was added. Distillation of the mixture gave a colorless oil. This oil was dried over CaH_2 and distilled, giving a colorless oil (3.87 g, 95%). This material was identical in all respects to the same compounds reported in the literature.[22]

(*S*)-2-Phenyl-1,2-ethanediamine (3c). (*S*)-*N*-(Benzyloxycarbonyl)-α-phenylglycinol mesyl ester (20.0 g, 57.2 mmol) was dissolved in toluene (150 mL) and water (130 mL). Sodium azide (29.8 g, 458 mmol) and (^{n}Bu)$_4$NBr (2.0 g, 6.2 mmol) were added. The reaction mixture was then heated overnight at 85−90 °C. After the reaction mixture was cooled to room temperature, the layers were separated, and the organic layer was washed with phosphate buffer (pH ~5.4, 0.5 M, 60 mL × 2) and brine (60 mL) and dried over $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel (Et_2O:hexane 1:10), giving a yellowish oil of (*S*)-2-[(benzyloxycarbonyl)amino]-2-phenyl ethyl azide (12.0 g, 78%): ^{1}H NMR δ 3.63 (brm, 2H), 4.92 (brm, 1H), 5.10 (m, 2H), 5.33 (brm, 1H), 7.27−7.39 (m, 5H).

The azide (10 g, 37.1 mmol) was hydrogenated using MeOH−HCl (~3 M, 65 mL) as solvent and Pd/C (10%, 2.0 g) as catalyst under 90 psi of hydrogen. After the mixture was stirred at room temperature for 48 h, the catalyst was removed by filtration, and the solvent was evaporated. Recrystallization (MeOH:ether 1:3) of the residue gave yellowish crystals of (*S*)-2-phenyl-1,2-ethanediamine·2HCl (4.0 g, 78%). To these dried crystals was added a powder of sodium hydroxide (18.0 g, 450 mmol). Distillation of the mixture gave a colorless oil. This oil was dried over CaH_2 and distilled (oven 55−60 °C/0.1 mmHg), and a colorless oil was obtained (3.87 g, 95%): ^{1}H NMR (D_2O) δ 2.83 (d, J = 6.7 Hz, 2H), 3.87 (t, J = 6.7 Hz, 1H), 7.34−7.49 (m, 5H); ^{13}C NMR (D_2O) δ 51.2, 60.0, 129.7, 130.5, 131.8, 146.2.

(*S*)-4-Methyl-Δ^2-imidazoline (4b). The mixture of (*S*)-1,2-propanediamine (3.87 g, 52.2 mmol) and dimethylformamide dimethyl acetal (6.7 g, 52.9 mmol) was heated under argon at 60−65 °C overnight. The resulting yellowish oil was distilled (60−61/~0.1 mmHg) to give a colorless oil of (*S*)-4-methyl-Δ^2-imidazoline (3.91 g, 89%): ^{1}H NMR δ 1.14 (d, J = 6.4 Hz, 3H), 3.09 (dd, J = 7.4, 11.5 Hz, 1H), 3.63 (t, J = 10.2 Hz, 1H), 3.8−4.0 (m, 1H), 4.61 (brs, 1H), 6.96 (s, 1H); ^{13}C NMR δ 21.6, 55.4, 56.2, 135.5.

(*S*)-4-Phenyl-Δ^2-imidazoline (4c). The mixture of (*S*)-2-phenyl-1,2-ethanediamine (2.0 g, 15.0 mmol) and dimethylformamide dimethyl acetal (1.9 g, 15.0 mmol) was heated under argon at 60−65 °C overnight. A yellowish oil was obtained (2.2 g) and used for the next step without future purification: ^{1}H NMR δ 3.40 (ddd, J = 0.98, 8.7, 12.2 Hz, 1H), 3.95 (dd, 1H, J = 1.1, 11.0 Hz), 4.79 (dd, J = 8.7, 10.9 Hz, 1H), 5.01 (brs, 1H), 7.07 (s, 1H), 7.1−7.3 (m, 5H); ^{13}C NMR δ 58.4, 63.0, 126.1, 127.2, 128.5, 143.6, 154.3.

(*S*)-*N*-(Benzyloxycarbonyl)-4-methyl-Δ^2-imidazoline (5b). (*S*)-4-Methyl-Δ^2-imidazoline (3.5 g, 41.6 mmol) was dissolved in dichloromethane (60 mL) and triethylamine (5.0 g, 49.4 mmol). This reaction mixture was cooled to 0 °C, and then benzyl chloroformate (8.5 g, 47.3 mmol) was added. After being stirred at room temperature overnight, the solution was washed with 1 N HCl (30 mL), 5% Na_2CO_3 (30 mL), and brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a yellow oil that was chromatographed on silica gel (hexane/EtOAc 1:1) to give an unstable colorless oil (4.0 g, 44%): ^{1}H NMR δ 1.27 (d, J = 6.8 Hz, 3H), 3.22 (dd, J = 7.2, 10.3 Hz, 1H), 3.78 (t, J = 10.0 Hz, 1H), 4.23 (m, 1H), 5.20 (m, 2H), 7.31−7.37 (m, 5H), 7.48 (brs, 1H).

(*S*)-*N*-(Benzyloxycarbonyl)-4-phenyl-Δ^2-imidazoline (5c). (*S*)-4-Phenyl−Δ^2-imidazoline (2.2 g, 14.7 mmol) was dissolved in dichloromethane (30 mL) and triethylamine (1.7 g, 16.7 mmol). This reaction mixture was cooled to 0 °C, and then benzyl chloroformate (3.0 g, 16.7 mmol) was added. After being stirred at room temperature overnight, the solution was washed with 1 N HCl (30 mL), 5% Na_2CO_3 (30 mL), and brine

(22) Reihler, H.; Weinbrenner, E.; v. Hessling, G. *Ann. Chem.* **1932**, *494*, 43.

(30 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a yellow oil that was chromatographed on silica gel (hexane/EtOAc 1:1) to give a colorless oil (2.5 g, 61% from (*S*)-2-phenyl-1,2-ethanediamine): $[\alpha]^{21}_D$ −112.7° (*c* 1.85, CH_2Cl_2); ^{1}H NMR δ 3.58 (brt, J = 8.6 Hz, 1H), 4.11 (t, J = 10.7 Hz, 1H), 5.22 (s, 2H), 5.30 (brt, J = 9.1 Hz, 1H), 7.06−7.37 (m, 5H), 7.73 (brs, 1H); ^{13}C NMR δ 50.9, 67.8, 126.3, 127.4, 128.1, 128.4, 128.5, 128.6, 135.2, 141.2; IR (KBr) ν 1722, 1619, 1405, 1348, 1278, 1219, 1125 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.00; H, 5.92; N, 10.04.

2,6-Dimethyl-6-methoxyl-1,4-diazabicyclo[3.2.0]heptan-7-one (6b). Pentacarbonyl(methoxymethylcarbene)chromium(0) (680 mg, 2.7 mmol) and (*S*)-*N*-(benzyloxycarbonyl)-4-methyl-Δ^2-imidazoline (**5b**) (590 mg, 2.7 mmol), were dissolved in CH_2Cl_2 (20 mL) under argon in a Pyrex pressure tube. After three freeze-thaw degassings, the resulting red brown solution was irradiated with a 4 × 500 W halogen lamp under 90 psi of CO pressure at 70 °C. The progress of the reaction was indicated by the fading of the color. After the reaction, the solvent was evaporated. The residue was triturated with MeOH and kept for a few hours at −20 °C. Filtration of chromium hexacarbonyl, evaporation of MeOH, and purification by chromatography on silica gel gave the *N*-(benzyloxycarbonyl)azapenam (190 mg, 23%): ^{1}H-NMR δ 1.16, 1.18, (2d, J = 3.3 Hz, 3H), 1.55, 1.57 (2s, 3H), 3.46 (brs, 3H), 3.3−3.5 (m, 1H), 3.95−4.15 (m, 1H), 5.0−5.3 (m, 3H), 7.2−7.4 (m, 5H). Because of the low yield this material was not further studied.

6-Methoxy-6-methyl-2-phenyl-1,4-diazabicyclo[3.2.0]-heptan-7-one (6c). Pentacarbonyl(methoxymethylcarbene)-chromium(0) (270 mg, 1.1 mmol) and (*S*)-*N*-(benzyloxycarbonyl)-4-phenyl-Δ^2-imidazoline (**5c**) (300 mg, 1.1 mmol) were dissolved in CH_2Cl_2 (20 mL) under argon in a Pyrex pressure tube. After three freeze-thaw degassings, the resulting red brown solution was irradiated with a mercury lamp under 90 psi of CO pressure at 30 °C. The progress of the reaction was indicated by the fading of the color. After the reaction, the solvent was evaporated. The residue was triturated with MeOH and kept for a few hours at −20 °C. Filtration of chromium hexacarbonyl, evaporation of MeOH, and purification by chromatography on silica gel gave the crude *N*-(benzyloxycarbonyl)-azapenam in 35% yield (137 mg). This material was impure and because of the low yield was not further studied.

(2*S*,4*S*)-3-Benzoyl-4-methyl-2-phenyl-1,3-oxazolidin-5-one (7a).[15b] (*S*)-Alanine (32.9 g, 370 mmol) was added into a solution of NaOH (15.1 g, 370 mmol) in H_2O (50 mL), and methanol (250 mL) was added to this solution. The solution was heated until the solid dissolved, and then the solvent was evaporated until precipitation began (∼30 mL). The residue was dissolved in ethanol (250 mL), and benzaldehyde (59 g, 556 mmol) was added. This mixture was stirred at room temperature for 3 h. The ethanol and most of water was removed under vacuum, and the residue was dissolved in ethanol (200 mL) and dried over 4 Å molecular sieves. Filtration and evaporation of the solvent gave a white solid that was dried in vacuo overnight. This solid was suspended in dichloromethane (500 mL), and a solution of benzoyl chloride (52.0 g, 370 mmol) in dichloromethane (100 mL) was added dropwise at 0 °C. After 3 h, the reaction mixture was allowed to stir at room temperature overnight. This turbid mixture was washed with H_2O, 5% $NaHCO_3$, 5% of $NaHSO_3$, and H_2O again and then dried over Na_2SO_4. Evaporation of the solvent gave a white solid. Fractional recrystallizations of this solid from CH_2Cl_2 and ether (1:2) gave white crystals of (2*S*,4*S*)-3-benzoyl-4-methyl-2-phenyl-1,3-oxazolidin-4-one (60 g, 58%): $[\alpha]^{21}_D$ +225° (lit[15b] $[\alpha]^{21}_D$ +225.0°). This material was identical in all respects to the same compound reported in the literature.

(2*S*,4*S*)-3-Benzoyl-4-methyl-4-(phthalimidomethyl)-2-phenyl-1,3-oxazolidin-5-one (8). Into a solution of hexamethyldisilazane (17.5 g, 106 mmol) in THF (100 mL) was added *n*-butyllithium (1.58 M in hexane, 50 mL, 78.5 mmol) −78 °C. After 5 min at −78 °C, the solution was allowed to warm to 0 °C for 30 min and then cooled to −78 °C again. A solution of (2*S*,4*S*)-3-benzoyl-4-methyl-2-phenyl-1,3-oxazolidin-5-one (dried overnight in vacuo before using, 20 g, 71 mmol) in THF (250 mL) was added slowly under argon, and the dark red brown solution was stirred at this temperature for 3 h. A solution of *N*-(bromomethyl)phthalimide (22.2 g, 92.5 mmol) in THF (200 mL) was then added dropwise. The reaction mixture was allowed to warm to 20 °C in 4 h and stirred at this temperature overnight. The solvent was evaporated. The residue was dissolved in 10% NH_4Cl (250 mL) and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated. Recrystallization from CH_2Cl_2 and ether (1:4) gave a white crystal (23 g, 74%) of (2*S*,4*S*)-3-benzoyl-4-methyl-4-(phthalimidomethyl)-2-phenyl-1,3-oxazolidin-5-one: mp 204−205 °C; $[\alpha]^{21}_D$ +220° (*c* 1.12, $CHCl_3$); ^{1}H NMR δ 2.21 (s, 3H), 4.32 (d, J = 14.3 Hz, 1H), 4.78 (d, J = 14.4 Hz, 1H), 6.45 (s, 1H), 6.85 (s, 1H), 6.87 (s, 1H), 7.0−7.3 (m, 8H), 7.76−7.79 (m, 2H), 7.90−7.95 (m, 2H); ^{13}C NMR δ 23.3, 42.1, 63.1, 90.4, 123.8, 126.1, 126.8, 128.3, 128.5, 129.7, 129.8, 131.7, 134.4, 136.0, 136.2, 168.0, 169.4, 172.2; IR (KBr plate) ν 1799, 1720, 1657, 1394, 1356, 1227, 1175 cm^{-1}. Anal. Calcd for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36. Found: C, 71.09; H, 4.50; N, 6.43. From the mother liquor, (2*S*,4*R*)-3-benzoyl-4-methyl-4-(phthalimidomethyl)-2-phenyl-1,3-oxazolidin-5-one was obtained (3g, 9.4%).

(*S*)-α-Aminomethylalanine Methyl Ester (9). A solution of (2*S*,4*S*)-3-benzoyl-4-methyl-4-(phthalimidomethyl)-2-phenyl-1,3-oxazolidin-5-one (**8**) (21 g, 0.5 mol) in 48% of HBr (200 mL) was heated at reflux (120 °C oil bath) overnight. After being washed with dichloromethane, the solution was evaporated to give a brownish white crystalline material (14.5 g) of crude diamino acid dihydrobromide salt.

Thionyl chloride (60 g, 0.50 mmol) was added to methanol (130 mL) at −10 °C slowly, and then the solution was stirred at room temperature for 30 min. Diamino acid dihydrobromide salt was added, and the solution was heated at reflux overnight. Evaporation of the solvent followed by drying under vacuum gave a yellowish foam. This residue was dissolved in CH_2Cl_2 (50 mL), and triethylamine (30 mL) was added. The solvent was evaporated, and the residue was dissolved in THF (100 mL). Filtration and evaporation gave a red yellow oil that was distilled rapidly. The colorless distillate was dissolved in CH_2Cl_2 (15 mL) and dried over CaH_2. Evaporation of solvent and distillation gave a colorless oil (4.9 g, 77%). It is essential that this diamine be absolutely dry to ensure good yields in the next step. Dryness was assessed by comparing the integration of the OMe peak at 3.73 with the NH_2 peak at 1.5, which also contained H_2O peaks. If this ratio exceeded 4:3, the product was redried and redistilled: bp 58−61 °C/vacuum (0.05−0.01 mmHg); $[\alpha]^{21}_D$ −6.4° (*c* 1.12, $CHCl_3$); ^{1}H NMR δ 1.27 (s, 3H), 1.52 (s, 4H), 2.64 (d, 1H, J = 5.6 Hz), 3.01 (d, 1H, J = 5.6 Hz), 3.73 (s, 3H); ^{13}C NMR δ 24.2, 51.0, 52.2, 59.3, 177.6; IR(KBr) ν 3294, 2953, 1731, 1592, 1458, 1212 cm^{-1}.

(*S*)-*N*-(Benzyloxycarbonyl)-4-methyl-4-carbomethoxy-Δ^2-imidazoline (10). As solution of CH_2Cl_2 (50 mL), (*S*)-α-aminomethylalaninemethyl ester (**9**) (4.1 g, 31 mmol) and dimethylformamide dimethyl acetal (3.9 g, 31 mmol) was heated at reflux under argon at 55−60 °C for 6 h. Evaporation of solvent gave a yellowish oil of 4-(methoxycarbonyl)-4-phenyl-Δ^2-imidazoline (crude ∼6 g), which was used for the next step without purification.

4-Methyl-4-carbomethoxy-Δ^2-imidazoline was dissolved in dichloromethane (50 mL) and triethylamine (16 g, 0.15 mol). This reaction mixture was cooled to 0 °C, and then benzyl chloroformate (6.1 g, 34 mmol) was added slowly. After being stirred 1 h at 0 °C and 4 h at room temperature, the solution was washed with 1 N HCl, 5% Na_2CO_3, and brine and dried over Na_2SO_4. Evaporation of the solvent gave a yellow oil that was chromatographed on silica gel (hexane/Et_2O 1:1) to give a yellowish oil (6.1 g, 70%): $[\alpha]^{21}_D$ −115° (*c* 1.05, ether); ^{1}H NMR δ 1.53 (s, 3H), 3.51(d, J = 4.8 Hz, 1H), 3.76 (s, 3H), 4.17 (d, J = 4.8 Hz, 1H), 5.22 (s, 2H), 7.29−7.38 (m, 5H), 7.57 (brs, 1H); ^{13}C NMR δ 25.5, 52.3, 52.7, 68.0, 128.3, 128.4, 128.5, 128.5, 134.9, 172.8; IR (KBr) ν 1729, 1617, 1407 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.60; H, 5.59; N, 9.94.

(2*S*,5*R*,6*S*)-2,6-Dimethyl-6-methoxy-2-carbomethoxy-1,4-diazabicyclo[3.2.0]-heptan-7-one (11). Pentacarbonyl-(methoxymethylcarbene)chromium(0) (360 mg, 1.4 mmol) and

(*S*)-*N*-(benzyloxycarbonyl)-4-(methoxycarbonyl)-4-methyl-Δ^2-imidazoline (**10**) (360 mg, 1.3 mmol) were dissolved in CH_2Cl_2 (20 mL) under argon in a Pyrex pressure tube. After three freeze-thaw degassings, the resulting red brown solution was irradiated with 4 × 500-W halogen lamps (work lamps, Ace Hardware, Fort Collins, CO) under 90 psi of CO pressure at 70 °C. The progress of the reaction was indicated by the fading of the color. After the reaction, the solvent was evaporated. The residue was triturated with MeOH and kept for a few hours at −20 °C. Filtration of chromium hexacarbonyl, evaporation of MeOH, and purification by chromatography on silica gel gave the *N*-(benzyloxycarbonyl)azapenam as a single diastereomer (354 mg, 75%): ^{1}H-NMR δ 1.22, 1.33 (2s, 3H), 1.80 (s, 3H), 3.25 (d, J = 5.1 Hz, 1H), 3.40,3.51 (2s, 3H), 3.73 (s, 3H), 4.37 (d, J = 5.1 Hz, 1H), 5.10−5.30 (m, 3H), 7.46 (s, 5H); IR (KBr) ν 1782, 1741, 1714, 1411 cm^{-1}.

The *N*-(benzyloxycarbonyl)azapenam (260 mg, 0.72 mmol) was dissolved in methanol (10 mL) and triethylamine (2 mL). Hydrogenation with palladium on carbon(100 mg) at 80 psi for 3 h, filtration through washed Celite, and evaporation of the solvent gave the corresponding azapenam (155 mg, 95%): $[\alpha]^{21}_D$ −211° (*c* 1.09, CH_2Cl_2); ^{1}H NMR δ 1.27 (s, 3H), 1.73 (s, 3H), 2.32 (brs, 1H), 2.65 (d, J = 5.3 Hz, 1H), 3.46 (s, 3H), 3.64 (d, J = 5.3 Hz, 1H), 3.72 (s, 3H), 4.85 (s, 2H); ^{13}C NMR δ 14.0, 16.9, 52.3, 53.0, 60.3, 65.8, 79.0, 90.1, 171.7, 174.9; IR (KBr plate) ν 3374, 1738, 1666 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.44; H, 7.25; N, 12.14.

(2*S*,6*S*,9*S*,13*S*)-6,13-Dimethoxy-2,6,9,13-tetramethyl-2,9-dicarbomethoxy-1,4,8,11-tetraazacyclotetradecane-5,12-dione (12). The azapenams **11** (100 mg) and a catalytic amount (10 mg) of racemic camphorsulfonic acid in CH_2Cl_2 (10 mL) were stirred 2 h at 80 °C. The solution washed with 5% $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent gave the cyclic diimines. The cyclic diimine, $NaBH_3$-CN (30 mg, 0.48 mmol), and a small amount of bromocresol green were dissolved in MeOH (15 mL)/CH_2Cl_2 (15 mL) at 0 °C. HCl (1 N)/MeOH was added dropwise until a yellow-green color remained, and the resulting solution was warmed to room temperature and stirred 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 of dioxocyclam that was purified by radial layer chromatography (Si gel, 1:1 ether/ethyl acetate) (85 mg, 85%): mp 173−174 °C; $[\alpha]^{21}_D$ +25° (*c* 0.5, CH_2Cl_2); ^{1}H NMR δ 1.27 (s, 6H), 1.59 (s, 6H), 2.60−2.81 (m, 8H), 3.25(s, 6H), 3.81 (s, 6H), 7.90 (brs, 2H); ^{13}C NMR δ 18.3, 21.2, 50.0, 52.8, 53.0, 54.8, 61.3, 79.9, 172.0, 174.5; IR (KBr) ν 2958, 2835, 1738, 1681, 1520, 1454, 1262 cm^{-1}. Anal. Calcd for $C_{20}H_{36}N_4O_8$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.25; H, 8.09; N, 12.21.

Bisazapenam (14). Bis-chromium alkoxycarbene complex (**13**)[14] (1.9 g, 2.6 mmol) and (*S*)-*N*-(benzyloxycarbonyl)-4-(methoxycarbonyl)-4-methyl-Δ^2-imidazoline (**10**) (1.5 g, 5.4 mmol) were dissolved in CH_2Cl_2 (110 mL) under argon in a Pyrex pressure tube. After three freeze-thaw degassings, the resulting red brown solution was irradiated with 4 × 500W halogen lamps under 90 psi of CO pressure at 70 °C. The progress of the reaction was indicated by the fading of the color. After the reaction, the solvent was evaporated. The residue was triturated with MeOH, and kept for a few hours at −20 °C. Filtration of chromium hexacarbonyl, evaporation of MeOH, and purification by radial layer chromatography (ether:hexane 1:1) gave the *N*-(benzyloxycarbonyl)bisazapenam as a single diastereomer (1.4 g, 75%): ^{1}H-NMR δ 1.22, 1.33 (2s, 3H), 1.80 (s, 3H), 3.25 (d, J = 5.1 Hz, 1H), 3.40, 3.51 (2s, 3H), 3.73 (s, 3H), 4.37 (d, J = 5.1 Hz, 1H), 5.10−5.30 (m, 3H), 7.46 (s, 5H); IR (KBr) ν 1782, 1741, 1714, 1411 cm^{-1}.

The *N*-(benzyloxycarbonyl)bisazapenam (1.0 g, 1.36 mmol) was dissolved in methanol (20 mL) and triethylamine (5 mL). Hydrogenation with palladium on carbon (300 mg) at 80 psi for 3 h, filtration through washed Celite, and evaporation of the solvent gave the corresponding bisazapenam (**14**) (605 mg, 95%): $[\alpha]^{21}_D$ −177° (*c* 1.01, CH_2Cl_2); ^{1}H NMR δ 1.19 (s, 3H), 1.63 (s, 3H), 1.76 (brt, 2H), 2.43 (brs, 2H), 2.55 (d, J = 5.3 Hz, 2H), 3.63 (s, 3H), 3.45−3.75 (m, 6H), 4.78 (s, 2H); ^{13}C NMR δ 14.4, 17.1, 29.9, 52.5, 60.52, 61.7, 66.0, 79.8, 89.6, 171.9, 175.3; IR (KBr) ν 3352, 2951, 1759, 1742 cm^{-1}. Anal. Calcd for $C_{21}H_{32}N_4O_8$: C, 53.84; H, 6.88; N, 11.96. Found: C, 53.65; H, 6.70; N, 11.76.

Bis-dioxocyclam (16). The bisazapenam (**14**) (400 mg, 0.85 mmol) and a catalytic amount (10 mg) of racemic camphorsulfonic acid in CH_2Cl_2 (50 mL) were stirred for 2 h at 80 °C. The solution was washed with 5% $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent gave the bis-cyclic diimine (**15**) (270 mg, 67%). The bis-cyclic diimine, $NaBH_3$-CN (220 mg, 3.5 mmol), and a small amount of bromocresol green were dissolved in MeOH (20 mL)/CH_2Cl_2 (20 mL) at 0 °C. HCl (1 N)/MeOH was added dropwise until a yellow-green color remained, and the resulting solution was warmed to room temperature and stirred 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 of bis-dioxocyclam, which was purified by radial layer chromatography (Si gel, 1:1 ether/ethyl acetate) (230 mg, 85%): mp 245 °C dec; $[\alpha]^{21}_D$ −0.4° (*c* 4.8, CH_2Cl_2); ^{1}H NMR δ 1.26 (s, 12H), 1.57 (s, 12H), 1.65 (s, 4H), 1.96 (quint, J = 3.2 Hz, 4H), 1.7−2.9 (m, 12H), 3.28 (dd, J = 3.2, 5.2 Hz, 4H), 3.35−3.55 (m, 8H), 3.78 (s, 12H), 8.35 (s, 4H); ^{13}C NMR δ 19.5, 20.3, 31.6, 52.9, 53.7, 54.9, 59.9, 60.8, 79.6, 172.4, 174.4; IR (KBr) ν 3391, 2950, 1738, 1676, 1519, 1451 cm^{-1}. Anal. Calcd for $C_{42}H_{72}N_8O_{16}$: C, 53.38; H, 7.68; N, 11.86. Found: C, 53.32; H, 7.48; N, 12.02.

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 No. GM49631.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds not characterized by elemental analyses (12 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.

JO962343E