Enantioselective Synthesis of Substituted Pipecolic Acid Derivatives

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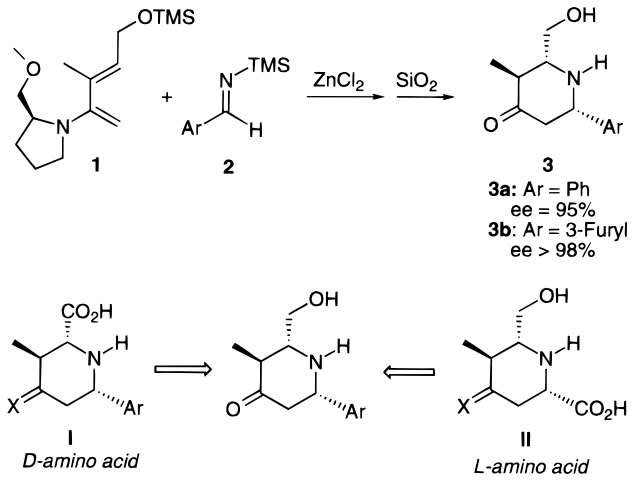
Enantiomerically pure 4-piperidones, prepared by asymmetric [4 + 2] Diels−Alder cycloadditon of chiral 2-aminodienes with imines, have been used as starting materials for the synthesis of several derivatives of pipecolic acid. The α-amino acid moiety is obtained after the oxidation of a hydroxy group or a furan ring of a conveniently protected 2-aryl-6-(hydroxymethyl)-4-piperidone. Depending on the starting piperidone and the synthetic strategy, it is possible to obtain D- or L-functionalized pipecolic acid derivatives by a short synthetic procedure. Moreover, a stereoselective epimerization of the α-carbon atom of a particular pipecolate allows for the preparation of both *cis*- and *trans*-6-(hydroxymethyl)pipecolic acids, structures related with dipeptide isosteres.

Molecules with rigid frameworks containing the α-amino acid moiety are attractive synthetic targets since they can be used as conformationally restricted modules in the design of new peptidomimetic structures with biological activity.[1] In this context, a naturally occurring example is found in the piperidine-based structure of pipecolic acid,[2] a nonproteinogenic α-amino acid, and its derivatives, which are present in a number of natural and synthetic compounds with biological activity.[3] Moreover, substituted pipecolic acids have been employed as key intermediates in the synthesis of different types of other piperidine natural products.[4] In particular, enantiomerically pure pipecolates have been used as synthetic precursors of indolizidine alkaloids.[4c] For these reasons, the asymmetric synthesis of substituted pipecolic acid derivatives constitutes an interesting synthetic objective that has attracted significant attention in recent years.[5]

We have recently reported the enantioselective synthesis of functionalized 4-piperidones **3** by [4 + 2] cycloaddition of *N*-silylaldimines **2** with chiral 2-amino-1,3-butadienes **1** (Scheme 1),[6] a reaction that proceeds with good yields and very high enantiomeric excesses. Due to the high functionalization of the resulting piperidones **3**, we envisioned them as potential precursors

Scheme 1



of different families of enantiomerically pure pipecolic acid derivatives **I** and **II**. These compounds are conformationally restricted α-amino acids which have the α-amino acid structure included not only in a six-membered ring but also in a sterically demanding environment. These compounds offer further interest as synthetic precursors of natural products. For instance, a structure closely related with these amino acids is found in the piperidine A-ring of the marine hepatotoxin cylindrospermopsin.[7] In fact, pipecolates with the same sterochemistry and similar functionality as some of the

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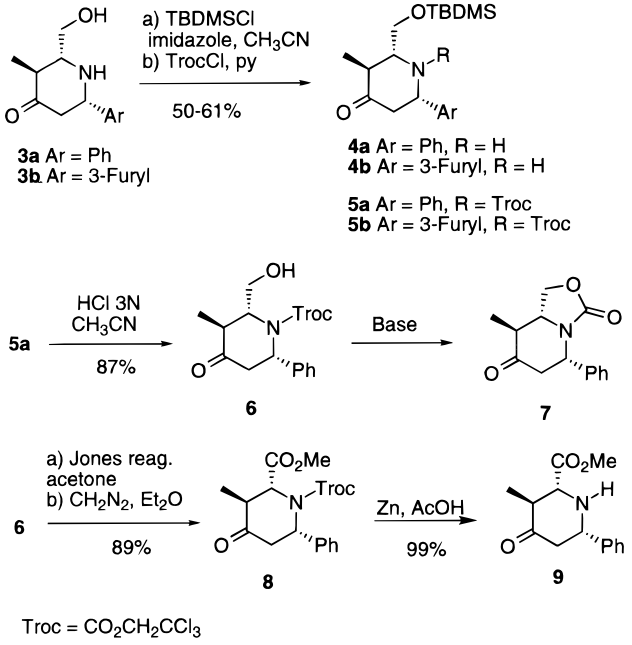
Scheme 2



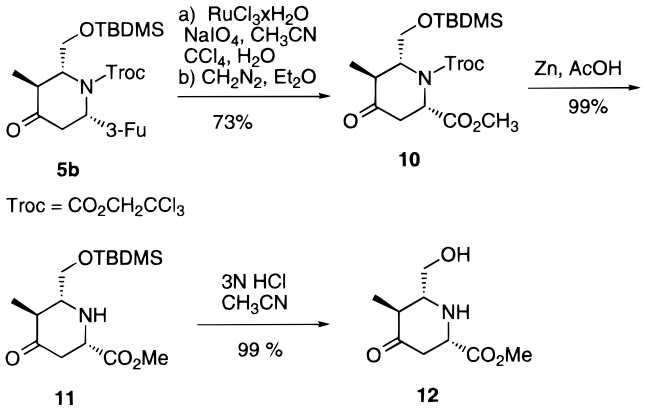
compounds described in the present paper have been proposed by Weinreb et al. as key compounds in the synthesis of this marine alkaloid.[8] In this paper we report our efforts regarding the synthesis of these classes of pipecolates.

As depicted in Scheme 1, the selection of the proper subtituents in the starting piperidone and the subsequent synthetic pathway can allow for the preparation of both families of pipecolic acids. Thus, oxidation of the hydroxy group in **3** will lead to derivatives of type **I**, while oxidative degradation of an aromatic ring, typically a furan, will furnish type **II** amino acids. Moreover, amino acids **I** and **II**, obtained from 4-piperidones, will have opposite absolute configurations (D or L) on the α-carbon atom.

A key step in the conversion of piperidones **3** into pipecolates is the orthogonal protection of both hydroxy and amino functionalities. The hydroxy group was selectively protected as TBDMS ether (*tert*-butyldimethylsilyl chloride, imidazole, CH_3CN, rt, overnight). Protection of the amino group, however, was not trivial, probably due to the steric hindrance around the N−H functionality, and reaction with classic protecting reagents did not proceed (Boc_2O) or proceeded with very low conversion and only under harsh conditions (CbzCl). Nevertheless, excellent results were obtained by treatment of piperidones **4** with 2,2,2-trichloroethyloxycarbonyl chloride (TrocCl) in pyridine to furnish fully protected derivatives **5**,[9] which were used in the synthesis of both types of amino esters (Schemes 2 and 3).

We approached type **I** compounds from piperidone **3a**, available in 95% ee, as starting material. After the protection described above, the *tert*-butyldimethylsilyl ether is selectively cleaved by treatment of a solution of **5a** in CH_3CN with aqueous 3 N HCl (rt, 3 h). Hydroxy compound **6** is stable in organic solvents or acidic media.

Scheme 3



However, in the presence of traces of base it undergoes cyclization to yield the undesired bicyclic carbamate **7**.[10] Oxidation of **6** with Jones reagent, followed by esterification with diazomethane, yielded fully protected pipecolate **8**. Finally, cleavage of the Troc protective group was performed in quantitative yield by treatment with zinc dust in AcOH to furnish the first compound of these series, D-methyl ketopipecolate **9** (Scheme 2).

For a type **II** amino acid, we decided to use a furan ring as a masked carboxylate group. The required 4-piperidone **3b** was obtained in ee > 98%. After the same protective group strategy, the furan ring of compound **5b** was transformed into a carboxylic acid by oxidation with $RuCl_3 \cdot H_2O/NaIO_4$ using the Sharpless procedure.[11] The crude acid was converted into carboxylic ester **10** by treatment with diazomethane in diethyl ether. Deprotection of the amino group was again performed by treatment with zinc dust in acetic acid to obtain ketopipecolic ester **11**, and cleavage of the TBDMS group was carried out by treatment with aqueous HCl to yield methyl L-(hydroxymethyl)ketopipecolate **12** (Scheme 3).

As an alternative method, we believed the synthesis of hydroxyamino acid derivatives such as **12** might be approached in a more straightforward way by simultaneously protecting the amino and hydroxy groups as a cyclic carbamate. In fact, this transformation was carried out in nearly quantitative yield by treatment of **4b** with triphosgene and triethylamine in THF to yield the bicyclic carbamate **13** (Scheme 4). To avoid undesired epimerizations on the stereocenter bearing the methyl group, the carbonyl functionality was stereoselectively reduced with K-Selectride (THF, −80 °C, 90 min) to give hydroxy compound **14**, which was alkylated with BnBr (NaH, DMF, reflux) to give bicyclic carbamate **15**.[12]

The furan ring was then transformed into a carboxylic acid by oxidation. This time the transformation was carried out by ozonolysis in the presence of H_2O_2, which turned out to be much more convenient than the $RuCl_3$ oxidation. Esterification of the crude acid was carried out either by treatment with diazomethane in ether to furnish methyl ester **16a** or by formation of the corresponding acid chloride (oxalyl chloride, CH_2Cl_2, reflux, 4

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(12) A detailed NMR study of the configuration of the new stereocenter created in the reduction step can be found in a previous publication (see ref 6b).

Scheme 4

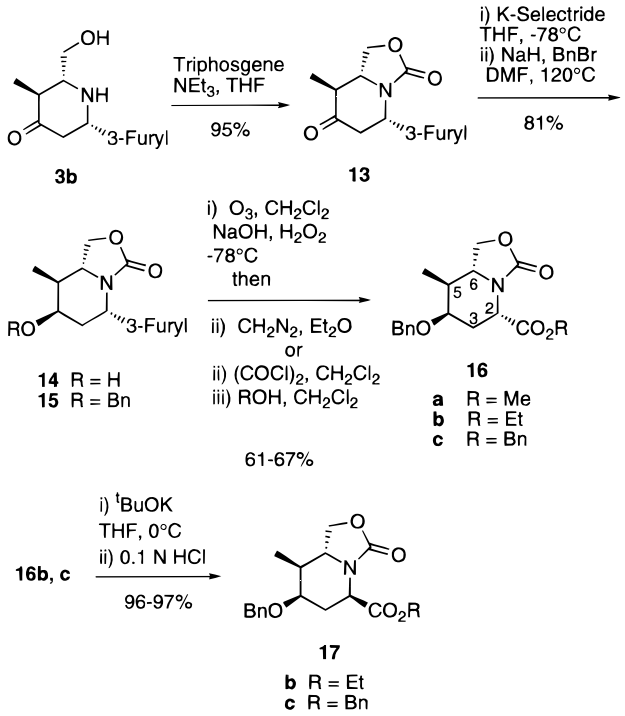
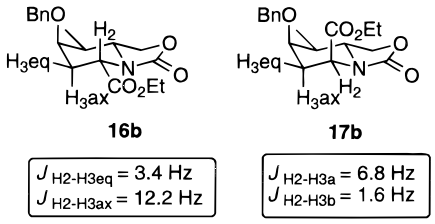


Chart 1

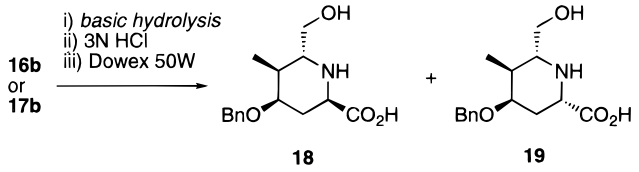


h) followed by treatment with a primary alcohol to yield esters **16b**,**c**.

In our synthetic strategy we had planned to open the cyclic carbamate by treatment with ^{t}BuOK in anhydrous THF at 0 °C, a method that had proven useful previously for similar systems.[13] However, when esters **16** were subjected to these conditions, the bicyclic system was not cleaved. Instead, epimerization of the amino ester occurred affording new bicyclic ester **17** as a single diastereoisomer. The stereochemical configuration of these new compounds was established based on the values of the coupling constants in the ^{1}H NMR spectra for compounds **17** and by comparison with the corresponding couplings of compounds **16**. For example, for ester **16b** (Chart 1) the equatorial arrangement of the ester group at C-2 is indicated by the large axial−axial coupling constant between H_2 and H_{3ax} (J_{H2-H3} = 12.2 Hz). On the other hand, for **17b** no axial−axial coupling constants were observed between H_2 and the hydrogens at C-3 (J_{H2-H3a} = 6.8 Hz, J_{H2-H3b} = 1.6 Hz), which suggests that the ester group must be in the axial position. Moreover, the large coupling constant between H_5 and H_6 (J_{H5-H6} = 10.1 Hz) confirms the equatorial−equatorial cis relationship of the substituents at C-5 and C-6.

The ring opening of cyclic carbamates such as **16** usually requires harsh conditions (typically concentrated NaOH or KOH solutions).[14] When this procedure was examined for our system (6 N NaOH, MeOH, reflux overnight) we obtained, as expected, the desired hydroxyamino acid, but as a 1:1 mixture of the C-2 epimers **18** and **19** (Scheme 5). In this case, equilibration of the stereocenter at C-2 had taken place. Better results were obtained with ^{t}BuOK, but in refluxing THF. Thus, refluxing a solution of **17a**,**b** and ^{t}BuOK in THF for 1 h afforded a 6:1 mixture of epimeric amino acids **18** and **19** (Scheme 5). As expected, an identical mixture was obtained when **16a**,**b** were treated under the same conditions. Clearly, under strongly basic conditions both the ester and carbamate functionalities are cleaved, but an unselective epimerization at C-2 simultaneously occurs.

Scheme 5



basic hydrolysis	**18**	:	**19**
6N NaOH, MeOH, 8h, reflux	1		1
^{t}BuOK, THF, 1h, reflux	6		1

Ratio **18: 19** depending on the hydrolytic conditions

It seemed that in order to obtain amino acids **18** or **19** as pure stereoisomers it was crucial to avoid or control the epimerization process. To this purpose we decided to perform the same reaction on the carboxylic acid instead of the ester. The lower acidity of the α-hydrogen in the carboxylic salt compared with the ester should prevent the epimerization induced by bases. To carry out this reaction it was a prerequisite to obtain the carboxylic acid as a pure compound, which could be easily attained by purification of ester **16** and further deprotection of the carboxylic ester. Initial attempts at basic hydrolysis of the methyl ester **16a** led to mixtures of epimers, and therefore we prepared the benzyl ester **16c**, cleavable under neutral conditions by hydrogenolysis. In fact, after chromatography purification of **16c**, the ester functionality was cleanly cleaved by hydrogenation in EtOH in the presence of Pd/C to obtain pure carboxylic acid **20** as a single stereoisomer (Scheme 6). To our delight, when acid **20** was refluxed in THF in the presence of ^{t}BuOK, (hydroxymethyl)pipecolic acid **19** was obtained as a single diastereoisomer. No epimerization had occurred. Moreover, interestingly, when ester **17c** (coming from the epimerization of **16c**) was subjected to the same sequence—hydrogenation to obtain acid **21** and cleavage of the carbamate—(hydroxymethyl)pipecolic acid **18** was obtained, also as a single stereoisomer. A method, therefore, has been developed that allows for the diastereo- and enantioselective syntheses of both *cis*- and *trans*-D and L-6-(hydroxymethyl)pipecolic acids **18** and **19** from the same starting material.

In conclusion, we have described the diastereo- and enantioselective syntheses of a variety of pipecolic acid derivatives from easily available optically active 4-pip-

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Scheme 6

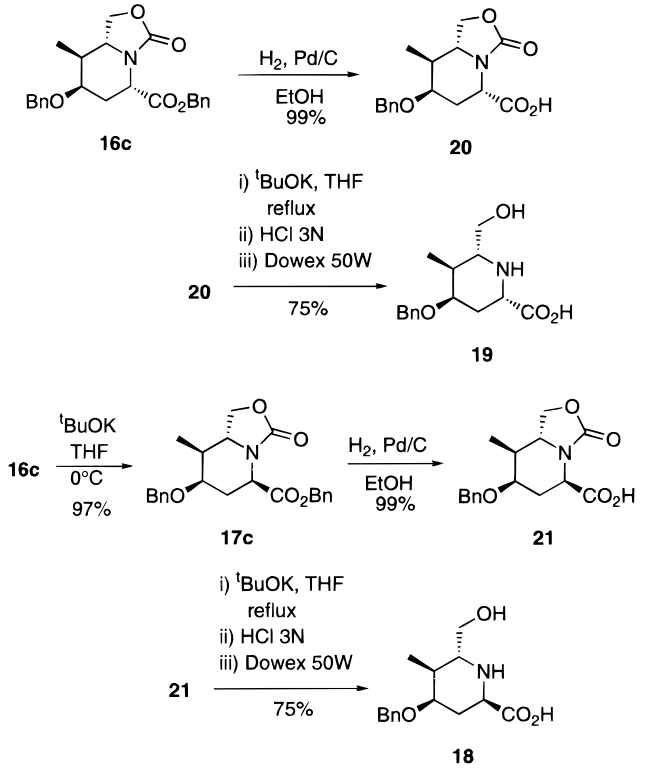
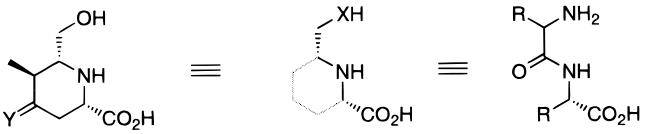


Chart 2



dipeptide isostere

eridones. It is worth pointing out that hydroxyamino acids **18** and **19** and also hydroxyamino ester **12** are conformationally constrained dipeptide isosteres[15] in which the R group and a carbonyl group in the original dipeptide are replaced by the six-membered ring (Chart 2). On the other hand, structure **9** features the amino acid moiety in a sterically crowded environment. We are currently pursuing the synthesis of new compounds of these families, to study their potential application in the design of peptidomimetics with defined and predictable conformations. Moreover, hydroxyamino acid **19** and ester **16** have the same substitution and sterochemistry as the A-ring of cylindrospermopsin and can therefore be used as intermediates in developing a total synthesis of this marine hepatotoxin. Finally, it should be noted that the absolute configuration of the compounds described in this paper derives from the chiral auxiliary ((*S*)-prolinol) used in the cycloaddition step (Scheme 1). Since (*R*)-prolinol, although more expensive, is also commercially available, the enantiomers of those compounds are also accessible by these synthetic routes.

Experimental Section

General. All reactions were carried out under N_2 employing solvents dried following standard procedures.[16] For isolation, organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Column chromatography was carried out using 230−400 mesh silica gel. TLC analyses were performed on silica gel 60 F_{254} plates, and compounds were visualized with UV light and by spraying with acidic $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O/Ce(SO_4)_2$ solution. ^{1}H NMR spectra were recorded at 200 or 300 MHz at room temperature employing $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ peak; *J* values are given in Hz. ^{13}C NMR spectra were performed at 50 or 75 MHz. 4-Piperidones **3** were prepared as described in ref 6.

Synthesis of Aminodiene 1. This procedure is an optimization of the methodology that we have reported previously. Mercury(II) acetate (9.56 g, 30 mmol) was placed in a Schlenck flask containing a magnetic stirring bar and was heated to 100 °C under vacuum (10^{-3} Torr) for 4 h. The heat was removed, and the flask was allowed to cool to room temperature and filled with dry nitrogen. Dry THF (90 mL) and 3-methyl-5-[(trimethylsilyl)oxy]-3-penten-1-yne (5.05 g, 30 mmol) were added to the flask successively, and the mixture was stirred for 5 min. Dry diisopropylamine (10.5 g, 75 mmol) was added to the mixture, and the stirring was continued for 15 min. Dry 2-(methoxymethyl)pyrrolidine was added to the solution, and the reaction was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum (do not use water aspirator!) until the solid formed made stirring difficult. The flask was filled with dry nitrogen, and 60 mL of dry hexanes was added to the mixture. After the suspension was stirred and shaken for 30 min, the solution was filtered under a dry atmosphere and the solid was washed with additional dry hexanes (2 × 50 mL). The filtrates were combined and concentrated to 40 mL of solution. The resulting mixture was kept under a dry atmosphere at −20 °C for 10 h. The clear solution was separated from the solid by cannula and concentrated under vacuum. The oily liquid so obtained is essentially pure aminodiene that can be further purified by bulb-to-bulb distillation under vacuum (10^{-3} Torr, preheated oil bath 130 °C, bp 75−85 °C) to give 5.6 g (67%) of aminodiene **1**.

Synthesis of Piperidones 3. Compounds **3** were prepared as described in ref 6b.

Silylation of the Hydroxy Group of 4-Piperidones 3. Synthesis of Piperidones 4. To a solution of 4-piperidone **3** (3.0 mmol) in acetonitrile (20 mL) at room temperature were added imidazole (9.0 mmol, 613 mg) and *tert*-butyldimethylchlorosilane (9.0 mmol, 1.36 g). The resulting solution was stirred overnight, and the reaction was quenched with H_2O (7 mL) and EtOAc (7 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting orange oil was purified by column chromatography.

(−)-(2*R*,3*S*,6*S*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-methyl-6-phenyl-4-piperidone, 4a. Piperidone **3a** (658 mg) was employed as starting material. The silylated compound **4a** was isolated in 65% yield (650 mg). For spectroscopic data, see ref 6b; ee = 95%; $[\alpha]^{18}_D = -78$ (*c* 0.8, $CHCl_3$).

(−)-(2*R*,3*S*,6*S*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-(3-furyl)-3-methyl-4-piperidone, 4b. Piperidone **3b** (628 mg) was employed as starting material. The silylated compound **4b** was isolated in 69% yield (670 mg). For spectroscopic data, see ref 6b; ee > 98%; $[\alpha]^{18}_D = -33$ (*c* 0.5, $CHCl_3$).

Protection of the Amino Group of 4-Piperidones 4. Synthesis of *N*-Troc-Protected Piperidones 5. To a solution of the corresponding silylated 4-piperidone **4** (1.8 mmol) in pyridine (15 mL) cooled to 0 °C was added 2,2,2-trichloroethyl chloroformate (5.4 mmol, 0.74 mL) dropwise. The resulting mixture was vigorously stirred at room temperature for 2 h. The reaction was quenched by careful addition of H_2O (5 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were

(15) For similar dipeptide isosteres based on sugars, see: Graf von Roerden, E.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 687.

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washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting orange oil was purified by column chromatography.

(−)-(2*R*,3*S*,6*S*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-*N*-[(2,2,2-trichloroethoxy)carbonyl]-3-methyl-6-phenyl-4-piperidone, 5a. Piperidone **4a** (600 mg) was employed as starting material. The protected compound **5a** was isolated in 93% yield (850 mg) as a yellow oil: $R_f = 0.32$ (SiO_2, hexane/EtOAc, 8:1); $[\alpha]^{18}_D = -32.3$ (*c* 0.7, CH_2Cl_2); ^{1}H NMR (200 MHz, C_6D_6, 75 °C) δ 7.59−7.22 (m, 5H), 5.76 (t, 1H, J = 7.0 Hz), 4.83 (s, 2H), 4.79 (td, 1H, J = 6.0, 2.9 Hz), 3.84−3.70 (m, 2H), 3.01 (dd, 1H, J = 16.5, 7.0 Hz), 2.88 (qd, 1H, J = 7.3, 2.9 Hz), 2.86 (dd, 1H, J = 16.5, 7.0 Hz), 1.39 (d, 3H, J = 7.3 Hz), 1.09 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 209.5, 155.7, 143.7, 129.4, 128.1, 126.8, 96.4, 75.9, 66.1, 61.8, 56.4, 44.6, 43.3 (br), 26.5, 18.9, 17.5 (br), −5.0; HRMS (EI) calcd for $C_{21}H_{29}Cl_3NO_4Si$ (M − CH_3) 492.0931, found 492.0937.

(−)-(2*R*,3*S*,6*S*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-*N*-[(2,2,2-trichloroethoxy)carbonyl]-6-(3-furyl)-3-methyl-4-piperidone, 5b. Piperidone **4b** (582 mg) was employed as starting material. The protected compound **5b** was isolated in 70% yield (629 mg) as a yellow oil: $R_f = 0.24$ (SiO_2, hexane/EtOAc, 8:1); $[\alpha]^{20}_D = -9.7$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37−7.34 (m, 2H), 6.37 (s, br, 1H), 5.82 (s, br, 1H), 4.94 (d, 1H, J = 12.1 Hz), 4.82 (d, 1H, J = 12.1 Hz), 4.40 (td, 1H, J = 5.7, 2.9 Hz), 3.38−3.28 (m, 2H), 3.14−3.03 (m, 1H), 2.79−2.72 (m, 2H), 1.32 (d, 3H, J = 7.0 Hz), 0.81 (s, 9H), −0.05 (s, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 209.5, 154.4 + 154.0 (due to rotamers), 143.1, 139.5, 126.6, 109.5, 95.2, 74.9, 63.5 (br), 61.4, 48.3 (br), 43.4, 40.1 + 39.2 (due to rotamers), 25.4, 17.8, 17.1 + 16.3 (due to rotamers), −4.1; HRMS (EI) calcd for $C_{20}H_{30}Cl_3NO_5Si$ 497.0959, found 497.0960.

Desilylation of the Hydroxy Group of 5a. Synthesis of (−)-(2*R*,3*S*,6*S*)-*N*-[(2,2,2-Trichloroethoxy)carbonyl]-2-(hydroxymethyl)-3-methyl-6-phenyl-4-piperidone, 6. To a solution of **5a** (610 mg, 1.2 mmol) in acetonitrile (15 mL) cooled to 0 °C was added 10 mL of a 3 N HCl aqueous solution. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting yellow oil was purified by column chromatography. The desilylated piperidone **6** was isolated in 87% yield (415 mg) as a yellow oil: $R_f = 0.28$ (SiO_2, hexane/EtOAc, 2:1); $[\alpha]^{18}_D = -24.6$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44−7.26 (m, 5H), 5.81 (t, 1H, J = 6.0 Hz), 4.82 (s, 2H), 4.43 (dd, 1H, J = 11.4, 5.6 Hz), 3.65−3.41 (m, 2H), 3.09 (dd, 1H, J = 17.2, 5.4 Hz), 2.93 (dd, 1H, J = 17.2, 7.0 Hz), 2.64 (qd, 1H, J = 7.0, 5.0 Hz), 1.27 (d, 3H, J = 7.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 209.4, 155.1, 141.5, 128.8, 127.7, 125.8, 95.0, 75.1, 64.3, 61.0, 54.5, 43.4, 41.5 (br), 15.7; HRMS (EI) calcd for $C_{15}H_{15}Cl_3NO_3$ (M − CH_3O) 362.0118, found 362.0104.

Jones Oxidation of the Hydroxy Group of 6 and Esterification. Synthesis of (+)-Methyl (2*R*,3*S*,6*S*)-*N*-[(2,2,2-Trichloroethoxy)carbonyl]-3-methyl-6-phenyl-4-oxopipecolate, 8. Jones reagent was added dropwise to a yellow solution of 2-(hydroxymethyl)-4-piperidone **6** (200 mg, 0.5 mmol) in acetone (6 mL) at 0 °C until the color of the reaction mixture remained deep orange. Stirring was continued for 2 h, and the reaction was quenched by careful addition of EtOH to destroy the excess of the oxidizing reagent. The green solid was filtered through Celite and washed with acetone (2 × 5 mL). The colorless solution was concentrated under reduced pressure, and the resulting oil was disolved in H_2O (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The foam obtained was redissolved in Et_2O and cooled to 0 °C, and a large excess of freshly prepared diazomethane in Et_2O solution was added. After 15 min of stirring, AcOH was added dropwise to the yellow solution in order to destroy the excess of diazomethane, followed by brine (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting yellow oil was purified by column chromatography. The ester **8** was isolated in 89% yield (195 mg) as a colorless oil: $R_f = 0.26$ (SiO_2, hexane/EtOAc, 4:1); $[\alpha]^{20}_D = +12.0$ (*c* 0.9, CH_2Cl_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.67−7.31 (m, 5H), 5.70 (t, 1H, J = 5.0 Hz), 4.99 (s, 2H), 4.82 (d, 1H, J = 8.2 Hz), 3.74 (s, 3H), 3.24 (dd, 1H, J = 17.1, 5.1 Hz), 3.10 (dd, 1H, J = 17.1, 4.9 Hz), 2.70−2.55 (m, 1H), 1.10 (d, 3H, J = 6.9 Hz); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 206.5, 171.1, 154.1, 141.0, 128.3, 127.1, 126.0, 95.3, 74.6, 59.9, 54.3, 52.2, 44.8, 43.4, 12.1 (br); HRMS (EI) calcd for $C_{17}H_{18}Cl_3NO_5$ 421.0251, found 421.0261.

Deprotection of Troc Group of Ester 8. Synthesis of (−)-Methyl (2*R*,3*S*,6*S*)-3-Methyl-6-phenyl-4-oxopipecolate, 9. Zinc dust (900 mg) was added at room temperature to a solution of 90 mg of **8** (0.21 mmol) in 9 mL of acetic acid. The suspension was stirred for 1 h and then filtered through Celite, and the Celite was thoroughly washed with EtOAc. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in 10 mL of EtOAc, and the solution was washed with a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, concentrated under reduced pressure, and dried under vacuum to afford 51 mg of pure pipecolate **9**: 96% yield; $[\alpha]^{20}_D = -23.0$ (*c* 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (m, 5H), 4.01 (dd, 1H, J = 10.7, 3.8 Hz), 3.78 (s, 3H), 3.45 (d, 1H, J = 10.7 Hz), 2.71 (dq, 1H, J = 10.8, 6.5 Hz), 2.65 (m, 2H), 1.15 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.0, 171.5, 141.2, 128.7, 128.0, 126.4, 65.6, 60.9, 52.3, 49.9, 47.7, 10.3; HRMS (EI) calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1213.

Oxidation of Furan 5b. Synthesis of (−)-Methyl (2*S*,5*S*,6*R*)-*N*-[(2,2,2-Trichloroethoxy)carbonyl]-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-methyl-4-oxopipecolate, 10. To a solution of furan **5b** (350 mg, 0.7 mmol) in a biphasic mixture of 10 mL of acetonitrile, 10 mL of water, and 7 mL of carbon tetrachloride was added 613 mg (2.87 mmol) of sodium metaperiodate ($NaIO_4$). Then $RuCl_3 \cdot xH_2O$ (5 mg) was added, and the mixture was stirred until no starting material could be detected by TLC (typically 2 h). EtOAc (20 mL) was added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with additional EtOAc (2 × 20 mL). The combined organic layers were treated with Na_2SO_4 and charcoal and filtered through Celite, and the solvent was evaporated under reduced pressure to afford the crude acid that was not further purified. The residue was dissolved in 15 mL of Et_2O and treated with a solution of freshly prepared diazomethane in ether (3 mmol). After 1 h the reaction was quenched with 0.5 mL of acetic acid and neutralized with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting oily residue was purified by column chromatography (SiO_2, hexane/EtOAc, 8:1) to afford 240 mg (73%) of ester **10** as a yellow oil: R_f = 0.54 (SiO_2, hexane/EtOAc, 4:1); $[\alpha]^{20}_D = -1.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.05 (quint, 1H, J = 4.6 Hz), 4.98−4.66 (m, 2H), 4.43−4.36 (m, 1H), 3.92 (ddd, 1H, J = 10.5, 4.5, 2.2 Hz), 3.79 (dd, 1H, J = 5.7, 3.8 Hz), 3.72 (s, 3H), 3.01 (dd, 1H, J = 17.5, 5.5 Hz), 2.78 (dd, 1H, J = 17.5, 9.0 Hz), 2.61 (qd, 1H, J = 7.3, 1.9 Hz), 1.21 (dd, 3H, J = 7.3, 2.6 Hz), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 206.8 + 206.7 (due to rotamers), 170.6 + 170.4 (due to rotamers), 154.4 + 154.3 (due to rotamers), 95.1 + 94.9 (due to rotamers), 75.4 + 75.1 (due to rotamers), 65.5 + 65.4 (due to rotamers), 59.7, 53.6 + 53.3 (due to rotamers), 52.6 + 52.5 (due to rotamers), 44.1 + 44.0 (due to rotamers), 36.1, 25.8, 18.4, 16.5 + 16.3 (due to rotamers), −4.8, −4.9; HRMS (EI) calcd for $C_{17}H_{27}Cl_3NO_6Si$ (M − CH_3) 474.0673, found 474.0677.

Deprotection of Troc Group of Pipecolate 10. Synthesis of (−)-Methyl (2*S*,5*S*,6*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5-methyl-4-oxopipecolate, 11. The method is identical to that described above for **9**. Compound **10** (180 mg, 0.36 mmol) afforded 112 mg (99%) of pipecolate **11**: $[\alpha]^{20}_D = -42.1$ (*c* 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz)

δ 3.87 (dd, 1H, J = 9.9, 2.6 Hz), 3.77 (s, 3H), 3.68 (m, 2H), 2.73 (dd, 1H, J = 13.8, 3.5 Hz), 2.62 (ddd, J = 10.4, 6.5, 2.6 Hz), 2.46 (dd, 1H, J = 13.8, 12.4 Hz), 2.35 (dq, 1H, J = 10.4, 6.5 Hz), 1.05 (d, 3H, J = 6.5 Hz), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.6, 171.7, 64.3, 62.8, 57.8, 52.3, 47.0, 44.7, 25.8, 18.2, 9.5; HRMS (EI) calcd for $C_{15}H_{29}NO_4Si$ 315.1866, found 315.1867.

Deprotection of the TBDMS Group of Pipecolate 11. Synthesis of (−)-Methyl (2*S*,5*S*,6*R*)-6-(Hydroxymethyl)-5-methyl-4-oxopipecolate, 12. A solution of pipecolate **11** (100 mg, 0.31 mmol) in 15 mL of CH_3CN and 15 mL of aqueous 3 N HCl was vigorously stirred for 3 h at room temperature and neutralized with a saturated $NaHCO_3$ solution. The organics were extracted with EtOAc (3 × 25 mL), dried over Na_2SO_4, and concentrated in a vacuum. The crude residue was filtered through a short silica gel column (5% MeOH in CH_2Cl_2) to afford 61 mg (99% yield) of pipecolate **12**: $[\alpha]^{20}_D$ = −22 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.91 (dd, 1H, J = 10.5, 2.9 Hz), 3.75 (s, 3H), 3.80−3.60 (m, 2H), 2.76 (dd, 1H, J = 14.1, 3.5 Hz), 2.49 (ddd, 1H, J = 10.5, 5.5, 2.9 Hz), 2.6−2.4 (m, 2H), 1.05 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.2, 171.8, 63.9, 62.7, 57.9, 52.6, 46.8, 44.5, 29.7, 9.6; HRMS (EI) calcd for $C_8H_{12}NO_3$ (M − CH_2OH) 170.0817, found 170.0824.

Formation of the Bicyclic Carbamate. Synthesis of (+)-(2*S*,5*S*,6*R*)-1-Aza-2-(3-furyl)-5-methyl-8-oxa-4,9-dioxobicyclo[4.3.0]nonane, 13. Triphosgene (980 mg, 3.3 mmol) was slowly added to an ice-cooled solution of hydroxypiperidone **3b** (700 mg, 3.3 mmol) in 40 mL of THF. Then, a solution of triethylamine (0.93 mL, 6.6 mmol) in 15 mL of THF was added dropwise. After 30 min of stirring, the reaction was quenched with water (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc, 8:1) to give rise to 736 mg of carbamate **13** (yield 95%): R_f = 0.45 (SiO_2, CH_2Cl_2/EtOAc, 4:1), $[\alpha]^{20}_D$ = +18 (*c* 0.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (m, 2H), 6.41 (s, 1H), 4.95 (dd, 1H, J = 5.8, 4.9 Hz), 4.4 (m, 1H), 4.00 (m, 2H), 2.94 (dd, 1H, J = 15.6, 5.8 Hz), 2.80 (dd, 1H, J = 15.6, 4.9 Hz), 2.48 (m, 1H), 1.06 (d, 3H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.5, 156.0, 143.5, 139.5, 124.9, 109.0, 67.3, 58.4, 48.0, 46.3, 44.0, 10.0; HRMS (EI) calcd for $C_{12}H_{13}NO_4$ 235.0844, found 235.0840.

Reduction of the Carbonyl Group. Synthesis of (−)-(2*S*,4*R*,5*S*,6*R*)-1-Aza-2-(3-furyl)-4-hydroxy-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane, 14. A solution of ketone **13** (730 mg, 3.1 mmol) in 25 mL of dry THF was cooled to −80 °C. A solution of K-Selectride (1 M) in THF (5 mmol, 5 mL) was added dropwise, and the mixture stirred for 60−90 min (the reaction can be monitored by TLC and quenched when the spot of the starting material has disappeared). The reaction was quenched with 5 mL of water, and the cold bath was removed. Once the reaction mixture reached rt, EtOH (3 mL) and 3 N NaOH (4 mL) were added. After 5 min, the mixture was treated with 5 mL of H_2O_2 (30% vol), and the stirring continued for 20 min. The mixture was then treated with 10 mL of saturated aqueous Na_2CO_3 solution, and the organics were extracted with EtOAc (3 × 40 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc, 4:1) to obtain 721 mg (98%) of **14**: R_f = 0.1 (SiO_2, hexane/EtOAc, 1:1); $[\alpha]^{20}_D$ = −58.9 (*c* 0.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (s, 2H), 6.43 (s, 1H), 4.58 (dd, 1H, J = 10.3, 4.8 Hz), 4.35 (t, 1H, J = 7.3 Hz), 4.01 (td, 1H, J = 2.6, 2.1 Hz), 3.85 (m, 2H), 1.95 (m, 2H), 1.71 (qdd, 1H, J = 10.3, 6.7, 2.1 Hz), 1.01 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 142.6, 139.7, 123.4, 109.9, 67.9, 66.4, 56.5, 44.6, 40.9, 39.0, 12.8; HRMS (EI) calcd for $C_{12}H_{15}NO_4$ 237.1001, found 237.0994. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.07; H, 5.60; N, 5.89.

Alkylation of 14. Synthesis of (−)-(2*S*,4*R*,5*S*,6*R*)-1-Aza-4-(benzyloxy)-2-(3-furyl)-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane, 15. To a solution of alcohol **14** (475 mg, 1.95 mmol) and benzyl bromide (5.7 mmol, 0.7 mL) in 25 mL of dry DMF under dry atmosphere was slowly added 300 mg of NaH. The mixture was stirred at 120 °C for 4 h, allowed to reach rt, and carefully quenched with 20 mL of saturated aqueous $NaHCO_3$ solution. The organics were extracted with EtOAc (3 × 40 mL), and the aqueous layer was washed with brine (3 × 25 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Bicyclic carbamate **15** was purified by column chromatography (SiO_2, hexane/EtOAc, 1:1) to obtain 530 mg (yield 83%): R_f = 0.45 (SiO_2, hexane/EtOAc, 1:1); $[\alpha]^{20}_D$ = −64 (*c* 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (m, 7H), 6.47 (s, 1H), 4.67 (d, 1H, J = 11.6 Hz), 4.50 (dd, 1H, J = 12.0, 3.0 Hz) 4.47 (d, 1H, J = 11.6 Hz), 4.31 (m, 1H), 3.82 (m, 2H), 3.70 (m, 1H), 2.22 (dt, 1H, J = 14.2, 3.5 Hz), 1.85−1.70 (m, 2H), 1.02 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 142.3, 139.3, 137.9, 127.9, 127.3, 127.1, 123.3, 109.7, 75.0, 70.7, 66.0, 56.9, 44.7, 38.7, 36.2, 12.7; HRMS (EI) calcd for $C_{19}H_{21}NO_4$ 327.1470, found 327.1461.

Ozonolysis of the Furan Ring. Synthesis of (−)-Methyl (2*S*,4*R*,5*S*,6*R*)-1-Aza-4-(benzyloxy)-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-2-carboxylate, 16a. Furan **15** (450 mg, 1.37 mmol) was dissolved in a mixture of 60 mL of CH_2Cl_2, 10 mL of methanol, 4.5 mL of H_2O_2 (30% v/v), and 400 mg of NaOH. The solution was stirred for 10 min and cooled to −78 °C. Then a stream of O_3/O_2 (300 L/h, 2.5 g of O_3) was bubbled through the solution using a gas diffusion tube. The ozone stream was mantained until complete disappearance of the starting material was observed by TLC (40 min). The ozonizer was turned off, and the oxygen stream was maintained for 15 min. The mixture was stirred at room temperature for 1 h, and the reaction was quenched with 1 N HCl (30 mL). After addition of 60 mL of CH_2Cl_2, the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude acid obtained was dissolved in 40 mL of THF, and a large excess of a freshly prepared solution of diazomethane (4 mmol) in ether (15 mL) was added. After 15 min at room temperature 3 mL of AcOH and 25 mL of water were added successively. The aqueous layer was extracted with EtOAc (2 × 40 mL). The organic layers were combined and dried, and the solvent was evaporated to afford a colorless oil that was purified by column chromatography (SiO_2, hexane/EtOAc, 3:1) to afford 288 mg of ester **16a** (67% yield): R_f = 0.40 (SiO_2, hexane/EtOAc, 1:1); $[\alpha]^{20}_D$ = −52 (*c* 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.2 (m, 5H), 4.65 (d, 1H, J = 11.6 Hz), 4.45 (d, 1H, J = 11.6 Hz), 4.39 (dd, 1H, J = 8.2, 7.0 Hz), 4.08 (dd, 1H, J = 11.9, 3.6 Hz) 3.95 (dd, 1H, J = 8.2, 7.9 Hz), 3.81 (s, 3H), 3.79 (m, 2H), 2.33 (dt, 1H, J = 14.0, 3.6 Hz), 1.79 (ddd, 1H, J = 14.0, 11.9, 2.1 Hz), 1.72 (dqd, 1H, J = 10.6, 6.7, 2.4 Hz), 1.05 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 156.4, 137.7, 128.3, 127.8, 127.5, 74.5, 71.2, 67.5, 56.2, 52.5, 51.2, 38.3, 30.7, 13.0; HRMS (FAB) calcd for $C_{17}H_{22}NO_5$ (M + 1) 320.1497, found 320.1482.

Esterification of the Crude Acid via Formation of the Acid Chloride: Synthesis of (−)-Ethyl (2*S*,4*R*,5*S*,6*R*)-1-Aza-4-(benzyloxy)-5-methyl-8-oxa-9-oxobicyclo-[4.3.0]nonane-2-carboxylate, 16b. After the ozonolysis described above, the crude acid was dissolved in 30 mL of dry CH_2Cl_2, treated with 0.5 mL of oxalyl chloride, and refluxed for 4 h. The hot bath was removed, and the volatiles were evaporated under vacuum. The resulting residue was redissolved in 20 mL of CH_2Cl_2, and 5 mL of dry ethanol were added to the solution. After 2 h of stirring at room temperature, the reaction was quenched with saturated $NaHCO_3$, and the organics were extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in a vacuum. The carboxylic ester was then purified by column chromatography (SiO_2, hexane/EtOAc, 3:1) to afford 283 mg of ester **16b**: 62% yield; R_f = 0.43 (SiO_2, hexane/EtOAc, 1:1); $[\alpha]^{20}_D$ = −38.3 (*c* 0.12, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.31 (m, 5H), 4.68 (d, 1H, J = 12.0 Hz), 4.43 (d, 1H, J = 12.0 Hz), 4.39 (dd, 1H, J = 8.2, 7.3 Hz), 4.33−4.22 (m, 3H), 4.05 (dd, 1H, J = 12.2, 3.4 Hz), 3.95 (t, 1H, J = 8.2 Hz), 3.80−3.70 (m, 2H), 2.32 (dt, 1H, J = 14.2, 3.4 Hz), 1.78 (ddd, 1H, J = 14.2, 12.2, 2.1 Hz), 1.75−1.63 (m, 1H), 1.31 (t, 3H, J = 7.3 Hz), 0.99 (d, 3H, J = 6.9 Hz); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 169.8, 156.9, 137.8, 128.3, 127.8, 127.5, 74.6, 71.2, 67.5, 61.6, 56.3, 51.4, 38.0, 13.9, 13.1; HRMS (EI) calcd for $C_{18}H_{23}NO_5$ 333.1576, found 333.1567.

Synthesis of (−)-Benzyl (2*S*,4*R*,5*S*,6*R*)-1-Aza-4-(benzyloxy)-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-2-carboxylate, 16c. The procedure is identical to that described for the ethyl ester **16b**. Once the acid chloride had been redissolved in CH_2Cl_2, 2 mL of benzyl alcohol was added to the solution. After 2 h of stirring at room temperature, the reaction was quenched with 15 mL of a saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The excess of benzyl alcohol was eliminated by Kugelröhr distillation (10^{-3} Torr, 100 °C). The ester was purified by column chromatography (SiO_2, hexane/EtOAc, 4:1) to afford 330 mg (61%) of **16c**: R_f = 0.15 (SiO_2, hexane/EtOAc, 4:1); $[\alpha]^{20}_D$ = −43.7 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.3 (m, 10H), 5.25 (s, 2H), 4.65 (d, 1H, *J* = 11.9 Hz), 4.43 (d, 1H, *J* = 11.9 Hz), 4.39 (dd, 1H, *J* = 8.2, 7.0 Hz), 4.13 (dd, 1H, *J* = 12.2, 3.0 Hz), 3.95 (dd, 1H, *J* = 8.2, 8.0 Hz), 3.8−3.7 (m, 2H), 2.33 (dt, 1H, *J* = 14.3, 3.6 Hz), 1.82 (ddd, 1H, *J* = 14.3, 12.2, 2.1 Hz), 1.72 (dqd, 1H, *J* = 10.6, 6.8, 2.1 Hz), 0.99 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 156.5, 137.7, 135.3, 128.5, 128.4, 128.3, 128.2, 127.7, 127.4, 74.6, 71.2, 67.4, 67.3, 56.2, 51.3, 38.2, 30.7, 12.9; HRMS (EI) calcd for $C_{23}H_{25}NO_5$ 395.1733, found 395.1739.

Epimerization of 16. Synthesis of Carboxylic Esters 17. A solution of ester **16** (0.24 mmol) in 15 mL of THF was cooled to 0 °C with an ice bath. Then a sonicated solution of ^{t}BuOK (108 mg, 0.96 mmol) in 5 mL of dry THF was added dropwise, and the solution was stirred for 30 min and poured into a 3 N HCl aqueous solution (10 mL). The organics were extracted with EtOAc (3 × 15 mL) and the combined organic layers washed with brine, dried over Na_2SO_4, and concentrated in a vacuum to afford essentially pure ester **17**, which can be further purified by filtration through a short chromatographic column (SiO_2). By this method were prepared the following.

Ethyl (2*R*,4*R*,5*S*,6*R*)-1-Aza-4-(benzyloxy)-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-2-carboxylate, 17b. Compound **16b** (50 mg) afforded 48 mg of **17b** (yield 96%): R_f = 0.32 (SiO_2, hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.23 (m, 5H), 4.62 (d, 1H, *J* = 11.8 Hz), 4.51 (t, 1H, *J* = 7.3 Hz), 4.48 (dd, 1H, *J* = 6.8, 1.6 Hz), 4.31 (d, 1H, *J* = 11.8 Hz), 4.07−3.85 (m, 4H), 3.62−3.57 (m, 1H), 2.85 (ddd, 1H, *J* = 14.6, 3.4, 1.6 Hz), 1.76 (ddd, *J* = 14.6, 6.8, 1.3 Hz), 1.56 (dqd, 1H, *J* = 10.1, 6.9, 1.4 Hz), 1.12 (t, 3H, *J* = 7.3 Hz), 0.95 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 170.3, 156.9, 137.8, 128.4, 128.1, 127.4, 74.4, 70.8, 67.8, 61.4, 52.6, 49.1, 39.7, 29.6, 13.8, 13.3; HRMS (EI) calcd for $C_{18}H_{23}NO_5$ 333.1576, found 333.1578.

(−)-Benzyl (2*R*,4*R*,5*S*,6*R*)-1-Aza-4-(benzyloxy)-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-2-carboxylate, 17c. Compound **16c** (65 mg) afforded 63 mg (97%) of **17c**: R_f = 0.29 (SiO_2, hexane/EtOAc, 1:1); $[\alpha]^{20}_D$ = −43 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.1 (m, 10H), 4.98 (d, 1H, *J* = 12.2 Hz), 4.83 (d, 1H, *J* = 12.2 Hz), 4.6−4.45 (m, 3H), 4.29 (dd, 1H, *J* = 9.1 Hz), 4.1−3.9 (m, 2H), 3.60 (m, 1H), 2.83 (ddd, 1H, *J* = 14.5, 3.6, 1.5 Hz), 1.78 (dd, 1H, *J* = 14.5, 7.0, 1.8 Hz), 1.55 (m, 1H), 0.95 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 156.9, 137.8, 135.1, 128.4, 128.3, 128.2, 128.0, 127.6, 127.4, 74.2, 70.7, 67.9, 67.1, 52.6, 49.2, 39.6, 29.2, 13.2; HRMS (EI) calcd for $C_{23}H_{25}NO_5$ 395.1733, found 395.1742.

Cleavage of Benzyl Esters. Synthesis of Carboxylic Acids 20 and 21. A flask containing the benzyl ester **16c** or **17c** (120 mg, 0.30 mmol) and 10% Pd/C (50 mg) and capped with a rubber septum was evacuated with the aid of a needdle and filled with hydrogen with a balloon. After the operation was repeated twice, 10 mL of EtOH was added to the flask through the septum with a syringe and a needle. The mixture was stirred at room temperature for 90 min when the balloon and the septum were removed. The solution was filtered through Celite, the Celite was washed with 15 mL of ethanol, and the combined filtrates were concentrated under vacuum to afford 92 mg (99% yield) of pure carboxylic acid **20** or **21**, respectively. Using this procedure were prepared the following.

(−)-(2*S*,4*R*,5*S*,6*R*)-1-Aza-4-(benzyloxy)-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-2-carboxylic acid, 20: $[\alpha]^{20}_D$ = −46 (*c* 0.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 4.68 (d, 1H, *J* = 11.6 Hz), 4.42 (m, 2H), 4.09 (dd, 1H, *J* = 12.0, 3.0 Hz), 3.95 (t, 1H, *J* = 8.6 Hz), 3.77 (m, 1H), 3.72 (m, 1H), 2.40 (dt, 1H, *J* = 13.8, 3.0 Hz), 1.79 (m, 1H), 1.70 (m, 1H), 0.96 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4, 157.2, 137.7, 128.4, 127.8, 127.6, 74.4, 71.2, 67.9, 56.4, 51.3, 38.2, 30.9, 13.0; HRMS (FAB) calcd for $C_{16}H_{20}NO_5$ 306.1341, found 306.1352.

(−)-(2*R*,4*R*,5*S*,6*R*)-1-Aza-4-(benzyloxy)-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-2-carboxylic acid, 21: $[\alpha]^{20}_D$ = −48 (*c* 0.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4 (m, 5H), 4.62 (d, 1H, *J* = 12 Hz), 4.50 (m, 2H), 4.29 (d, 1H, *J* = 12 Hz), 4.00 (m, 1H), 3.92 (m, 1H), 3.58 (m, 1H), 2.78 (m, 1H), 1.75 (m, 1H), 1.53 (m, 1H), 0.95 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.9, 157.1, 136.6, 128.4, 127.6, 127.2, 74.2, 70.8, 67.7, 52.6, 48.8, 39.6, 28.9, 13.2; HRMS (FAB) calcd for $C_{16}H_{20}NO_5$ (M + 1) 306.1341, found 306.1348.

Cleavage of the Cyclic Carbamate. Synthesis of Hydroxyamino Acids 18 and 19. Carboxylic acid **20** or **21** (80 mg, 0.26 mmol) was dissolved in 8 mL of dry THF under N_2 atmosphere. A sonicated solution of ^{t}BuOK in 2 mL of dry THF was added dropwise, and the mixture refluxed for 60 min. The solution was poured into a mixture of 3 N HCl aqueous solution (10 mL) and ether (5 mL). The organic layer was discarded. The aqueous layer was evaporated to dryness under vacuum, and the organic material was extracted with methanol (10 mL). The methanol solution was filtered through Celite and concentrated to afford the hydrochloric salt of the hydroxyamino acid, which was desalted by ion-exchange chromatography as follows: A column was loaded with Dowex 50Wx8-100 ion-exchange resin and washed with water until neutral pH. Then the hydrochloric salt was dissolved in 1 mL of water and loaded into the column. The column was eluted with water until the pH of the eluent coming out of the column was neutral. Then, the column was eluted with 20% ammonium hydroxide aqueous solution. The basic fractions were collected and concentrated under vacuum to afford 54 mg of the hydroxyamino acid **18** or **19** (yield 75%). By this procedure were prepared the following.

(−)-(2*S*,4*R*,5*S*,6*R*)-4-[(Benzyloxy)methyl]-6-(hydroxymethyl)-5-methylpipecolic acid, 19: $[\alpha]^{20}_D$ = −23 (*c* 0.5, H_2O); ^{1}H NMR (D_2O, 300 MHz) δ 7.4 (m, 5H), 4.94 (d, 1H, *J* = 12.0 Hz), 4.68 (d, 1H, *J* = 12.0 Hz), 4.2−4.0 (m, 3H), 3.89 (dd, 1H, *J* = 12.4, 5.6 Hz), 3.45 (m, 1H), 2.85 (m, 1H), 2.2−1.9 (m, 2H), 1.18 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 174.3, 138.4, 129.2, 129.1, 128.6, 74.3, 71.1, 59.9, 55.0, 53.4, 34.0, 27.2, 13.9; HRMS (FAB) calcd for $C_{15}H_{22}NO_4$ (M + 1) 280.1549, found 280.1549.

(−)-(2*R*,4*R*,5*S*,6*R*)-4-[(Benzyloxy)methyl]-6-(hydroxymethyl)-5-methylpipecolic acid, 18: $[\alpha]^{20}_D$ = −12 (*c* 0.2, H_2O); ^{1}H NMR (D_2O, 300 MHz) δ 7.5 (m, 5H), 4.85 (d, 1H, *J* = 11.6 Hz), 4.48 (d, 1H, *J* = 11.6 Hz), 4.2−3.8 (m, 5H), 3.03 (m, 1H), 2.2−2.0 (m, 2H), 1.11 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 173.0, 137.2, 128.0, 127.9, 127.4, 73.1, 69.8, 58.7, 53.7, 52.1, 32.7, 26.0, 12.7; HRMS (EI) calcd for $C_{14}H_{18}NO_3$ (M − CH_2OH) 248.1286, found 248.1273.

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Supporting Information Available: Copies of the ^{13}C NMR spectra of all the compounds described (20 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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