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STEREOSELECTIVE SYNTHESIS OF γ-HYDROXY-α-AMINO ACIDS via INTRAMOLECULAR AMIDOMERCURATION

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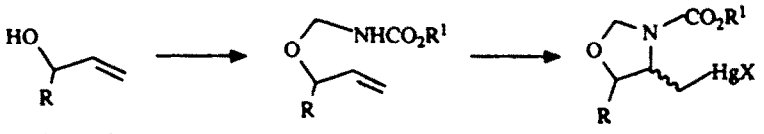
Abstract - A general method for the stereoselective conversion of homoallylic alcohols to *erythro*- or *threo*-γ-hydroxy-α-amino acids is described. The key step is the stereoselective mercuric ion-initiated cyclofunctionalization of acylaminomethyl ether derivatives of the homoallylic alcohols (3 --> 8). The stereochemistry of the products obtained from the cyclofunctionalization is controlled by the choice of reaction conditions. Reaction under conditions of kinetic control leads to predominant formation of cis 4,6-disubstituted tetrahydro-1,3-oxazines, while reaction under conditions which allow for equilibration of the organomercurial intermediates results in the formation of the trans stereoisomer with very high stereoselectivity. Oxidative demercuration and oxidation of the resulting alcohol produces a protected form of the title amino acids (8 --> 9 --> 10). Cleavage of the tetrahydrooxazine ring with hydrobromic acid then produces the amino acid products as γ-butyrolactone hydrobromides (11 and 12). This general method thus allows for stereoselective synthesis of either diastereomer of the amino acid product starting with a single homoallylic alcohol.

Introduction

Non-proteinogenic γ-hydroxy-α-amino acids are an important class of naturally occurring amino acids.[1] Our studies on stereoselectivity in intramolecular amidomercuration reactions of unsaturated carbamates (Rxn 1)[2a,b,c] and acylaminomethyl ether derivatives of unsaturated alcohols (Rxn 2)[2d] led us to consider the application of these reactions to the stereoselective synthesis of γ-hydroxy-α-amino acids (Scheme 1).

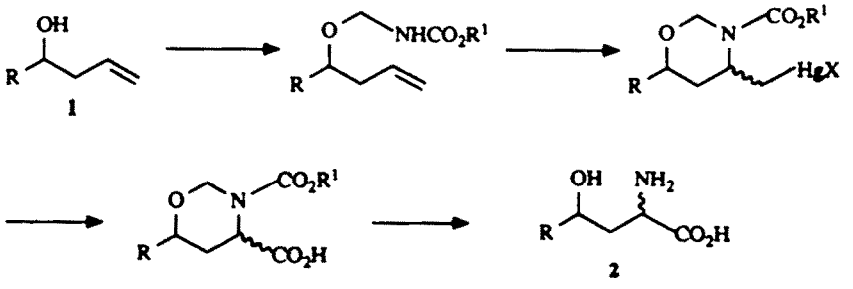
(Rx 1)



(Rx 2)

The overall transformation (Scheme 1, 1 --> 2) converts a terminal alkene to an α-amino acid with a cyclofunctionalization reaction used as the method for control of stereochemistry in this "oxidative-addition". The cyclofunctionalization strategy is based on the premise that the cyclic nature of the diastereomeric transition states and products in this reaction would differ sufficiently in energy so that one diastereomer is formed preferentially (either kinetically or thermodynamically). In this way, the stereochemistry of the new chiral center at the α-carbon of the amino acid 2 would be controlled by the configuration of the γ-carbon in the starting homoallylic alcohol (relative asymmetric induction).[3] Our earlier studies on intramolecular amidomercuration have shown that many of these reactions can be conducted under conditions of either kinetic or thermodynamic control with resultant changes in the stereoselectivity of the reaction.[2c,4] This paper[5] reports our studies on the development of methods

Scheme 1 General Strategy for Synthesis of γ-Hydroxy-α-amino Acids

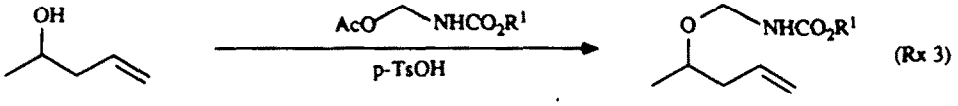


to effect the transformations shown in Scheme 1. In addition, the synthetic utility of the strategy is demonstrated by stereoselective syntheses of both the *erythro* and *threo* isomers of racemic γ-hydroxynorvaline[1a] from 4-penten-2-ol. The amino acids prepared in this study were racemic since racemic 4-penten-2-ol was used as the starting material. However, enantiomerically pure 4-hydroxy-1-alkenes are readily available;[6] thus this method can be considered a general solution to stereoselective synthesis of any desired stereoisomer of γ-hydroxy-α-amino acids.

Results and Discussion

The strategy outlined in Scheme 1 contains several features that required experimental investigation. Two major requirements were (a) establishing stereoselective cyclofunctionalization procedures and (b) developing efficient methods for conversion of the organomercurial group to a carboxylic acid. Specific experimental conditions to meet these requirements were developed in these studies.

The application of a cyclofunctionalization strategy to the amination of homoallylic alcohols requires conversion of the alcohol to a system with an appropriately located nucleophilic nitrogen functional group. Research in these laboratories[2d,4] has concentrated on the use of acylaminomethyl ether derivatives ($R\text{-}O\text{-}CH_2NHCO_2R^1$).[7] The homoallylic ether derivatives used in this study were formed by treatment of 4-penten-2-ol with an N-(acetoxymethyl)carbamate (Rx 3). Alternatively, the benzyl carbamate derivative could be formed by reaction with benzyl N-(hydroxymethyl)carbamate. The benzyl derivative **3a** was obtained by these two methods in 64% and 60% yields, respectively.



(Rx 3)

3

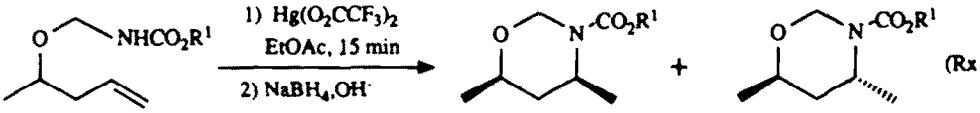
a) R^1 = benzyl

b) R^1 = isobutyl

The N-(acetoxymethyl)carbamates were prepared by treatment of the carbamate with formaldehyde and acetic anhydride,[8] or by acetylation of the N-(hydroxymethyl)carbamate. Benzyl N-(hydroxymethyl)carbamate was obtained readily in high yields by condensation of benzyl carbamate with formaldehyde[9] because it precipitates out of the reaction mixture. This reaction was much less satisfactory with isobutyl carbamate, but direct conversion to the N-acetoxymethyl derivative was satisfactory.

Although mercuric acetate has been used in the cyclization of several unsaturated carbamates,[2a-d] it was not effective for the cyclization of carbamates **3a** and **3b**. Cyclization was found to be promoted by either mercuric trifluoroacetate or mercuric nitrate. Cyclization yields were lower under conditions where cyclization was slow, apparently a result of acid-catalyzed cleavage of the acyclic carbamoyl ether linkage. This cleavage generates a dimeric ether of the N-(hydroxymethyl)carbamate.

The first objective was determination of the stereoselectivity of the cyclization reaction. The organomercurial intermediates generated in the intramolecular amidomercuration reaction were treated with sodium borohydride to effect reductive demercuration and form stable tetrahydrooxazine derivatives. Thus, treatment of carbamate **3a** with mercuric trifluoroacetate in ethyl acetate for 30 min. followed by treatment with basic sodium borohydride gave a mixture of 4,6-disubstituted tetrahydrooxazines **4** and **5** in 60% yield (Rx 4).[10] Analysis by NMR and GC-MS indicated that the two isomers were formed in a ratio of 3:1.



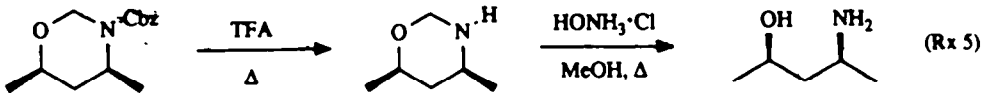
(Rx 4)

3 a) R^1 = benzyl b) R^1 = isobutyl

4 + **5** 3 : 1

The stereochemical assignment was confirmed by conversion of a pure sample[11] of the major isomer to 4-amino-2-pentanol, for which both stereoisomers have been characterized (Rx 5). Treatment of **4a** with refluxing trifluoroacetic acid cleaved the carbobenzyloxy group, but the tetrahydrooxazine ring remained intact. Ring cleavage could not be effected with refluxing oxalic acid.[12] Treatment with *p*-toluenesulfonic acid in refluxing methanol or with ammonium chloride in MeOH led to incomplete ring opening. However, addition of excess hydroxylamine hydrochloride to a refluxing methanol solution of the tetrahydrooxazine **6** led cleanly to

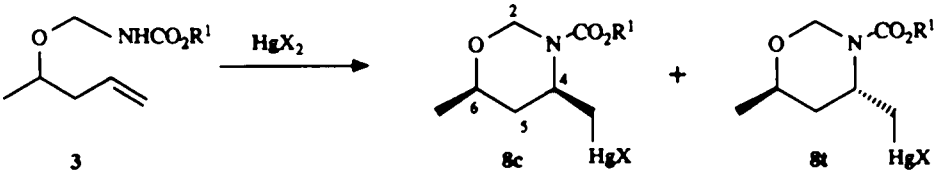
4-amino-2-pentanol. NMR analysis confirmed that the product was the *erythro* isomer.[13]



(Rx 5)

4a 6 7

Because our prior studies had shown that the stereochemical outcome of some intramolecular amidomercuration reactions can be changed by equilibration of the organomercurial intermediates,[2c] the cyclization of carbamate **3b** was examined under conditions which allowed for equilibration. Mercuric nitrate gave higher yields than mercuric trifluoroacetate under these conditions. A solution of carbamate **3b** and mercuric nitrate (each ~ 3M) in acetone-d_6 was examined by ^{1}H NMR over a period of time. The cis/trans ratio of the organomercurial **8** (X = NO_3) changed from ~4:1 at 30 min, to 1:1 at 14 h, to ~5:95 at 46 h. Reduction of the organomercurial intermediate at that time gave tetrahydrooxazines **4b** and **5b** in a ratio of ~6:94 (NMR analysis). Thus, cyclization for short periods (kinetic control) gives the cis isomer as the major product, while cyclization for long periods (thermodynamic control) produces the trans isomer with very high stereoselectivity.



3 8c 8t

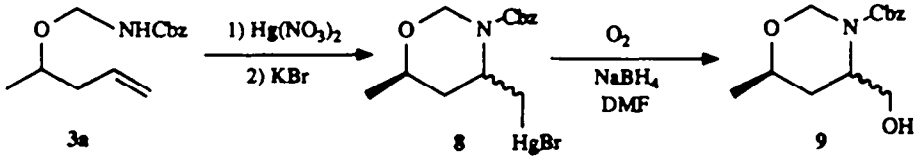
A more detailed NMR analysis was conducted at 200 MHz ($CDCl_3$ solution) with organomercurial **8** (R^1 = CH_2Ph, X = Br) formed by ligand exchange of Br$^-$ for NO_3^-.[14] The ratio of cis to trans isomers is best observed in the 4.50 to 5.50 ppm region of the NMR spectrum. The signals for the protons on the methylene carbon between oxygen and nitrogen (C_2) of the cis isomer are observed as two doublets at 4.91 and 5.03 ppm (J_{gem} = 10.4 Hz), while the signals for these protons in the trans isomer are observed as two broad doublets at 5.46 and 4.55 ppm (J_{gem} = 10.4 Hz). In addition, the conformation of the cis isomer can be ascertained from the coupling constants and splitting patterns of the protons at C_5. The signal for the equatorial proton (H_{5e}) is observed as a doublet of doublets of doublets at 1.92 ppm (J = 5.5, 3.2, and 14.0 Hz). The signal for the axial proton (H_{5a}) is observed as a doublet of triplets at 1.63 ppm (J = 11.2 and 14.0 Hz). The two large ^{3}J coupling constants (11.2 Hz) for H_{5a} demonstrate that the protons at both C_4 and C_6 are axial. Thus, the substituents at C_4 and C_6 are equatorial. The same ^{1}H NMR peak patterns are observed in the spectrum of the tetrahydrooxazines obtained from reductive demercuration and oxidative demercuration (Rx 6 below) of the organomercurials.

The cyclization studies described above demonstrate not only that the intramolecular amidomercuration reaction proceeds stereoselectively, but that the reaction can be directed to generate either the cis or the trans isomer as the predominant product. The stereoselectivity of these cyclizations can be rationalized only partially. The preferential formation of the trans isomer upon equilibration of the organomercurial products can be explained in terms of the thermodynamic stability of *cis*- and *trans*-N-acyl-4,6-dialkyltetrahydrooxazines. Both chair conformations of the cis isomer contain unfavorable steric interactions. The conformation with diequatorial substituents contains an $A^{1,3}$-type interaction between the equatorial group at C_4 and the planar carbamate functionality. The alternative chair conformation of the cis isomer contains a highly unfavorable 1,3-diaxial interaction between the axial substituents at C_4 and C_6. The trans isomer in the chair conformation with only the C_4 substituent axial has no highly unfavorable interaction.[15] Thus, equilibration of organomercurial **8** results in predominant formation of the trans isomer **8t**. The preference for formation of the cis isomer under kinetic control is less readily analyzed, but it is obvious that the interactions that destabilize the cis organomercurial must be much less important in the cyclization transition state.

The remaining transformation necessary for use of the cyclofunctionalization reaction as a method for synthesis of α-amino acids (Scheme 1) was the conversion of the mercurical functional group into a carboxylic acid. The oxidative demercuration of organomercurials to form alcohols has found application in a number of recent synthetic efforts.[17] Successful application of this procedure to organomercurial **8**, however, required a detailed study of the reaction conditions. Under many conditions reported to be successful for other systems, we obtained either simple reductive demercuration or conversion back to starting acyclic carbamate **3a**. The usual oxidative demercuration conditions involve reaction of an organomercurial salt with sodium borohydride in dimethylformamide with oxygen

passing through the solution at a rapid rate.[17] The yield of alcohol 9 obtained from oxidative demercuration of organomercurial 8 (Rx 6) was found to be dependent upon the following parameters: the ligand attached to mercury, the order and rate of addition of reactants, flow rate of oxygen, concentration of organomercurial, and amount of sodium borohydride used.

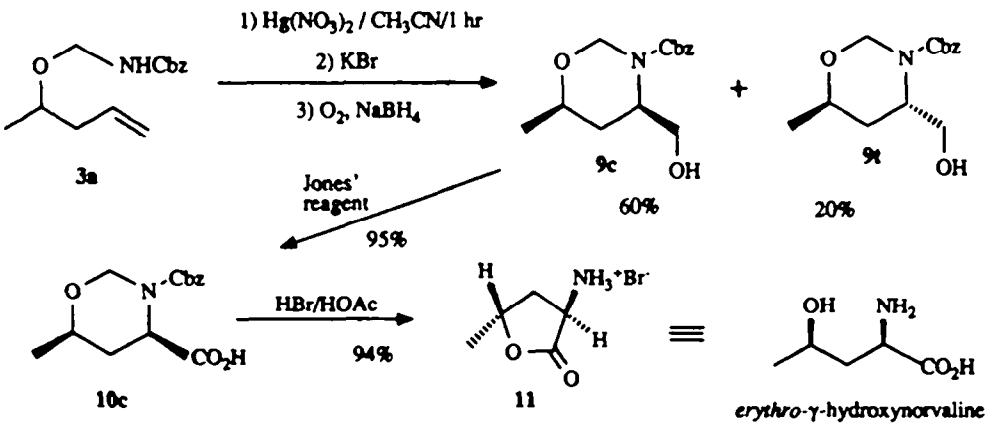
Although the order of addition of reactants has been reported not to affect the yield of some oxidative demercurations,[17] addition of sodium borohydride to a solution of organomercurial bromide 8 produced acyclic carbamate 3a as the major or only product. Although addition of organomercurial 8 to sodium borohydride resulted in formation of significant amounts of alcohol 9, the reductive demercuration product 4a was usually obtained as a major side product. Tetrahydrooxazine 4a became the major product if the organomercurial was added rapidly or if very large excesses of sodium borohydride were used. The best results (80% yield of 9 from carbamate 3a) were obtained with slow addition of ~200 mM organomercurial bromide in dimethylformamide to two molar equivalents of sodium borohydride in dimethylformamide (~100 mM solution) while O_2 was passed through the solution at 300-400 mL/min.



(Rx 6)

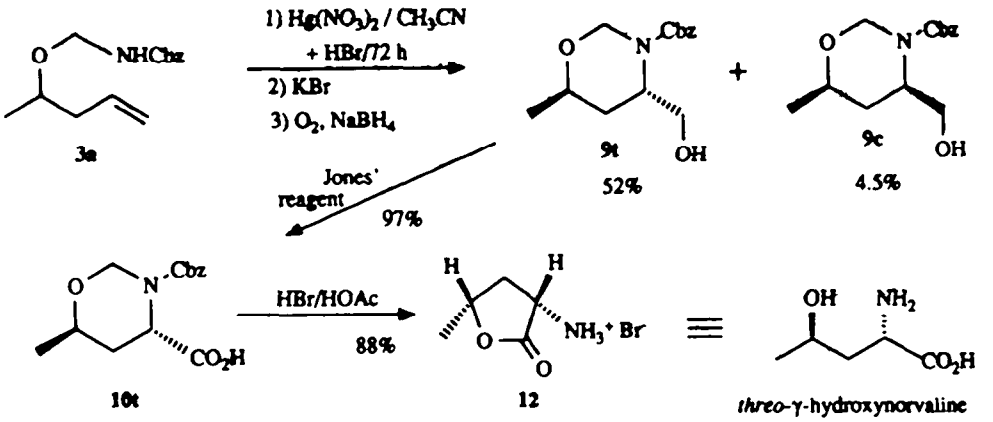
Once conditions for oxidative demercuration were determined, the synthesis of both diastereomers of racemic γ-hydroxynorvaline was readily accomplished. The synthesis of racemic *erythro*-γ-hydroxynorvaline is shown in Scheme 2. The cyclization was conducted under conditions for kinetic control. Oxidative demercuration of the organomercurial bromide and chromatographic separation gave the cis alcohol 9c in 60% yield and the trans alcohol 9t in 20% yield. Oxidation of 9c with Jones' reagent gave the cis acid 10c in high yield. Attempted cleavage of the Cbz group by hydrogenolysis resulted in concomitant reductive cleavage of the tetrahydrooxazine ring and formation of the N-methyl derivative of γ-hydroxynorvaline.[18] However, treatment of 10c with HBr in acetic acid resulted in cleavage of the Cbz group, hydrolytic opening of the tetrahydrooxazine ring, and ring closure of the resulting γ-hydroxyamino acid to the lactone hydrobromide 11. The structure and stereochemistry of this derivative of *erythro*-γ-hydroxynorvaline was identified by comparison of spectral data with that reported in the literature.[18]

Scheme 2 Synthesis of (±)-*erythro*-γ-hydroxynorvaline



The synthesis of *threo*-γ-hydroxynorvaline, as shown in Scheme 3, required cyclization under conditions where the organomercurial intermediate would equilibrate to the more stable trans isomer (thermodynamic control). Reaction of 3a with mercuric nitrate in acetonitrile-d_3 (conc of 3a was 0.29 M) showed no significant equilibration after several days of reaction.[19] However, equilibration began after a small amount of HBr gas was added to the solution. After the organomercurial had been allowed to equilibrate for 72 h, the product was converted to the organomercurial bromide by treatment with aqueous KBr. Oxidative demercuration produced alcohols 9t and 9c in a 92:8 ratio. The trans alcohol 9t was isolated by preparative TLC in a 52% yield. Oxidation to acid 10t followed

Scheme 3 Synthesis of (±)-*threo*-γ-hydroxynorvaline



by acidic cleavage of the Cbz group and the tetrahydrooxazine ring gave *threo*-γ-hydroxynorvaline as the lactone hydrobromide **12** in 85% yield. The structure and stereochemistry of **12** was confirmed by comparison of spectral data with that reported in the literature.[1a]

In addition to comparison with the published spectral data,[1a] the stereochemistry of lactones **11** and **12** can be ascertained by differences between the spectral data for each compound. The ^{1}H NMR data provide two points of comparison which allow for assignment of stereochemistry. The chemical shift difference between the geminal protons at C_3 (0.88 ppm for **12** and < 0.2 ppm for **11**) is diagnostic for this type of lactone.[20] In additon, the sum of the ring proton vicinal coupling constants for the cis isomer **12** is 5.7 Hz greater than the sum for the trans isomer **11** in accord with the spectra of other 2,4-disubstituted γ-butyrolactones.[21] The ^{13}C NMR spectra of lactones **11** and **12** show smaller differences than the ^{1}H spectra; however, small downfield shifts in the signals for C-2 (2.1 ppm) and for C-3 (2.6 ppm) in the spectrum of the cis lactone **12** are consistent with results from other 2,4-disubstituted γ-butyrolactones.[20,22]

The synthetic method presented in this paper represents another example of the application of a cyclofunctionalization strategy to the control of stereochemistry in the synthesis of acyclic compounds.[3,7] The intramolecular amidomercuration used in this method is particularly advantageous since the reaction can be directed to the synthesis of either diastereomer of a γ-hydroxy-α-amino acid.

Experimental

General Procedures. All compounds discussed in this section are racemic; the designation "±" is omitted. Proton nuclear magnetic resonance (NMR) spectra were obtained on Varian Associates T-60, EM-390, or XL-200 spectrometers. ^{13}C NMR spectra were recorded on a JEOL PFT-100 spectrometer (25.034 MHz) or on a Varian XL-200 spectrometer (50.31 MHz). Infrared spectra were measured on a Sargent-Welch Pye-Unicam Model SP3 infrared spectrophotometer or IBM FT/IR (IR/30S). Gas chromatographic separations were performed on a Hewlett-Packard 5790A Series gas chromatograph with a 5970A Series mass selective detector using 25 meter Vitreous Silica capillary columns. Thin layer chromatography (TLC) was performed using pre-coated plastic plates having a 0.2 mm layer of Silica Gel 60 F-254 (EM Reagents). Preparative TLC was carried out using pre-coated 20 X 20 cm glass plates having a 2 mm layer of Silica Gel GF (Analtech) that was activated overnight at 140 °C. Gravity column chromatography was performed with Baker Silica Gel 40-140 mesh using the stated elution solvents. High performance liquid chromatography (HPLC) was performed on a preparative or semi-preparative scale using a Waters Associates PrepLC/System 500 chromatograph. Preparative separations were performed on Waters Associates PrepPAK-500/Silica columns. Semi-preparative separations were carried out on columns using Waters Associates 37-55 micron Silica Gel. Melting points were taken on a Thomas-Hoover capillary melting point apparatus. All melting points are uncorrected. Bulb-to-bulb distillation refers to Kugelrohr distillation in an air oven. The temperature cited for these distillations is the maximum temperature of the oven during distillation.

Ether was distilled under nitrogen immediately before use from the sodium benzophenone ketyl. Tetrahydrofuran (THF) was distilled under nitrogen immediately prior to use from the potassium benzophenone ketyl. Acetonitrile and dimethylformamide were dried over molecular sieves (4 Å). Mercuric nitrate was dried in a vacuum dessicator for 2 days before use. Mercuric trifluoroacetate was prepared by treatment of mercuric oxide with trifluoroacetic anhydride (mp = 160-165 °C; lit.[23] mp = 167-169 °C). Unless otherwise indicated, the purity of

all title compounds was shown to be greater than 90% by chromatographic and spectral analysis.

Benzyl N-(Hydroxymethyl)carbamate. Benzyl carbamate (6.00 g, 40 mmol) was added to a solution consisting of 37% formalin (4.43 g, 55 mmol), sodium carbonate (2.22 g, 20 mmol), and 65 mL of water. The mixture was heated with a heat gun until a clear solution was obtained. The heat source was removed and precipitation occurred immediately. The suspension was stirred at room temperature for 3 h, then extracted three times with 50 mL of dichloromethane. The combined organic phase was washed (brine and water) and dried over anhydrous magnesium sulfate. Filtration, concentration, and recrystallization from dichloromethane/hexane gave the product (5.5 g, 76% yield) as white crystals (mp 84-85.5 °C): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.35 (s, 5 H, C_6H_5), 5.82 (broad, 1 H, NH), 5.13 (s, 1 H, CH_2Ph), 4.71 (t, 2 H, J = 6.2 Hz, OCH_2N), 3.40 (broad, 1 H, OH); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 156.53 (C=O), 135.95, 128.56, 128.29, and 128.11 (Ph), 67.08, and 66.20 (CH_2); IR (KBr) 3345, 2941, 1698, 1670, 1280, 1010, 960 cm^{-1}.

Benzyl N-(Acetoxymethyl)carbamate. A. Preparation from Benzyl Carbamate. A solution of benzyl carbamate (1.51 g, 10 mmol), paraformaldehyde (0.30 g, 10 mmol), acetic acid (10 mL), and acetic anhydride (30 mL) was heated at 75-80 °C for 15 hours with stirring. The clear solution was concentrated by high vacuum rotary evaporation. The pale yellow oil was flushed through a silica gel column using ethyl acetate as solvent. The resulting clear oil was purified by preparative HPLC (30% ethyl acetate in hexane) to give 1.813 g (86.7%) of product: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (s, 5 H, Ph), 6.41 (broad, 1 H, NH), 5.16 (d, 2 H, OCH_2N), 5.10 (s, 2 H, CH_2Ph), 1.99 (s, 3 H, CH_3); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 171.61 (CH_3C=O), 156.00 (NC=O), 135.92, 128.52, 128.27, and 128.00 (Ph), 67.214, 66.70 (CH_2), 20.85 (CH_3); IR (Neat) 3343, 1720, 1702, 1538, 1258, 1187 cm^{-1}.

B. Preparation from Benzyl N-(Hydroxymethyl)carbamate. Benzyl N-(hydroxymethyl)carbamate (850 mg, 4.7 mmol) was dissolved in 30 mL of dry THF and added dropwise to a solution of 20 mL of acetic anhydride (210 mmol) and 2.5 mL (31 mmol) of pyridine. The mixture was stirred for 2 h. The THF was removed by rotary evaporation under aspirator vacuum. The pyridine and acetic anhydride were removed by Kugelrohr distillation at a temperature of 25 °C (1.0 mm Hg). The remaining clear oil was dissolved in Et_2O and washed with $NaHCO_3$ solution. The ether layer was dried with $MgSO_4$, filtered, and concentrated. Benzyl N-(acetoxymethyl)carbamate was obtained as a clear oil in 74% yield (770 mg).

Isobutyl N-(Acetoxymethyl)carbamate. A solution of isobutyl carbamate (2.34 g, 20 mmol), paraformaldehyde (0.60 g, 20 mmol), acetic acid (10 mL), and acetic anhydride (60 mL) was heated at 70 °C for 16 hours. The clear solution was concentrated by high vacuum rotary evaporation. The pale yellow oil was flushed through a silica gel column using ethyl acetate as solvent. The resulting clear oil was purified by preparative HPLC (2:3 ethyl acetate/hexane) to give 2.951 g (78%) of product: ^{1}H NMR (200 MHZ, $CDCl_3$) δ 6.05 (broad, 1 H, NH), 5.20 (d, 2 H, J = 7.6 Hz, OCH_2N), 3.90 (d, 2 H, J = 6.8 Hz, OCH_2CH), 2.08 (s, 3 H, CH_3C=O), 0.93 (d, 6 H, J = 6.8 Hz, CH_3); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 171.88 (CH_3C=O), 156.21 (NC=O), 71.70 (OCH_2N), 66.76 (OCH_2CH), 27.91 ($CHMe_2$), 21.00 (CH_3C=O), 18.98 (CH_3); IR (Neat) 3344, 2922, 1735, 1720, 1490, 980 cm^{-1}.

4-(N-(Benzyloxycarbonyl)aminomethoxy)-1-pentene (3a). A. Preparation from Benzyl N-(Acetoxymethyl)carbamate. Benzyl N-(acetoxymethyl)carbamate (1.01 g, 14.5 mmol) and 4-penten-2-ol (0.59 g, 7 mmol) were dissolved in 10 mL of dry ether. *p*-Toluenesulfonic acid monohydrate (45 mg) was added, and the mixture was heated at reflux for 1 h. This mixture was diluted with 20 mL of ether and washed with saturated sodium bicarbonate. The ether layer was dried over magnesium sulfate, filtered, and concentrated. The residue was concentrated under high vacuum to remove excess 4-penten-2-ol. The crude oil was purified by preparative HPLC (15% ethyl acetate/hexane) to give 0.715 g (64%) of ether **3a**: TLC Silica Gel (Rf 0.45; 2:3 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 5 H, Ph), 5.80 (ddt, 1 H, J = 6.7, 10.7, and 17.2 Hz, CH=), 5.12 (s, 2 H, CH_2Ph), 5.06 (m, 2 H, $=CH_2$), 4.70 (d, 2 H, J = 7.0 Hz, OCH_2N), 3.70 (tq, 1 H, J = 6.2 Hz, OCH), 2.23 (m, 2 H, CH_2CH=), 1.07 (d, 3 H, J = 6.2 Hz, Me); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 156.28 (C-7), 136.13, 128.45, and 128.09 (Ph), 134.69 (C-2), 117.01 (C-1), 72.58 (C-4), 70.36 (C-6), 66.90 (C-8), 40.95 (C-3), 19.74 (Me); IR (Neat) 3335, 2975, 2930, 1725, 1715, 1540, 1245, 1050 cm^{-1}.

B. Preparation from Benzyl N-(Hydroxymethyl)carbamate. 4-Penten-2-ol (700 mg, 8.17 mmol) was dissolved in 15 mL of dry THF, and *p*-toluenesulfonic acid (30 mg, 0.16 mmol) was added. Benzyl N-(hydroxymethyl carbamate (2.21 g, 12.26 mmol) dissolved in 10 mL of dry THF was added dropwise to the reaction mixture. The solution was heated at reflux for 20 min. The cooled solution was washed (saturated sodium bicarbonate and water), dried with $MgSO_4$, filtered, and concentrated. The oil was purified by preparative HPLC using a 25% EtOAc/hexane solvent system. Ether **3a** was obtained in a 60% yield (1.22 g).

4-(N-(Isobutyloxycarbonyl)aminomethoxy)-1-pentene. (3b). Isobutyl N-(acetoxymethyl)carbamate (9.45 g, 50 mmol) was dissolved in 30 mL of dry THF. 4-Penten-2-ol (4.41 g, 51.2 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg) were added. The solution was heated at reflux for 20 min and stirred at room temperature for an additional hour. The solution was quenched with saturated $NaHCO_3$ and diluted with Et_2O. The two layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated. The clear oil was purified by preparative HPLC using 20% EtOAc/hexane as the solvent. Ether **3b** was obtained in 51% yield (5.59 g): ^1H NMR (90 MHz, $CDCl_3$) δ 0.92 (d, J = 6 Hz, 6 H, $(CH_3)_2CH$), 1.15 (d, J = 6 Hz, 3 H, CH_3), 1.66-2.47 (m, 3 H, $CH_2C{=}C$ and $(CH_3)_2CH$), 3.46-3.99 (m, 3 H, $OCHCH_3$ including $CHCH_2O$ doublet, J = 6 Hz, at 3.83), 4.64 (d, J = 7.5 Hz, 2 H, NCH_2O), 4.81-5.19 (m, 2 H, $C{=}CH_2$), 5.49-6.09 (m, 2 H, CH=C and NH); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 18.9 ($(CH_3)_2CH$), 19.7 (CH_3), 27.8 ($(CH_3)_2CH$), 40.9 ($CH_2C{=}C$), 70.3 (OCH_2N), 71.1 ($CHCH_2O$), 72.4 ($OCHCH_3$), 116.8 ($C{=}CH_2$), 134.6 (CH=C), 156.6 (C=O).

N-(Benzyloxycarbonyl)-4,6-dimethyltetrahydro-1,3-oxazine (4a). Ethyl acetate (0.5 mL) was added to anhydrous mercuric nitrate (1.08 g, 3.3 mmol). Alkene **3a** (590 mg, 2.4 mmol) was added dropwise over a 20 min period under N_2 atmosphere to the mercuric nitrate suspension. Complete dissolution was observed after 15 min. This solution was stirred for an additional 10 min. Saturated NaOAc (1 mL) and 5% KOH (1 mL) were added and the mixture was stirred for 15 min. Sodium borohydride (300 mg, 7.9 mmol) dissolved in 1 mL of 5% KOH was added dropwise. The solution was stirred for 1 h and then diluted with Et_2O. The two layers were separated and the organic phase was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Purification by semi-preparative HPLC using 10% EtOAc/hexane as solvent gave 350 mg (59% yield) of tetrahydrooxazines **4a** and **5a**. Analysis by GC-MS showed a 73:27 ratio of cis and trans isomers. cis Tetrahydrooxazine **4a**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.16 (d, J = 6 Hz, 3 H, $OCHCH_3$), 1.30 (d, J = 6 Hz, 3 H, $NCHCH_3$), 1.33-1.90 (m, 2 H, $CHCH_2CH$), 3.58-4.08 (m, 2 H, CHO and CHN), 4.92 (s, 2 H, OCH_2N), 5.11 (s, 2 H, OCH_2Ph), 7.12-7.38 (m, 5 H, Ph); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 20.6 ($NCHCH_3$), 21.8 ($OCHCH_3$), 37.7 ($CHCH_2CH$), 49.5 (CHN), 67.0 (OCH_2Ph), 69.7 (OCH_2N), 70.6 (CHO), 127.8, 128.4, and 136.4 (Ph), 155.2 (C=O).

Characteristic signals for trans isomer **5a**. ^1H NMR (90 MHz, $CDCl_3$) δ 4.33-4.64 (m, 2 H, CHN including OCH_aH_bN doublet, J = 11 Hz, at 4.47), 5.45 (d, J = 11 Hz, 1 H, OCH_aH_bN); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 16.1 ($NCHCH_3$), 21.8 ($OCHCH_3$), 37.3 ($CHCH_2CH$), 45.1 (CHN), 67.0 (OCH_2Ph), 68.5 (OCH_2N), 71.2 (CHO).

***trans*-N-(Isobutyloxycarbonyl)-4,6-dimethyltetrahydro-1,3-oxazine 5b.** Acetone-d_6 (0.5 mL) was added to anhydrous mercuric nitrate (560 mg, 1.7 mmol). Alkene **3b** (315 mg, 1.5 mmol) was added dropwise over a 15 min period. The equilibration of organomercurial nitrates **8c** and **8t** was followed by ^1H NMR (See Results and Discussion). The mixture was stirred for a total of 46 h, concentrated, then diluted with ethyl acetate, and 1 mL of 5% KOH was added. The mixture was stirred for 15 min, and then sodium borohydride (200 mg, 5.3 mmol) dissolved in 1 mL of 5% KOH was added dropwise. The mixture was stirred for 1 h, and then diluted with Et_2O. The organic phase was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The oil was purified by semi-preparative HPLC using 10% EtOAc/hexane as solvent. Tetrahydrooxazines **5b** and **4b** were obtained in 49% yield (154 mg). Analysis by ^1H NMR showed the product to contain 94% of the trans isomer **5b** and 6% of the cis isomer **4b**. trans isomer **5b**: ^1H NMR (90 MHz, $CDCl_3$) δ 0.94 (d, J = 6.5 Hz, 6 H, $(CH_3)_2CH$), 1.24 (t, J = 7 Hz, 6 H, $NCHCH_3$ and $OCHCH_3$), 1.38-2.17 (m, 3 H, $CHCH_2CH$ and $CH(CH_3)_2$), 3.56-4.02 (m, 3 H, CHO including OCH_2CH doublet, J = 6 Hz, at 3.84), 4.26-4.68 (m, 2 H, CHN including NCH_aH_bO doublet, J = 11 Hz, at 4.47), 5.39 (d, J = 11 Hz, 1 H, NCH_aH_bO); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 16.4 ($NCHCH_3$), 19.0 ($(CH_3)_2CH$), 21.5 ($OCHCH_3$), 27.9 ($CH(CH_3)_2$), 37.2 ($CHCH_2CH$), 44.9 (CHN), 68.4 ($CHCH_2O$), 71.1 and 71.5 (CHO and NCH_2O), 154.4 (C=O).

***erythro*-4-Aminopentan-2-ol (7).** Tetrahydrooxazine **4a** (145 mg, 0.6 mmol, cis sample obtained from D. Hollingsworth[11]) was dissolved in 2 mL of trifluoroacetic acid and heated at reflux for 6 h. The solution was concentrated and the concentrate was dissolved in 5 mL of MeOH. Hydroxylamine hydrochloride (410 mg, 6 mmol) was added. The solution was heated at reflux for 12 h, and then concentrated. Saturated Na_2CO_3 (1 mL) was added with stirring. The mixture was extracted three times with methylene chloride. The combined organic phase was dried with anhydrous K_2CO_3, filtered, and concentrated by rotary evaporation. *erythro*-4-Aminopentan-2-ol[13] was collected in a 50% yield (30 mg): ^1H NMR (90 MHz, $CDCl_3$) δ 0.82-1.71 (m, 8 H, CH_2 including CH_3 doublet, 6 H, J = 6 Hz, at 1.15), 2.50-3.20 (m, 4 H, CHN, OH, and NH_2), 3.70-4.12 (m, 1 H, CHO); ^{13}C NMR (25.03 MHz, $CDCl_3$) δ 23.8 ($HOCHCH_3$), 27.6 (NH_2CHCH_3), 45.9 (CH_2), 48.6 (CHN), 68.8 (CHO).

***cis*-N-(Benzyloxycarbonyl)-4-(hydroxymethyl)-6-methyltetrahydro-1,3-oxazine (9c).** Alkene **3a** (0.423 g, 1.7 mmol) was dissolved in 10 mL of acetonitrile with sodium bicarbonate (21.41 mg, 1.7 mmol). Mercuric nitrate

(82.7 mg, 2.5 mmol) was added to the reaction solution, and the mixture was stirred for 1 h at room temperature. Concentrated aqueous potassium bromide (5 mL) was added, and the mixture was stirred vigorously for 2 h. Ethyl acetate (20 mL) was added to the mixture to dilute the solution. The organic phase was separated from the aqueous phase, and the aqueous phase was extracted with 10 mL of ethyl acetate. The combined organic layer was concentrated under reduced pressure to give 0.897 g (>98%) of organomercurial bromide 8 (X = Br, $R^1 = CH_2Ph$). Analysis by ^1H NMR showed a 3:1 ratio of 8c and 8t. Dimethylformamide (3.0 mL) and sodium borohydride (13 mg) were placed in a 25-mL centrifuge tube, which was capped with a rubber septum containing an inlet and an outlet needle for oxygen. Oxygen was supplied to the bottom of centrifuge tube. The oxygen flow was controlled at a rate of 300-400 mL/min. The sodium borohydride mixture was flushed with oxygen for 20 min. The oxidative demercuration was accomplished by adding 10 mL of DMF containing the organomercurial bromide (0.120 g, 0.23 mmol) slowly over a 15 min period to the sodium borohydride solution by syringe pump. Elemental mercury precipitated immediately. Aqueous sulfuric acid (0.1 N, 10 mL) was added to the reaction mixture. The mixture was stirred for an hour at room temperature, and the organic phase was extracted twice with 50 mL of ether. The combined organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 58 mg of product mixture as an oil, which was purified by preparative TLC (40% ethyl acetate/hexane). The cis alcohol 9c was collected in 60% yield (36 mg) and trans alcohol 9t was collected in 20% yield (12 mg). cis Alcohol 9c: TLC Silica Gel (Rf 0.14; 2:3 ethyl acetate/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 5 H, Ph), 5.47 (d, 1 H, J = 10.5 Hz, OCH_aHN), 4.48 (d, 1 H, J = 10.5 Hz, $OCHH_aN$), 5.21 (d, 1 H, J = 12.4 Hz, $COOCH_aH$), 5.12 (d, 1 H, J = 12.4 Hz, $COOCHH_b$), 3.86-3.76 (m, 4 H, CHO and CH_2OH), 3.60 (m, 1 H, CHN), 1.64 (m, 2 H, $CHCH_2CH$), 1.24 (d, 3 H, J = 6.1 Hz, Me); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 155.29 (C-9), 135.96, 128.56, 128.22, and 127.98 (Ph), 76.09 (C-2), 72.60 (C-6), 67.48 (C-10), 64.06 (C-7), 59.10 (C-4), 34.34 (C-5), 21.51 (C-8); IR (Neat) 3450, 2970, 1700, 1420, 1265, 1070, 1030 cm^{-1}. trans Alcohol 9t: TLC Silica Gel (Rf 0.09; 2:3 ethyl acetate/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 5 H, Ph), 5.52 (d, 1 H, J = 10.4 Hz, OCH_aHN), 4.52 (d, 1 H, J = 10.4 Hz, $OCHH_aN$), 5.15 (s, 2 H, $COOCH_2$), 4.45 (m, 1 H, CHN), 3.39-3.69 (m, 3 H, CHO and CH_2OH), 1.92 (broad, 1 H, OH), 1.66 (m, 2 H, $CHCH_2CH$), 1.18 (d, 3 H, J = 6.1 Hz, Me); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 155.06 (C-9), 136.14, 128.51, 128.15, and 127.95 (Ph), 72.15 (C-2), 69.45 (C-6), 67.58 (C-10), 61.36 (C-7), 51.03 (C-4), 32.28 (C-5), 21.63 (Me); IR (Neat) 3450, 2970, 1700, 1424, 1275, 1100 cm^{-1}.

trans-N-(Benzyloxycarbonyl)-4-(hydroxymethyl)-6-methyltetrahydro-1,3-oxazine (9t). Alkene 3a (72 mg, 0.29 mmol) was dissolved in 0.5 mL of acetonitrile-d_3. Mercuric nitrate (11.6.mg, 0.35 mmol) was added to the solution in an NMR tube. The progress of the reaction was monitored by ^1H NMR spectroscopy. The ^1H NMR spectrum had not changed after 72 hours. Anhydrous hydrogen bromide gas was added to the reaction tube. Some equilibration was observable after 30 min. After the mixture had equilibrated for 72 hours, the doublets (4.80-5.00 ppm) corresponding to the cis isomer had disappeared almost completely. The reaction mixture was transferred to a 25-mL round-bottomed flask, and 5 mL of saturated potassium bromide was added. The mixture was stirred vigorously for 2 hours. Ethyl acetate (20 mL) was added to the mixture to dilute the solution. The organic phase was separated from the aqueous phase, and the aqueous layer was extracted with 10 mL of ethyl acetate. The combined organic layer was concentrated under reduced pressure to give organomercurial bromide 8. This organomercurial was oxidized with oxygen and sodium borohydride under conditions used above for the preparation of 9c. The product mixture was purified by preparative TLC (40% ethyl acetate/hexene) to give 34.6 mg (45%) of trans alcohol 9t and 3.1 mg (4%) of cis alcohol 9c.

cis-N-(Benzyloxycarbonyl)-4-carboxy-6-methyltetrahydro-1,3-oxazine (10c). The cis alcohol 9c (106.5 mg, 0.4 mmol) was dissolved in 5 mL of acetone. Jones' reagent (14 drops) was added to the reaction solution until the orange color persisted, and the mixture was stirred for 2 h at 5 °C. Isopropyl alcohol was added to quench the reaction. Ethyl acetate (15 mL) was added to dilute the solution, and the mixture was dried over anhydrous magnesium sulfate. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give 107 mg (95.4%) of acid 10c as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 10.00 (broad, 1 H, COOH), 7.34 (s, 5 H, Ph), 5.17 (s, 2 H, $COOCH_2$), 5.13 (d, 1 H, J = 6.4 Hz, OCH_aHN), 4.90 (d, 1 H, J = 6.4 Hz, $OCHH_aN$), 4.42 (dd, 1 H, J = 6.1 and 8.3 Hz, NCH), 3.87 (m, 1 H, CHO), 2.18 (ddd, 1 H, J = 4.4, 6.1, and 13.9 Hz, $CHCH_aHCH$), 1.19 (dt, 1 H, J = 8.3 and 13.9, $CHCHH_aCH$), 1.26 (d, 3 H, J = 6.4 Hz, Me), ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 175.96 (C-7), 155.24 (C-9), 135.80, 128.52, 128.20, and 127.94 (Ph), 73.08 (C-2), 69.89 (C-6), 67.83 (C-10), 53.60 (C-4), 32.42 (C-5), 20.71 (Me); IR (Neat) 3600-2700 (COOH), 3060, 3030, 2970, 2930, 1700-1735, 1270, 1420 cm^{-1}.

trans-N-(Benzyloxycarbonyl)-4-carboxy-6-methyltetrahydro-1,3-oxazine (10t). The trans alcohol 9t (41

mg, 0.15 mmol) was dissolved in 3 mL of acetone. Jones' reagent (7 drops) was added to the reaction solution until the orange color persisted, and the mixture was stirred for 2 h at 5 °C. Isopropyl alcohol was added to quench the reaction. Ethyl acetate (10 mL) was added to dilute the solution, and the mixture was dried over anhydrous magnesium sulfate. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give 43 mg (quantitative) of trans acid **10t**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.51 (broad, 1H, COOH), 7.35 (s, 5 H, Ph), 5.48 (s, 2 H, $COOCH_2$), 5.54 (d, 1 H, J = 10.4 Hz, OCH_aHN), 4.61 (d, 1 H, J = 10.4 Hz, $OCHH_aN$), 5.11 (m, 1 H, NCH), 3.61 (ddq, 1 H, J = 2.0, 6.2, and 12.2 Hz, OCH), 2.14 (ddd, 1 H, J = 2.0, 12.2, and 12.2 Hz, $CHCH_aHCH$), 1.81 (dt, 1 H, J = 6.2 and 12.2 Hz, $CHCHH_aCH$), 1.22 (d, 3 H, J = 6.0 Hz, Me); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 175.71 (C-7), 154.32 (C-9), 135.59, 128.51, and 127.95 (Ph), 74.31 (C-2), 70.71 (C-6), 67.91 (C-10), 52.53 (C-4), 33.22 (C-5), 21.21 (CH_3); IR (Neat) 3600-2700 (COOH), 2975, 1735, 1715, 1425, 1270, 1080 cm^{-1}.

***trans*-2-Amino-4-methyl-γ-butyrolactone Hydrobromide (11).** The cis acid **10c** (25 mg, 0.1 mmol) was treated with 5 mL of HBr/acetic acid (20 weight %). The mixture was stirred at room temperature for 90 min. Excess HBr gas was removed by a stream of nitrogen gas. Ether (15 mL) was added to precipitate the product. The precipitate was filtered through a plug of glass wool in a disposable pipette, and the precipitate was washed with ether. The precipitate was dissolved in water, and water was removed at reduced pressure to give the known[1a] trans lactone hydrobromide **11** in 94% yield (18 mg): ^{1}H NMR (200 MHz, D_2O) δ 4.86 (m, 1 H, $CHCH_3$), 4.41 (t, 1 H, J = 9.9 Hz, $CHNH_3$), 2.40 (m, 2 H, CH_2), 1.27 (d, 3 H, J = 6.8 Hz, CH_3); ^{13}C NMR (200 MHz, D_2O) δ 174.05 (C=O), 77.22 (CHO), 47.97 (CHN), 31.89 (CH_2), 19.88 (CH_3); IR (KBr) 3425, 3115, 2982, 1779, 1397, 1217 cm^{-1}.

***cis*-2-Amino-4-methyl-γ-butyrolactone Hydrobromide (12).** The trans acid **10t** (40 mg, 0.14 mmol) was treated with 5 mL of HBr/acetic acid (20 weight %). The mixture was stirred at room temperature for 90 min. Excess HBr gas was removed by a stream of nitrogen gas. Ether (15 mL) was added to precipitate the product. The precipitate was filtered through a plug of glass wool in a disposable pipette, and the precipitate was washed with ether. The precipitate was dissolved in water, and water was removed at reduced pressure to give the known[1a] cis lactone hydrobromide **12** in 88% yield (27.0 mg): ^{1}H NMR (200 MHz, D_2O) δ 4.66 (m, 1 H, CHO), 4.36 (dd, 1 H, J = 8.7 and 12.2 Hz, CHN), 2.76 (ddd, 1 H, J = 5.2, 8.7, and 12.4 Hz, CH_tH), 1.88 (ddd, 1 H, J = 10.4, 12.2, and 12.4 Hz, CHH_c), 1.33 (d, 3 H, J = 6.2 Hz, CH_3); ^{13}C NMR (50.0 MHz, D_2O) δ 173.90 (C=O), 77.08 (CHO), 50.04 (CHN), 34.45 (CH_2), 19.49 (CH_3); IR (KBr) 3425, 3120, 2990, 1775, 1400 cm^{-1}.

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15. The greater thermodynamic stability of a *trans*-N-acyl-4,6-dialkyltetrahydro-1,3-oxazine is predicted by MM2 calculations on N-carbomethoxy-4,6-dimethyltetrahydro-1,3-oxazines.[16]
16. These calculations were performed with the MMX force field parameters using the program PCMODEL Version 1.0 (Serena Software, Bloomington, Indiana).
17. *Inter alia* (a) C. L. Hill and G. M. Whitesides, *J. Am. Chem. Soc.* 1974, **96**, 870-876. (b) E. J. Corey, M. A. Tius and J. Das, *J. Am. Chem. Soc.* 1980, **102**, 1742-1744. (c) J. C. Sih and D. R. Graber, *J. Org. Chem.* 1982, **47**, 4919-4927. M. Nishizawa, H. Nishide and Y. Hayashi, *Tetrahedron Lett.* 1984, **25**, 5071-5074. (d) R. Cordova and B. B. Snider, *Tetrahedron Lett.* 1984, **25**, 2945-2948. (e) E. J. Corey, C. Shih, N.-Y. Shih and K. Shimoji, *Tetrahedron Lett.* 1984, **25**, 5013-5016. (f) R. C. Bernotas and B. Ganem, *Tetrahedron Lett* 1985, **26**, 1123-1126. (g) S. Hanessian, J. Kloss and T. Sugawara, *J. Am. Chem. Soc.* 1986, **108**, 2758-2759.
18. This procedure would be useful for direct synthesis of N-methyl derivatives of γ-hydroxy-α-amino acids. For a recent discussion of N-methylation of amino acids see: P. A. Grieco and A. Bahsas, *J. Org. Chem.* 1987, **52**, 5746-5749 and references cited therein.
19. The faster equilibration for the organomercurial obtained from reaction of **3b** with mercuric nitrate in acetone-d_6 is attributed to the higher concentration (3 M) of substrate in that reaction. This results in a higher concentration of nitric acid (one equivalent liberated for each mole of cyclization product) in the solution after cyclization. Our earlier studies have shown that acid promotes the equilibration of such organomercurials.[2c]
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