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# STEREOSELECTIVE SYNTHESIS OF (±)-*erythro*- and *threo*-γ-HYDROXYNORVALINE

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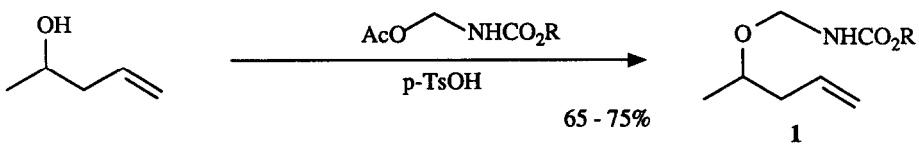
Both diastereomers of racemic γ-hydroxynorvaline were prepared from 4-penten-2-ol to illustrate a new general method for stereoselective synthesis of either *erythro*- or *threo*-1,3-amino alcohol systems from a single precursor.

Non-proteinogenic γ-hydroxy-α-amino acids are an important class of naturally occurring amino acids.[1] We have been interested in the application of intramolecular amidomercuration reactions to the control of stereochemistry in the synthesis of acyclic amino alcohol systems.[2] We now report results which show that intramolecular amidomercuration can be used as the key step in the stereoselective synthesis of either *erythro* or *threo* 1,3-amino alcohol systems from a single precursor. The utility of this method is demonstrated by the stereoselective synthesis of both diastereomers of racemic γ-hydroxynorvaline[1a] from 4-penten-2-ol.

The key step in these syntheses is the mercuric-ion initiated cyclization of carbamoyl ether **1**. These ether derivatives were formed by carbamoylmethylation of 4-penten-2-ol with N-acetoxymethyl carbamates (Rx 1). The N-acetoxymethyl carbamates were prepared by treatment of the carbamate with formaldehyde and acetic anhydride.[3]




(Rx 1)

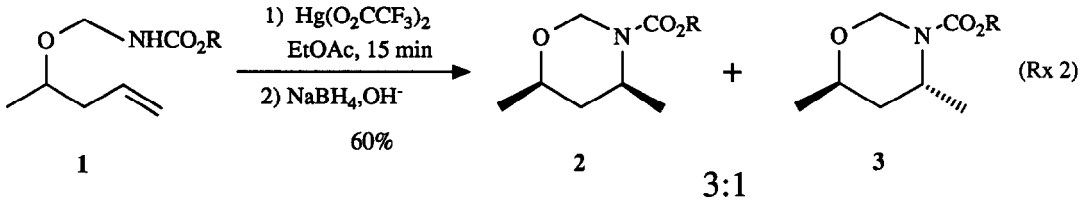
**1**

**a)** R = benzyl

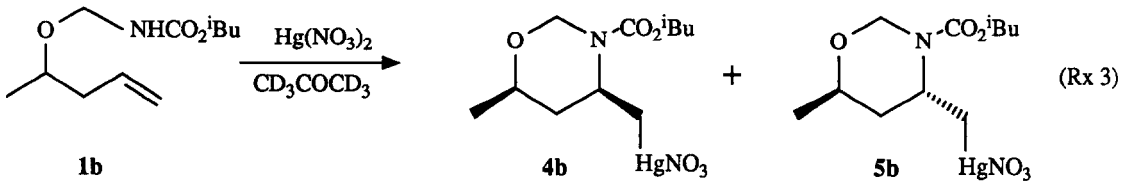
**b)** R = isobutyl

Initial cyclization reactions were conducted with mercuric trifluoroacetate in ethyl acetate, and the organomercurial was reduced with basic sodium borohydride after a short reaction period (Rx 2). These reactions demonstrated that the cyclization was moderately stereoselective and that the cis-tetrahydrooxazine **2** was the predominant isomer. The stereochemistry of **2a** was confirmed by hydrolysis of the CBZ group and cleavage of the tetrahydrooxazine ring to form authentic *erythro*-4-amino-2-pentanol.[4]

Because our prior studies had shown that the stereochemical outcome of some intramolecular amidomercuration reactions can be changed by equilibration,[5] we examined the cyclization of carbamoyl ether **1b** under conditions to effect equilibration (Rx 3). Thus, carbamate **1b** was treated with mercuric nitrate in acetone-$d_6$. Examination of the reaction mixture by $^1$H NMR after 30 minutes indicated that the cis organomercurial **4b** predominated by about a 4:1 ratio. After a reaction period of 14 hr, the ratio of **4b:5b** was 1:1. After reaction for 46 hr, the ratio had changed to approximately 5:95. Reduction of this mixture with sodium borohydride gave **2b**

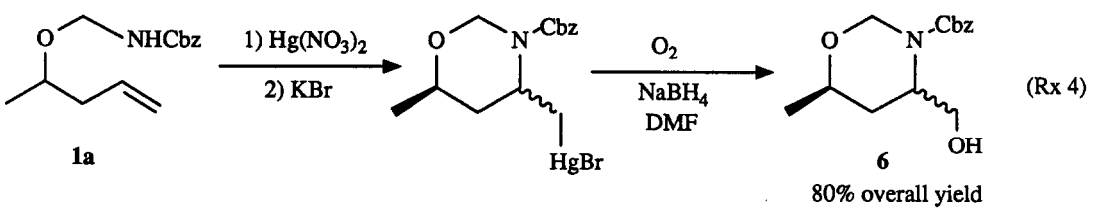



and **3b** in a 4:96 ratio. Thus, cyclization for short periods (kinetic control) gives predominately the cis product, and cyclization for long periods (thermodynamic control) gives the trans product with very high stereoselectivity.[6]




NMR analysis { 30 min 4:1; 14 hr 1:1; 46 hr <5:95

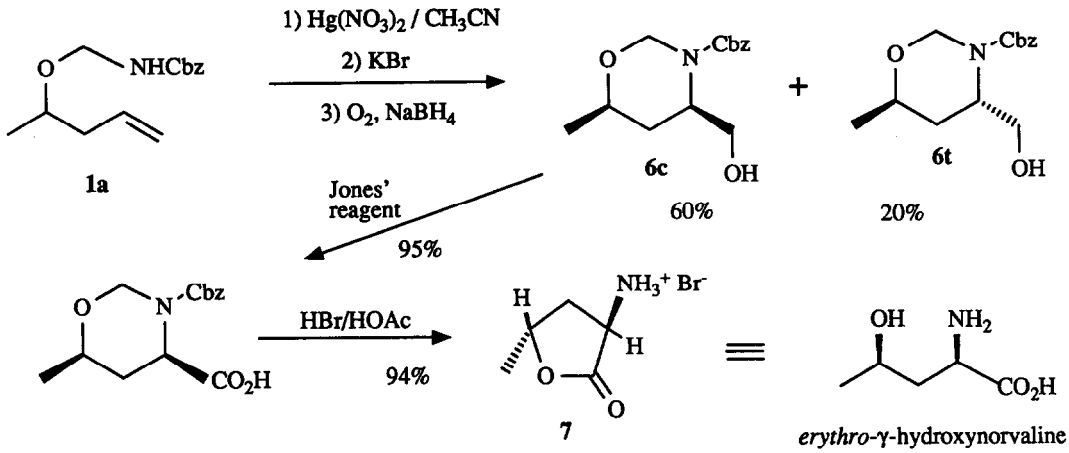
The remaining transformation necessary for synthesis of the title compounds was the conversion of the mercurical functional group into a carboxylic acid. The oxidative demercuration of organomercurials to form alcohols has found application in a number of recent synthetic efforts.[8] We found that conditions had to be carefully controlled for successful oxidative demercuration of the tetrahydrooxazines **4** and **5**. Under many conditions reported to be successful for other systems, we obtained either simple reductive demercuration or conversion back to starting carbamoyl ether **1**. However, conditions were found where alcohol **6** could be prepared from **1a** in 80% overall yield (Rx 4).[9]




The synthesis of racemic *erythro*-γ-hydroxynorvaline is shown in Figure 1. The cyclization was conducted under conditions for kinetic control. Oxidative demercuration of the organomercurial bromide and chromatographic separation gave the cis alcohol **6c** in 60% yield and the trans alcohol **6t** in 20 % yield. Oxidation of **6c** with Jones' reagent and deprotection with HBr/HOAc gave the *erythro* amino acid as the lactone hydrobromide **7**. The structure and stereochemistry of **7** was confirmed by comparison of spectral data with that reported in the literature.[1a,10]

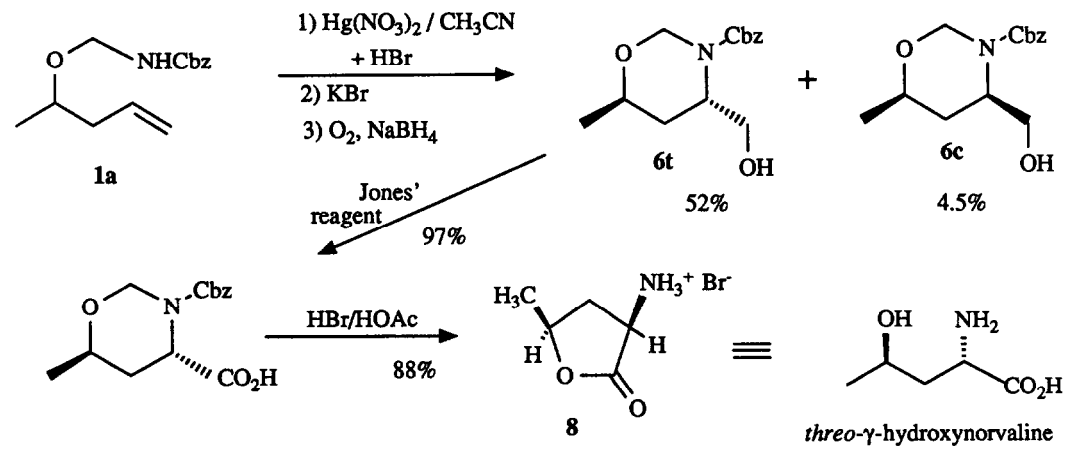
The synthesis of *threo*-γ-hydroxynorvaline as shown in Figure 2 required cyclization under conditions which allowed for equilibration of the organomercurial intermediate (thermodynamic control). Reaction of **1a** with mercuric nitrate in acetonitrile-$d_3$ (conc of **1a** was 0.29 M) showed no significant equilibration after several days of reaction.[14] However, equilibration was observed after addition of a small amount of HBr gas to the solution. After $^1$H NMR analysis indicated that equilibrium had been reached, the product was converted to the mercurial bromide

**Figure 1** Synthesis of (±)-*erythro*-γ-hydroxynorvaline




and subjected to oxidative demercuration. Alcohols **6t** and **6c** were isolated by preparative TLC in a 92:8 ratio. The isolated yield of pure **6t** was 52%. Oxidation followed by acidic cleavage of the CBZ group and the tetrahydrooxazine ring gave *threo*-γ-hydroxy norvaline as the lactone hydrobromide **8**. The structure and stereochemistry of **8** was confirmed by comparison of spectral data with that reported in the literature.[1a,10]

**Figure 2** Synthesis of (±)-*threo*-γ-hydroxynorvaline




Although only racemic amino acids were prepared in this study, the ready availability of enantiomerically pure (R)- and (S)-4-penten-2-ol[15] and related homoallylic alcohols empowers this method with the capability for preparation of enantiomerically pure γ-hydroxy-α-amino acids.[16]

**Acknowledgements.** We thank the Robert A. Welch Foundation and the National Institutes of Health for support of this research.

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6. 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. The energy of the diequatorial conformation of the cis isomer is increased by the $A^{1,3}$-type of interaction between the equatorial methyl and the planar carbamate functionality.[7]
7. These calculations were performed with the MMX force field parameters using the program PCMODEL Version 1.0 (Serena Software, Bloomington, Indiana).
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9. Cyclization was effected by treatment of 1.7 mmol of **1a** in 10 mL of acetonitrile containing 1.7 mmol of sodium bicarbonate with 2.5 mmol of mercuric nitrate for a period of 1 hr. Treatment with conc. aqueous KBr and extraction with ethyl acetate gave a quantitative yield of cyclic organomercurial after concentration. Then 0.23 mmol of the organomercurial bromide in 10 mL of DMF was added by syringe pump over a 15 min. period to 3 mL of DMF containing 0.34 mmol of sodium borohydride while $O_2$ was passed through the solution at 300-400 mL/min. For details and a discussion of reaction conditions which were not successful see: Nam, D.-H. Ph.D. Dissertation, Texas A&M University, Dec. 1987.
10. The $^1$H NMR spectra of **7** and **8** allow for unequivocal determination of stereochemistry.[1a] In addition, the chemical shift difference between the geminal protons at $C_3$ (0.88 ppm for **8** and < 0.2 ppm for **7**) is diagnostic.[11] The sum of the ring proton vicinal coupling constants for the cis isomer **8** is 5.7 Hz greater than the sum for the trans isomer **7** in accord with other 2,4-disubstituted γ-butyrolactones.[12] The $^{13}$C NMR spectra of lactones **7** and **8** show smaller differences than the $^1$H spectra; however, small downfield shifts for C-2 (2.1 ppm) and for C-3 (2.6 ppm) of the cis lactone **8** are consistent with results from other 2,4-disubstituted γ-butyrolactones.[11,13]
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14. The faster equilibration for the reaction shown in Rx 3 is attributed to a higher concentration (3 M) of substrate in that case, which produces a higher concentration of nitric acid in the solution after cyclization. Acid has been shown to aid equilibration of such organomercurials.[5]
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16. All new compounds were completely characterized by spectral ($^1$H and $^{13}$C NMR, IR) and analytical (HRMS or combustion analysis) methods.


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