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STEREOSELECTIVE SYNTHESIS OF (±)-*threo*-γ-HYDROXY-β-LYSINE LACTONE[1]

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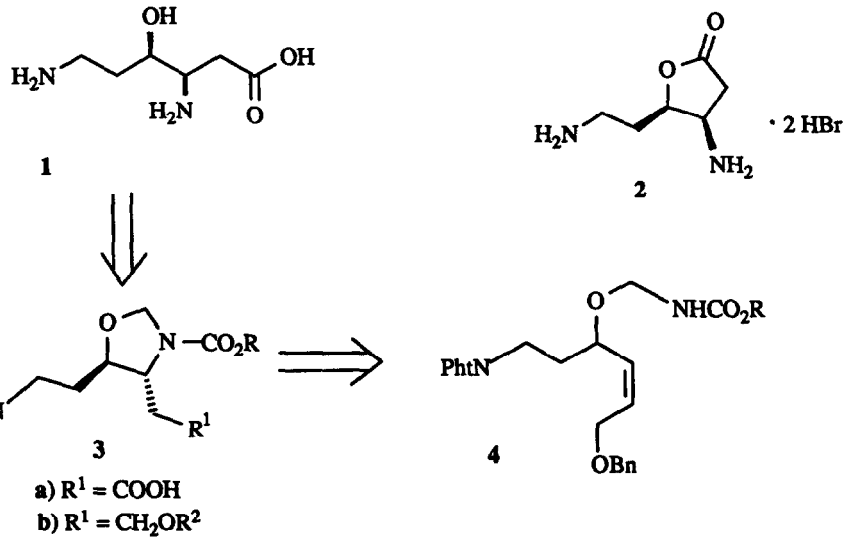
A stereoselective synthesis of racemic *threo*-γ-hydroxy-β-lysine is reported The *threo* aminoalcohol functionality is introduced by mercuric-ion initiated cyclofunctionalization of the acylaminomethyl ether **4a**

Our studies on intramolecular amidomercuration of acylaminomethyl ether derivatives of substituted allylic alcohols[1] provided the information necessary for application of the method to a rational synthesis of nonproteinogenic β-amino acids In this paper we report the synthesis of racemic *threo*-γ-hydroxy-β-lysine (**1**) Acid **1** is a basic amino acid isolated[2] as one of the composite amino acids from the hydrolysates of antitubercular peptides, tuberactinomycin A and N. Amino acid **1** is easily converted to lactone **2** under acidic conditions[2]

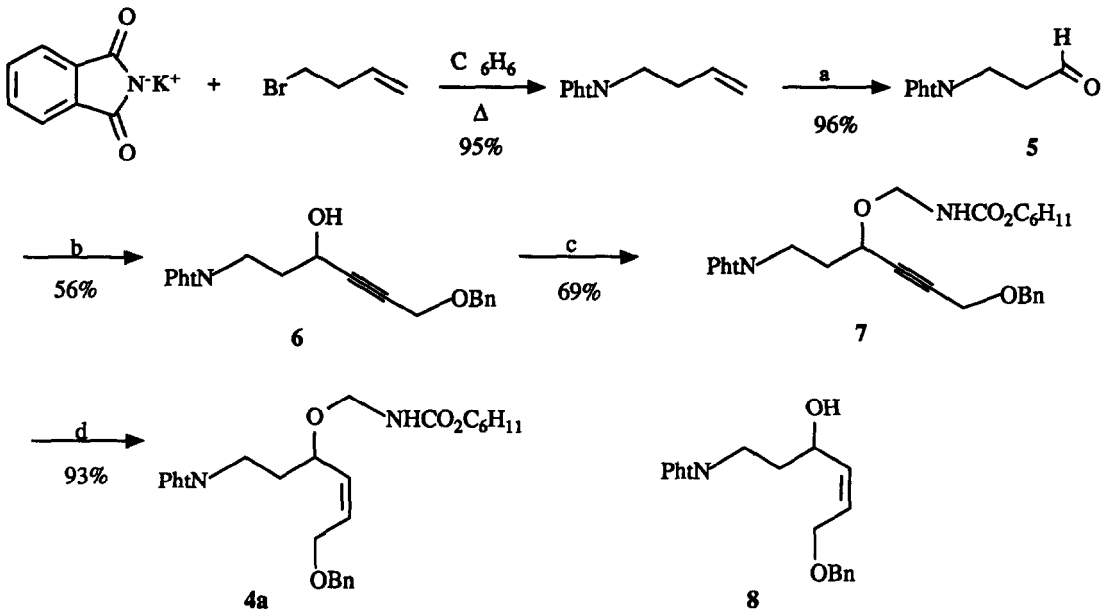


Based on our studies of intramolecular amidomercuration,[1] we considered that the *threo* 1,2-amino alcohol functionality of **1** could be formed from the trans oxazolidine derivative **3a**, in which the acid group could be generated from the corresponding alcohol **3b** (R^2 = H) by oxidation. The key step would be formation of oxazolidine derivative **3b** from acyclaminomethyl ether **4** by intramolecular amidomercuration The studies reported in the accompanying paper[1] predict that mercuric-ion initiated cyclization of the *Z* isomer **4** should be both regioselective and stereoselective with trans oxazolidine products predominating.

The synthesis of the cyclization substrate **4** is shown in Scheme 1. Gabriel type reaction[3] of potassium phthalimide[4] and 4-bromo-1-butene in refluxing benzene for 12 hours gave 4-phthalimido-1-butene in 95% yield Ozonolysis[3] of 4-phthalimido-1-butene followed by reductive cleavage of the ozonide by dimethyl sulfide gave aldehyde **5** in 96% yield. Sodium acetate was used in the ozonolysis to prevent formation of the corresponding dimethyl acetal. Aldehyde **5** was coupled with the magnesium salt of propargyl benzyl ether[5] to form alcohol **6** Yields in this reaction were only moderate under a variety of reaction conditions and with a variety of alkynyl salts Although alcohol **6** could be partially hydrogenated (H_2, $Pd/BaSO_4$, quinoline, MeOH) to give the cis allylic

alcohol **8**, the reaction was difficult to control to avoid overreduction. It was found to be much more convenient to convert **6** to the acylaminomethyl ether before partial hydrogenation

Scheme 1



(a) O_3, MeOH/CH_2Cl_2, -78 °C, Me_2S, NaOAc, (b) $BnOCH_2C{\equiv}CMgBr$, THF, -78 °C; (c) TsOH, $HOCH_2NHCO_2C_6H_{11}$, Et_2O, (d) H_2 (30 psi), $Pd/BaSO_4$, quinoline, MeOH

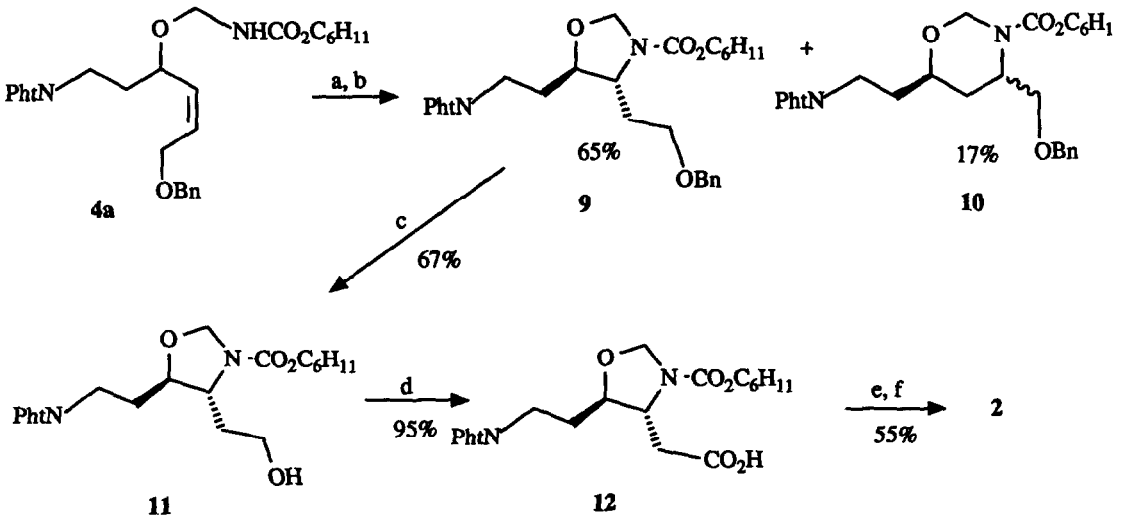
At this stage, the choice of protecting groups is important After cyclization, the benzyl ether must be cleaved to give the primary alcohol, which would then be oxidized to the acid. During these processes, the carbamate must remain intact, because an unprotected oxazolidine ring is not stable to acidic conditions [6] Thus, a benzyl carbamate could not be used. Various alkyl carbamates were investigated. The methyl derivative (**4**, R = CH_3) was difficult to purify, and conditions necessary for cleavage of an isobutyl carbamate caused problems at the end of the synthesis. In terms of deprotection and experimental convenience, the cyclohexyl carbamate proved most advantageous

The acyclaminomethyl ether **7** was formed in 69% yield by treatment of **6** with cyclohexyl (N-hydroxymethyl)carbamate [6] In contrast to the hydrogenation of alcohol **6**, partial catalytic hydrogenation of **7** was controlled easily. Optimum conditions for the reaction were· ether **7** at ~0.1 M in MeOH, 2 weight% of catalyst, 10 weight% of quinoline, 30 psi H_2, and reaction for 3-4 hr Under these conditions, the ether **4a** was formed in 93% yield

The conversion of ether **4a** into the lactone **2** is shown in Scheme 2 The conditions used in our previous cyclization studies[1,7] were modified slightly for cyclization of **4a**. Cyclization was effected with mercuric trifluoroacetate in ethyl acetate with sodium bicarbonate added to neutralize the acid formed during the amidomercuration Without sodium bicarbonate, more than 6 spots were observed by TLC, and yields were low Reductive demercuration with sodium borohydride gave oxazolidine derivative **9** in 65% yield as a single stereoisomer and tetrahydrooxazine derivative **10** in 17% yield as a mixture of cis and trans isomers Compounds **9**

and **10** were purified by chromatography, and structures were determined by proton NMR. The assignment of trans stereochemistry to the oxazolidine product **9** is based largely on analogy to the stereochemistry of the products obtained in our model studies.[1] This stereochemistry was confirmed by the further conversion of **9** to authentic **2**

Scheme 2



(a) $Hg(OTFA)_2$, EtOAc, $NaHCO_3$, (b) 5% NaOH, $NaBH_4$, (c) HCO_2H, MeOH, Pd/C; (d) Jones' reagent
(e) H_2NNH_2, MeOH, Δ, 9 hr; (f) HBr, HOAc, 64 °C (sealed ampoule), 4 hr

It is interesting to note that cyclization of **4a** gives a mixture of 5- and 6-membered ring products, while the cyclization of the non-branched 1,4-butendiol derivatives examined in our model studies gave only oxazolidine products [1] Thus, the α-alkyl substituent must disfavor ring closure to 5-membered ring products to some extent. It should also be noted that, in this case, the stereoselectivity of oxazolidine formation is higher than in the cyclization of the derivatives of 3-buten-2-ol examined in the preceeding paper [1]

The cleavage of the benzyl ether linkage under normal catalytic hydrogenolysis conditions was unsatisfactory Catalytic transfer hydrogenation[8] conditions were much more successful, even though a large amount of catalyst was required. Formic acid (10 volume%) in methanol was used as solvent and hydrogen source, and alcohol **11** was isolated in 67% yield. Alcohol **11** was oxidized with PDC[9] or Jones' reagent[10] to give acid **12** in good yield (90-95%). The pthalimide protecting group was removed by heating acid **12** with hydrazine in methanol. The resulting amino acid was heated with HBr in acetic acid[11] (sealed ampoule, 64 °C, 4 h) Under these conditions, the cyclohexyl carbamate was cleaved,[12] the oxazolidine ring was opened, and the resulting γ-hydroxyacid lactonized to produce racemic lactone **2** in 55% yield

The structure and stereochemistry of lactone **2** was confirmed by comparison of the 200MHz NMR spectrum of **2** with that reported in the literature [2,13] In particular the 5 1 Hz coupling constant between the β and γ protons clearly confirms the stereochemistry of **2**.[14]

The objective of the above synthesis was to confirm the high degree of regioselectivity and stereoselectivity (relative asymmetric induction)[15] predicted[1] for intramolecular amidomercuration of substituted diol derivatives such as **4** The synthesis of amino acid derivative **2** described in this paper leads to racemic material since the

cyclofunctionalization substrate **4a** was racemic. However, this method could be applied to synthesis of optically active **2** by preparation of non-racemic propargylic alcohol **6** through enantioselective reduction of the corresponding propargylic ketone.[16]

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

References and Notes

1. Applications of Intramolecular Amidomercuration 7. For paper 6 in this series see accompanying paper Harding, K. E ; Hollingsworth, D. R. *Tetrahedron Lett.* **1988**, *29*, preceding paper

2. Wakamiya, T., Shiba, T ; Kaneko, T. *Bull Chem. Soc. Jpn* **1972**, *45*, 3668-*3672*.

3. (a) Danishefsky, S., McKee, R , Singh, R. K *J Am Chem. Soc* **1977**, *99*, 4783-4788. (b) Danishefsky, S., McKee, R.; Singh, R K. *Ibid* **1977**, *99*, 7711-7713.

4 (a) Salzberg, P. L.; Supniewski, J. V *Org Syn Coll Vol I*, pp 119-121. (b) Landini, D ; Rolla, F *Synthesis* **1976**, 389-391

5 The propargyl benzyl ether was prepared from propargyl alcohol by alkylation of the sodium salt of propargyl alcohol with benzyl bromide in THF with tetrabutylammonium iodide added Czerneck, S ; Georgoulis, C., Provelenghiou, C *Tetrahedron Lett* **1976**, 3535-3536.

6 (a) Bergmann, E D. *Chem Rev.* **1953**, *53*, 309-352. (b) Jones, M., Harding, K., unpublished results, Texas A&M University.

7. (a) Harding, K. E.; Stephens, R.; Hollingsworth, D. R. *Tetrahedron Lett* **1984**, *25*, 4631-4632. (b) Harding, K E.; Marman, T H., Nam, D *Tetrahedron Lett* **1988**, *29*, 1627-1630.

8 (a) Rao, V. S., Perlin, A. S. *Carbohydrate Res* **1980**, *83*, 175-177. (b) El Amin, B , Anantharamaiah, G. M., Royer, G. P ; Means, G E *J Org Chem* **1979**, *44*, 3442-3444

9. Takano, S., Kashahara, C , Ogasawara, K. *Chem Lett* **1983**, 175-176

10 Thottathil, J. K., Moniot, J L , Mueller, R. H., Wong, M K. Y., Kissick, T. P *J Org Chem* **1986**, *51*, 3140-3143

11 Poroshin, K. T., Shibnev, V A., Lisovenko, A V , Grechishko, V. S *Izv Akad Nauk SSSR Ser Khim* **1966**, 922-924

12 Deprotection with HBr in refluxing acetic acid (conditions necessary to cleave an isobutyl carbamate) led to isolation of lactone product which contained significant amounts of the trans diastereomer

13. The 200 MHz spectrum of **2** cannot be compared directly with the published[2] 60 MHz spectrum. However, the peak pattern of the published spectrum is reproduced when the data from our spectra are transformed to 60 MHz using a spectral simulation program (PCPMR, Serena Software, Bloomington, Indiana) For example, the 8-line pattern observed at 200 MHz for the γ proton is transformed into the 5-line pattern shown in the published spectrum.

14 The coupling constants reported for **2** and its trans diastereomer are 4 9 and 3 1 Hz, respectively [2]

15 Bartlett, P A , *Tetrahedron* **1980**, *36*, 3-72

16 Nográdi, M *Stereoselective Synthesis* VCH: Weinheim, **1986**, Chapter 3

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