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SELECTIVITY IN THE AMINATION OF ALLYLIC ALCOHOLS via INTRAMOLECULAR AMIDOMERCURATION[1]

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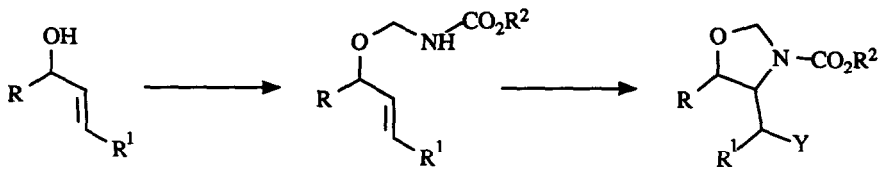
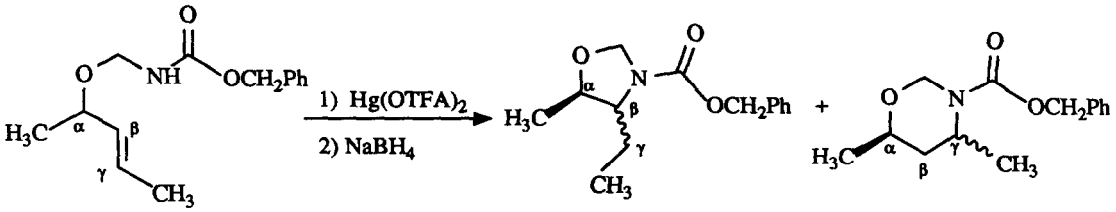
Intramolecular amidomercuration reactions of acylaminomethyl derivatives of γ-substituted allylic alcohols were examined. The effect of oxygen substitution on the δ carbon and of the geometry of the double bond on the regiochemistry and stereochemistry of the cyclization were established.

The use of cyclofunctionalization reactions for acyclic stereoselection in the synthesis of aminoalcohols has been the subject of recent interest.[2] Several groups, including ours, have developed methods for the conversion of acyclic allylic alcohols to vicinal aminoalcohols using cyclofunctionalization as a means of controlling stereochemistry.[3,4,5,6] Our initial studies on acylaminomethylation and mercuric-ion initiated cyclization of allylic alcohols (**1** ---> **2** ---> **3**) involved only alcohols with a terminal alkene functionality (R^1 = H).[3] Double bond substitution and stereochemistry have been found to affect regioselectivity and stereoselectivity in cyclofunctionalization reactions of other allylic systems.[4f,g,h,6b] Another variable in the intramolecular amidomercuration of disubstituted systems such as **2** ($R^1 \neq$ H) derives from the ability to conduct such reactions under conditions of either kinetic control or thermodynamic control.[7] This paper reports the results of our studies on regioselectivity and stereoselectivity in the intramolecular amidomercuration reactions of acylaminomethyl derivatives of allylic alcohols with disubstituted double bonds. These results provide the basis for a stereoselective synthesis of (±)-*threo*-γ-hydroxy-β-lysine.[8]



1 **2** **3**

Initial cyclization studies were conducted with carbamate **4**. Compound **4** was obtained by condensation of benzyl N-(hydroxymethyl)carbamate with 3-penten-2-ol in ether with a catalytic amount of p-toluenesulfonic acid. Treatment of **4** with with mercuric trifluoroacetate in acetonitrile for 15 minutes followed by reduction with sodium borohydride gave a mixture (ca. 20 : 80) of 5- and 6-membered ring products (**5** and **6**) in 60% yield. These isomers were separated by silica gel HPLC and characterized by ^{1}H and ^{13}C NMR.[9]

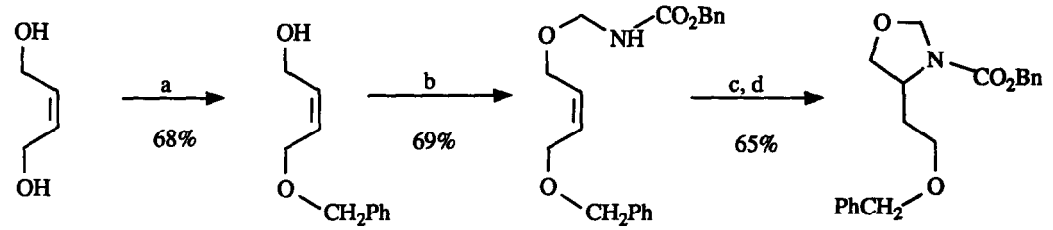


4 **5** **6**

One possible rationale for the predominant formation of six-membered ring products in this reaction is that cyclization occurs at the γ carbon owing to the electron-withdrawing effect of the ether oxygen on the α carbon

This effect would tend to destabilize carbocation character on the β carbon and favor nucleophilic attack at the γ-carbon [10] This rationale was tested by examination of the cyclization reactions of carbamate **9**.

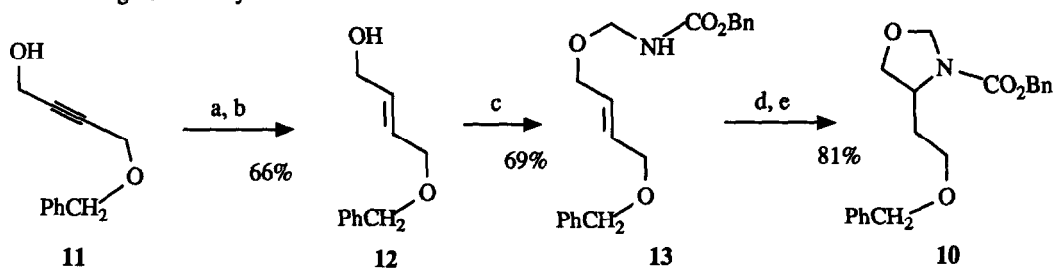
Carbamate **9** was prepared from commercially available *cis*-2-buten-1,4-diol (**7**). Monoalkylation of diol **7** with benzyl bromide gave alcohol **8** in 68% yield.[11] Condensation of benzyl N-(hydroxymethyl)carbamate and alcohol **8** provided ether **9** in 69% yield. Mercuric ion-initiated cyclization of **9** with mercuric nitrate followed by sodium borohydride reduction gave oxazolidine **10** in 65% yield No other isomers were detected The 5-membered ring structure of **10** was ascertained by proton decoupling and low temperature NMR experiments



7 **8** **9** **10**

(a) KOH, $PhCH_2Br$, (b) $HOCH_2NHCO_2Bn$, TsOH, (c) $Hg(NO_3)_2$, CH_3CN, (d) 10%NaOH, $NaBH_4$

Cyclization of the trans isomer **13** was investigated also. Monoalkylation of butyne-1,4-diol with benzyl bromide provided **11**, which was reduced with deoxygenated aqueous chromous sulfate[12] to give trans butenol **12** in 66% yield Condensation of alcohol **12** with benzyl N-(hydroxymethyl)carbamate by the usual procedure gave ether **13** in 69% yield Treatment of **13** with mercuric nitrate in acetonitrile followed by reduction with sodium borohydride gave oxazolidine **10** in 81% crude yield. The exclusive formation of 5-membered ring products in the cyclizations of **9** and **13** suggest that when the inductive effect of the ether oxygens on the disubstituted alkene is balanced, cyclization leads to preferential formation of 5-membered ring products. In contrast with Cardillo's results with iodocyclization of allylic imidates,[4f,g] the configuration of the double bond in isomers **9** and **13** had no effect on the regioselectivity

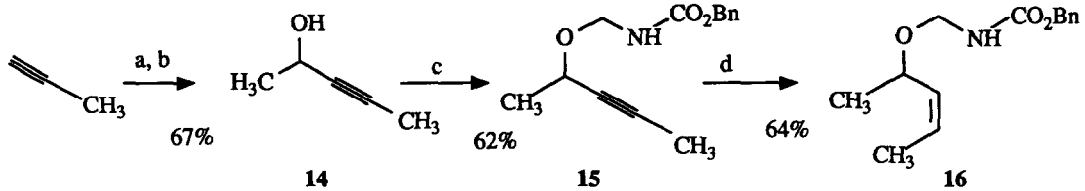


11 **12** **13** **10**

(a) $CrSO_4$, DMF, H_2O, 5 days, (b) NaOH, (c) $HOCH_2NHCO_2Bn$, TsOH, Et_2O; (d) $Hg(NO_3)_2$, CH_3CN, (e) NaOH, $NaBH_4$

The question of stereoselectivity in substrates with an alkyl substituent at the α carbon (e g **4**) must also be addressed In addition to **4**, the *Z* isomer **16** was studied Since *cis*-3-penten-2-ol is unavailable commercially, 3-pentyn-2-ol (**14**) was prepared by a standard procedure[13] using propyne, ethylmagnesium bromide, and acetaldehyde (67% yield) Several attempts were made to hydrogenate **14** with Lindlar catalyst and quinoline in various solvents However, pure *cis*-3-penten-2-ol could not be isolated owing to double bond isomerization The ratios of trans to cis alkene varied, and results were not reproducable Therefore, the acylaminomethyl ether **15** was prepared in 62% yield by reaction of **14** with benzyl N-(hydroxymethyl)carbamate in the presence of

p-toluenesulfonic acid Compound **15** was then partially hydrogenated with Lindlar catalyst and quinoline in methanol. Hydrogenation under 30 psi of hydrogen for one and a half hours gave pure **16** in 64% yield with no indication of double bond isomerization The purity of **16** was confirmed by capillary GC and 200 MHz NMR analysis



(a) EtMgBr, Et_2O, Δ, (b) CH_3CHO, O°C, (c) $HOCH_2NHCO_2Bn$, TsOH, Et_2O, (d) H_2, Lindlar, 30 psi

The intramolecular amidomercuration reactions of **4** and **16** were examined under conditions to evaluate the effect of reaction time on stereoselectivity and regioselectivity Cyclizations were conducted in acetonitrile-d_6 so that reaction mixtures could be examined by NMR Mercuric trifluoroacetate was used as the electrophile, and the reaction mixtures were reduced with sodium borohydride Four products were observed after reduction cis- and trans-**5** and cis- and trans-**6** The ratio of 5-membered ring (**5**) to six-membered ring (**6**) products varied little with time, but significant changes in stereochemistry were observed in some cases The results are shown in **Table I** The isomeric ratios were obtained by capillary GC analysis and were consistent with NMR analysis of the mixtures [14]

Table I. Product Ratios from cyclization of 4 and 5

Substrate	Reaction Time	*trans*-**5** *cis*-**5**	*trans*-**6** *cis*-**6**	**5** **6**
4	15 min	2 1	1 17	1 2
	20 hr	2 1	4 1	1 2
	11 days	2 1	29 1	1 15
16	19 min	10 1	1 2	2 1
	44 5 hr	9 1	20 1	2 1

If we consider the stereochemistry of the oxazolidine products (**5**) first, we note that the trans isomer was the major product in all cases However, the *Z* isomer **16** produced the trans isomer with higher stereoselectivity (10 1) than did the *E* isomer **4** (2 1) Little change is seen in the isomer ratio with increased reaction time More dramatic changes are noted for the tetrahydro-1,3-oxazine products (**6**) After short reaction times (kinetic control), the cis isomer is the major product However, with longer reaction times (> 40 hours), the trans isomer was obtained with high selectivity Similar results are observed with both stereoisomers **4** and **16**, although the level of stereoselectivity under kinetic control was much higher for the *E* isomer **4** Thus, the cis tetrahydro-1,3-oxazine is the initial product, but, as expected from our earlier results on cyclofunctionalization of homoallylic alcohol derivatives,[1] the more stable trans isomer is formed under equilibrating conditions

The double bond configuration also affected the ratio of oxazolidine products **5** to tetrahydrooxazine products **6** Cyclizations of the *E* isomer **4** gave a product mixture in which tetrahydrooxazine products predominated (2 1) Cyclization of the *Z* isomer **16** gave a mixture in which the oxazolidine products predominated by about the same

ratio It is not possible to rationalize these results with a simple set of transition state models,[15] but several synthetically important conclusions can be drawn Significant among these would be the prediction that intramolecular amidomercuration of a *Z* diol derivative with alkyl substitution at the α carbon (**2**, R = alkyl, R^1 = CH_2OR) would produce trans oxazolidine products with high selectivity Confirmation of this prediction and application of this method to total synthesis of a non-proteinogenic amino acid is reported in the accompanying paper [8]

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9 New compounds were characterized by combination of spectral (^1H and ^{13}C NMR, IR, and MS) methods

10 A similar effect of adjacent oxygen substitution on the regioselectivity of iodocyclization of allylic imidates was reported during the course of our studies See Ref 4h

11 *Inter alia* Kanao, M , Hashizume, T , Ichikawa, Y , Irie, K , Isoda, S *J Med Chem* **1982**, *25*, 1358-1363

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14 The stereochemistry of the major isomers could be assigned on the basis of detailed ^1H NMR analysis and was confirmed by conversion of *cis*-**6** to *erythro*-4-amino-2-pentanol[1] and by the amino acid synthesis described in the following paper [8]

15. In particular, it may be noted that either the -OR in-plane or -H in-plane transition state models discussed by Chamberlin and Hehre[16] would predict preferential formation of *trans*-**5**, but the preferential formation of *cis*-**6** by both the *E* and *Z* isomers cannot be rationalized by this model

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