time period indicated in Table I. The products were isolated as described above.

Hydrolysis of the Formamides. A solution of the formamide (2.5 mmol) in methanol which was 1.045 N in hydrogen bromide (23.9 mL, 25 mmol) was heated at reflux temperature for 12-48 h. The solvent was removed in vacuo, and the residue was crystallized from a suitable solvent system (see Table II). In this way the hydrobromide salts of *N*-methylphenacylamine, *N*-(2-phenylethyl)phenacylamine, and 1-(methylamino)-3-phenylacetone were obtained in 94%, 98%, and 85% yields, respectively. The physical constants of these compounds are given in Table II.

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Communications

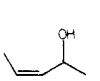
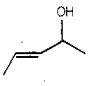
Stereoselective Bromination of Allylic Alcohols. A Facile Synthesis of (*E*)- or (*Z*)-Bromo Epoxides from a Common Starting Material

Summary: The addition of bromine to (*E*)- or (*Z*)-3-penten-2-ol may be directed to either face of the double bond. Depending upon the conditions subsequent reaction with base produces either an (*E*)- or (*Z*)-bromo epoxide.

Sir: The control of stereochemistry in an acyclic system is an important consideration in the synthesis of many complex molecules. However, despite the great advances which have been made in stereochemical control in cyclic systems, the control of stereochemistry in acyclic systems remains a challenge.[1] We report herein methods for controlling the addition of bromine to either diastereotopic face of the double bond of an allylic alcohol. Depending upon the procedure, further reaction produces either an (*E*)- or a (*Z*)-bromo epoxide of exceptionally high isomeric purity.

The hydroxyl group of allylic alcohols often provides a moderate to strong stereodirecting effect during additions to double bonds.[2] However, very little information is available on the stereodirecting effect of an alcohol group during the halogenation of acyclic allylic alcohols. It has been shown that allylic alcohols do not exhibit a neighboring-group effect.[3] On the other hand, Viala has shown that in certain instances bromination in sodium hydroxide solution can be highly selective while in most cases complex mixtures are formed.[4] According to Viala the stereochemistry was a consequence of product forming via direct closure of a bromonium ion or via formation of a dibromide. In cases where a directive effect of the hydroxyl group could be observed, the question of which diastereotopic face of the olefin reacts with bromine was not addressed. We have recently developed procedures to prepare simple straight-chain allylic alcohols (RCH=CHCHOHR) in high optical purity.[5] Development of effective stereoselective bromination procedures for these compounds could lead to the preparation of optically active epoxides. Hence we have investigated the stereochemistry of the bromination of such compounds.

Table I. Stereoselectivity of Bromination in Various Solvents

solvent	ratio of diastereomers 	
CH_2Cl_2[a]	3:1	2:1
n-C_5H_{12}[a]	4:1	2.5:1
$(C_2H_5)_2O$[a]	3.5:1	2.5:1
CH_3SOCH_3[b]		5:4
CH_3CO_2H[b]	2:1	1:1
CH_3OH[a]	10:1	4:1
C_2H_5OH[a]	10:1	3:1
H_2O[b]	5:1	2:1

[a] -78 °C. [b] 0 °C.

For our model study the bromination of (*E*)- and (*Z*)-3-penten-2-ols was investigated. The olefin was placed in a solvent and titrated with bromine at -78 or 0 °C. The products were then analyzed by VPC (Table I). In each case the *Z* isomer exhibited a greater stereoselectivity than the *E* isomer. The ratio of dibromo products was relatively insensitive to the solvent except in the case of the polar-protic solvents ethanol and methanol. In these cases the *Z* isomer gave a 10:1 ratio of products. The ratio could be increased to 12:1 by running the reaction at -120 °C. However, in the alcohol solvents, participation by the solvent to give ether products became a serious side reaction. The undesired ether product could be suppressed by saturating the alcohol with lithium bromide. The dibromo alcohol was then greater than 95% of the product. Simple extraction of the product into hexane, washing with water, drying ($MgSO_4$), and solvent removal give the dibromide in 88% yield.

The structure of the products was determined by conversion of the dibromide into the bromo epoxide (3 N NaOH, 60 °C, 1 h, 80% yield). The major isomer from either the *E* or *Z* allylic alcohol was identified as the *Z* epoxide by NMR analysis of the coupling constant across the epoxide (major product J = 3.2 Hz, minor product J = 1.8 Hz).[6]

The steric course of the reaction is outlined in Scheme I. For simplicity only one enantiomer of the alcohol is shown. The reaction was run on the racemic mixture. It

(1) For a review see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.
(2) For example, epoxidation: (a) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733; (b) Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549. Cyclopropanation: (c) Ratier, M.; Castaing, M.; Godet, J.-Y.; Pereyre, M. *J. Chem. Res. (S)* **1978**, 179, 2309.
(3) Winstein, S.; Goodman, L. *J. Am. Chem. Soc.* **1954**, *76*, 4368. However, under alkaline conditions 2-methyl-3-buten-2-ol does show neighboring group participation: Winstein, S.; Goodman, L. *Ibid.* **1954**, *76*, 4373.
(4) Santelli, M.; Viala, J. *Tetrahedron Lett.* **1977**, 4397. However, allylic alcohols of the RCH=CHCHOHR type were not studied.
(5) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867; Midland, M. M.; Preston, S. B. *J. Org. Chem.* **1980**, *45*, 747.
(6) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon: New York, 1969; p 287. Gaudemer, A. In "Stereochemistry", Kagan, H. B., Ed.; G. Thieme: Stuttgart, 1977; Vol. 1.

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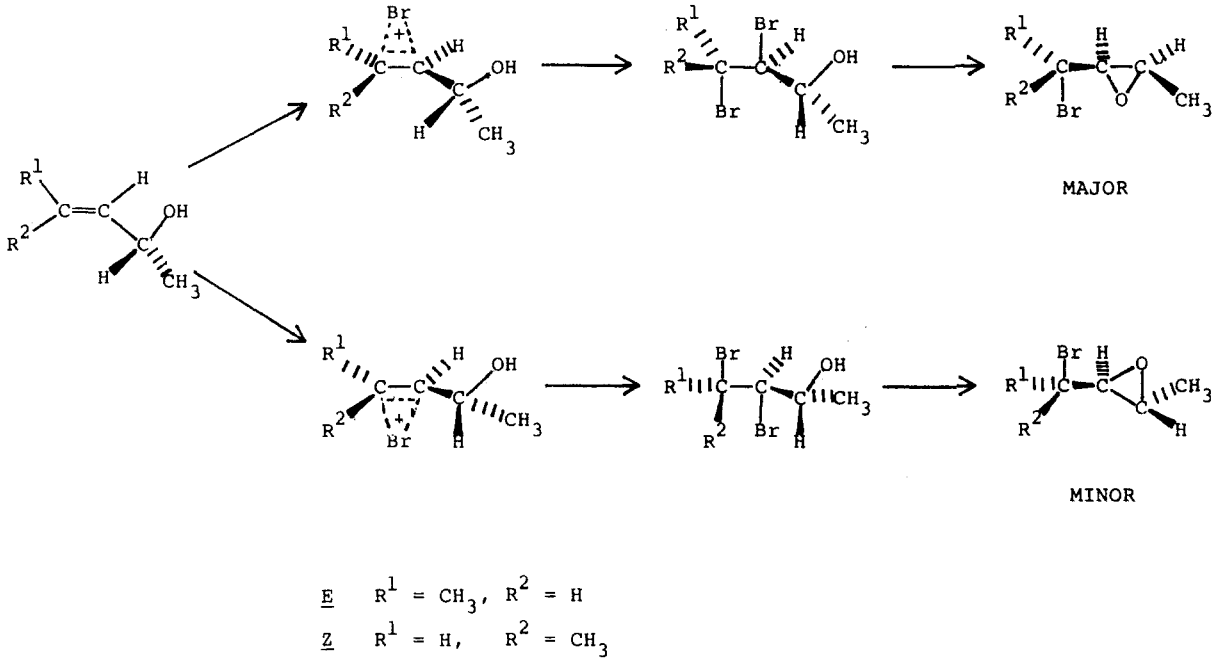
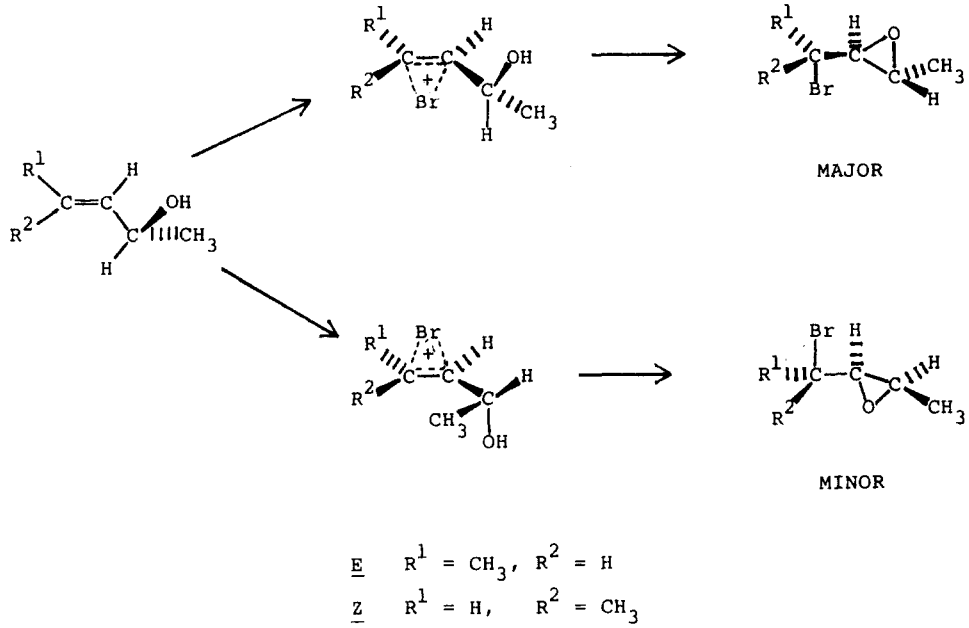
Scheme I



E $R^1 = CH_3$, $R^2 = H$

Z $R^1 = H$, $R^2 = CH_3$

Scheme II



E $R^1 = CH_3$, $R^2 = H$

Z $R^1 = H$, $R^2 = CH_3$

is assumed that bromine addition occurs in a trans manner. Opening of the bromonium ion by bromide is shown only at the carbon remote from the alcohol center. The electronegativity of the oxygen should favor bromide attack at the remote carbon.[7] Addition of bromide to the carbon adjacent to the alcohol would cause a crossover to the product which would come from the opposite bromonium ion. If one assumes that the most reactive conformation of the allylic alcohol has the hydrogen eclipsing the double bond[8] (rotation of the hydrogen down 60° in Scheme I), then the bromonium ion forms from the hydroxyl side of the olefin. The selectivity could be attributed to a steric effect or a directive effect of the hydroxyl group. However, this directing effect should be swamped out in methanol solvent. A better picture might be one in which the alcohol is anti to the double bond as depicted in Scheme I. The bromonium ion then has a choice of forming on the methyl side or the less hindered hydrogen side of the double bond. However, the cause for this selectivity must await further results before definite conclusions are made.

The bromination was then studied under Viala's conditions: addition of bromine to a 0.1 N solution of the alcohol in 1.5 N aqueous sodium hydroxide at 0 °C. Surprisingly the steric course of the reaction completely changed. The major product from either the *E* or *Z* allylic alcohol was now identified as an *E* epoxide by NMR. The *E* isomer gave a 5:1 ratio of products while the Z isomer gave only *one* product. The major epoxide product from the *E* allylic alcohol was identical with the minor product produced by first brominating the *Z* allylic alcohol and then treating the dibromide with base. Likewise the *Z* allylic alcohol under Viala's conditions gave a product identical with the minor product formed from the *E* allylic

(7) Bellucci, G.; Bianchini, R.; Ingrosso, G.; Mastrorilli, E. *Gazz. Chim. Ital.* **1978**, *108*, 643.

(8) Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167. Sharpless uses this conformation for peroxy acid epoxidations (ref 2a).

alcohol via the dibromide. The (*E*)-bromo epoxides formed from the same allylic alcohol by the two different processes were thus of opposite configuration at the bromide center. The reaction must thus follow the course outlined in Scheme II. In contrast to the formation of the dibromide, the bromonium ion must now form on the opposite face of the double bond. The bromo epoxide presumably forms directly from the bromonium ion through backside opening of the bromonium ion by the neighboring hydroxyl group. The steric interaction of the methyl at the alcohol center with the double bond is removed in the path leading to the major product.

The cause for this remarkable change in the steric course of the addition of bromine to the double bond remains to be explored.[9] Regardless of the explanation, the two processes provide a highly stereoselective approach to either (*E*)- or (*Z*)-bromo epoxides from a common starting material. Because of the stereospecificity of the bromination reaction, the chirality at the alcohol center may be used to control stereochemistry at two additional centers in an acyclic system. We are continuing to explore the mechanistic and synthetic aspects of this reaction.

Acknowledgment. This work was supported by the National Institutes of Health.

(9) The stereoselectivity of the reaction appears to be limited to the internal double-bond isomer. Thus bromination of 1-hepten-3-ol produces a 2:1 mixture of dibromo diastereomers under a variety of conditions including aqueous base. Similar results (although attributed to competing reactions of direct closure of the hydroxy bromonium ion and epoxide formation via the dibromide and not to addition of bromine to the two diastereotopic faces of the double bond) have been reported for 2-methyl-1-buten-3-ol.[4]

(10) Alfred P. Sloan Foundation Fellow, 1978–1982.

(11) Recipient of a President's Undergraduate Fellowship.

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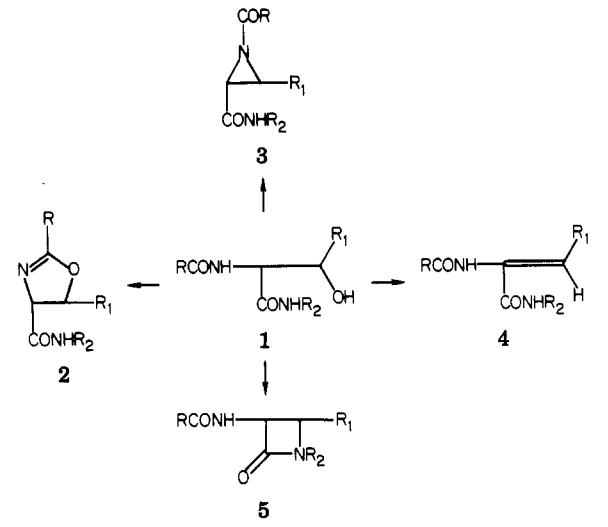
Stereoselective Chiral Synthesis of *N*-Aryl-α-amino-β-lactams from β-Hydroxy-α-amino Acids[1]

Summary: Arylamides of amino-protected β-hydroxy-α-amino acids were cyclized to optically pure, *cis*- or *trans*-3-amino-1-aryl-2-azetidinone derivatives by an intramolecular S_N2 reaction mediated by diethyl azodicarboxylate and triphenylphosphine or hexamethylphosphorus triamide.

Sir: Miller and co-workers[2] have reported recently a synthesis of β-lactams from N-protected serine hydroxamic acids by reaction with diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP). According to these authors, the key to the cyclization is the appreciable acidity of the NH bond of the hydroxamic acids.



Trying to extend the scope of the Mitsunobu reaction,[3,4] we[5-8] have been studying the replacement of hydroxyl groups with inversion mediated by phosphines (and phosphites) and diethyl azodicarboxylate. In the course of these studies we too had studied the possible synthesis of β-lactams from β-hydroxy-α-amino acids by this reaction.[1b] We report here our findings on the formation of both three- and four-membered heterocycles from N-protected amino acid derivatives.

A β-hydroxy-α-amino acid amide of the type **1** possesses multiple functionalities and can give rise to three-, four-, or five-membered heterocycles or acyclic products, such as **2**–**5**, through the loss of the elements of water.[9]

Compounds of type **1** are readily available from amino-protected β-hydroxy-α-amino acids and an amino compound under the influence of dicyclohexylcarbodiimide at room temperature or phosphorus oxychloride at −15 °C; the protection of the hydroxy group is unnecessary during this reaction.

When the *p*-toluidide (**6**) of *N*-(carbobenzyloxy)-L-serine was treated with DEAD–TPP in tetrahydrofuran at room temperature for 24 h, the β-lactam **7** was obtained in 53% yield. The 3-amino-1-(*p*-tolyl)-2-azetidinone (**8**) prepared from **7** by catalytic hydrogenolysis over 10% Pd/C in tetrahydrofuran was tested with a chiral shift reagent and was found to be monoenantiomeric.[10] Thus, β-lactam formation with DEAD–TPP must occur with total retention of chirality of the α-amino acid.[11]

β-Lactam formation from the L-threonine derivative (**9a**) was attempted, but the product (**10a**) obtained from the DEAD–TPP reaction in 54% yield after chromatographic

(1) (a) Part 62 in the series "Studies on Lactams". For part 61 see M. S. Manhas, A. K. Bose, and M. S. Khajavi, *Synthesis*, in press. (b) M. S. Manhas, D. P. Sahu, and A. K. Bose, presented at the 179th National Meeting of the American Chemical Society, TX, Mar 1980, MEDI-68.

(2) (a) P. G. Miller, P. G. Mattingly, M. A. Morrison, and J. F. Kerwin, Jr., *ibid.*, **102**, 7026 (1980).

(3) O. Mitsunobu, M. Wada and T. Sano, *J. Am. Chem. Soc.*, **94**, 679 (1972).

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(9) V. Schmidt, J. Hausler, E. Ohler, and H. Poisel, "Progress in the Chemistry of Organic Natural Products", Springer-Verlag, Wien, New York, 1979, Vol. 37, Chapter 2.

(10) Eu(tfac)$_3$ was used as the chiral shift reagent for studying the ^{1}H NMR spectra of **8** in $CDCl_3$ solution. The quartet pattern (J = 1.5 Hz) for the trans proton at C-4 of DL-**8** from *trans*-DL-serine was separated into two sets of quartets of equal area. Under the same conditions, **8a** from L-serine showed only the quartet at lower field.

(11) Similar results with serine hydroxamic acids have been reported by Miller et al. (see ref 2).

0022-3263/81/1946-1229$01.25/0