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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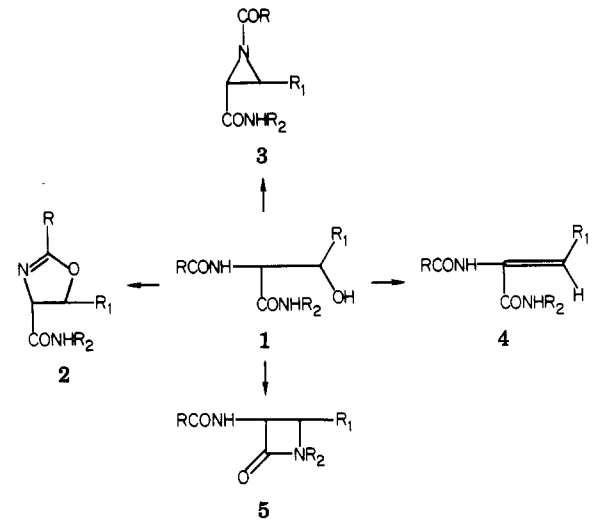
Received September 29, 1980

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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(7) M. S. Manhas, W. H. Hoffman, B. Lal, and A. K. Bose, *J. Chem. Soc., Perkin Trans. 1*, 461 (1975).

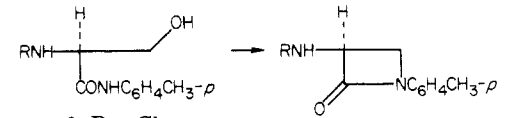
(8) (a) B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, *Tetrahedron Lett.*, 1977 (1977); (b) C. Gluchowski, B.S. Thesis, Stevens Institute of Technology, 1978.

(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.

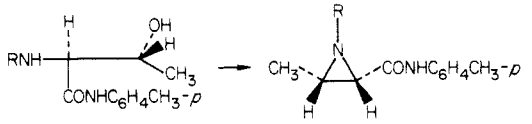
(11) Similar results with serine hydroxamic acids have been reported by Miller et al. (see ref 2).

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



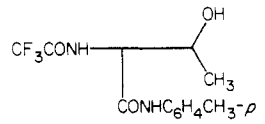
6, R = Cbz

7, R = Cbz
8, R = H



9a, R = Cbz
b, R = *t*-BOC

10a, R = Cbz
b, R = *t*-BOC



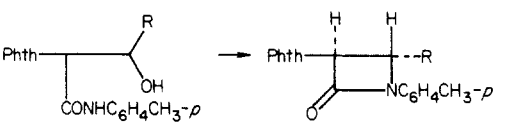
11

separation was not a β-lactam since the IR spectrum showed the presence of the arylamide group. Wojciechowska and co-workers[12] have reported the formation of the dehydroamino acids **4** from N-protected serine and threonine esters under the influence of DEAD–TPP reagents. The NMR spectrum of **10a**[13] was incompatible with structure **4**. The three-membered-ring structure **10a** was assigned in preferrence to the oxazoline structure of type **2** on the basis of spectral data.[13] In the ^{1}H NMR spectrum of **10a** the ring protons resonated at high field characteristic of an aziridine ring.[14] Removal of the *t*-BOC group with an excess of trifluoroacetic acid led to ring opening and the formation of the *p*-toluidide of *N*-trifluoracetylthreonine (**11**).[15]

On the basis of the 6-Hz coupling between the two protons on the aziridine ring in **10a** and **10b**, cis stereochemistry can be assigned to them. Such steric disposition of these protons indicates that ring formation involves inversion at the carbinol carbon.

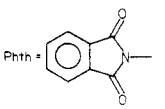
To circumvent the formation of aziridines, the amino group of L-serine, L-threonine, and DL-*threo*-phenylserine was protected by conversion to the phthalimido group. The corresponding amides **12**, **13**, and **14** afforded β-lactams **16** and **17** in 40–60% yield under the influence of DEAD–TPP reagents.

The β-lactams **16** and **17** were found to be of trans stereochemistry on the basis of NMR spectra. Since the starting materials were threonine and *threo*-phenylserine derivatives, ring closure must have involved inversion of the carbinol carbon. Previously, Mitsunobu et al.[3] as well as we[5-8] and others[16] have shown that the intermolecular substitution of a hydroxyl group by nucleophiles under the action DEAD–TPP reagent proceeds with inversion of



12, R = H
13, R = CH_3
14, R = C_6H_5

15, R = H
16, R = CH_3
17, R = C_6H_5



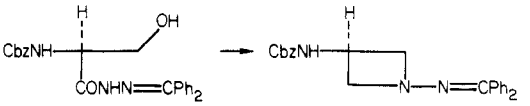
configuration. The intramolecular reaction, therefore, shows the same steric characteristics as the intermolecular reaction.

We have also studied the effect of changing the nature of the phosphine reagent. It was found that the conversion of amide **6** to the β-lactam **7** can be smoothly effected by replacing TPP with hexamethylphosphorus triamide, P-$(NMe_2)_3$. On the other hand, substitution of tributylphosphine or triethylphosphite for TPP led to dehydration products **20** and **21** from **18** and **19**.

18, R = Cbz;
R′ = C_6H_3-2,4-$(OCH_3)_2$
19, R = *t*-BOC;
R′ = $C_6H_4OCH_3$-*p*

20, R = Cbz;
R′ = C_6H_3-2,4-$(OCH_3)_2$
21, R = *t*-BOC;
R′ = $C_6H_4OCH_3$-*p*

The reaction of (carbobenzyloxy)serine with benzophenone hydrazone gave the acyl hydrazide **22** which on treatment with DEAD–TPP resulted in the formation of the β-lactam **23** in 30% yield.



22 **23**

In summary, chiral synthesis of 1-aryl-3-amido-2-azetidinones[17] from amino-protected β-hydroxy-α-amino acid amides can be achieved by the DEAD–TPP reaction if the appropriate protective group, amide group, and phosphorus(III) reagent are used. The cis or trans configuration of the β-lactam can be assured by choosing the threo or erythro configuration of the β-hydroxy-α-amino acid. Experimental details and the applications of this synthetic method to the preparation of key intermediates for nocardicin and analogues will be described elsewhere.

Acknowledgment. We are grateful to Provost L. Z. Pollara for his interest in this work and to Stevens Institute of Technology for partial support to one of us (D.P.S.) We thank Bikash Pramanik and Keiko Tabei for the chemical-ionization mass spectra.

(12) H. Wojciechowska, R. Pawlowicz, R. Andruszkiewcz, and J. Grzybowska, *Tetrahedron Lett.*, 4063 (1978).

(13) CI mass spectrum (CH_4), $(M + 1)^+$ at *m/e* 325 (calcd mol wt 324); IR (neat) 3300 (NH), 1715 (CbzCO), 1660 (amide CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3 H, *J* = 6 Hz), 2.30 (s, 3 H), 2.38 (quintet, 1 H, *J* = 6 Hz), 3.30 (d, 1 H, *J* = 6 Hz), 5.26 (s, 2 H), 7.08 (d, 2 H, *J* = 9 Hz), 7.28 (s, 5 H), 7.52 (s, 2 H, *J* = 9 Hz), 9.11 (br, 1 H).

(14) (a) K. Okawa, T. Kinutani, and K. Sakai, *Bull. Chem. Soc. Jpn*, 41, 1353 (1968); (b) M. Ohtsuru and K. Tori, *J. Mol. Spectrosc.*, 27, 296 (1968); (c) A. Hassner, G. J. Mathews, and F. W. Fowler, *J. Am. Chem. Soc.*, 91, 5046 (1969).

(15) IR (Nujol) 3280 (NH), 1698 (acid CO), 1640 cm^{-1} (amide CO); NMR ($CDCl_3$–Me_2SO-d_6) δ 1.20 (d, 3 H, *J* = 6 Hz), 2.30 (s, 3 H), 4.72 (quintet, 1 H, *J* = 6 Hz), 4.63 (br, 1 H), 6.92 (d, 1 H, *J* = 6 Hz), 7.08 (d, 2 H, *J* = 9 Hz), 7.53 (d, 2 H, *J* = 9 Hz), 8.3 (br, 1 H), 9.63 (br, 1 H); CI mass spectrum (NH_3), *m/e* 305 $[(M + 1)^+]$, 322 $[(M + NH_4)^+]$.

(16) (a) H. Loibner and E. Zbiral, *Helv. Chim. Acta*, 60, 417 (1977); (b) E. Grochowski and E. Falent-Kwastowa, *J. Chem. Res. S*, 300 (1978).

(17) All new β-lactams gave satisfactory elemental and spectral analyses.

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Received September 29, 1980