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RAPID SYNTHESIS OF β-HYDROXY-α-AMINO ACIDS, SUCH AS L-THREONINE, β-HYDROXYPHENYLALANINE, AND β-HYDROXYLEUCINE, VIA AN APPLICATION OF THE SHARPLESS ASYMMETRIC EPOXIDATION[1]

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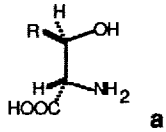
Abstract: The optically active epoxy alcohols **6abc**, prepared by a Sharpless kinetic resolution-epoxidation process, were converted to the optically pure β-hydroxy-α–amino acids **1abc** in four steps and high overall yield.

ß-Hydroxy-α-amino acids are an important class of compounds, appearing in nature both as natural products themselves (threonine, serine, 4-hydroxyproline) and as components of more complex natural compounds (e.g., ß-hydroxytyrosine and ß-hydroxyphenylalanine derivatives in the vancomycin group, bouvardin, and other cyclic peptides;[2] ß-hydroxyleucine in lysobactin;[3] MeBmt in cyclosporin;[4] 3-hydroxyhomotyrosine in echinocardin D[5]). They have also been used as intermediates in the synthesis of such important natural products as ß-lactams.[6] Despite their importance, there are only a few good non-enzymatic methods available for their asymmetric synthesis in high enantiomeric purity, most of which have been developed quite recently.[7] These results, and those in the racemic area,[8] prompt us to report our work on a short and efficient synthesis of ß-hydroxy-α-amino acids, exemplified by the synthesis of natural l-threonine **1a**, 2S, 3R-ß-hydroxyphenylalanine **1b**, and 2S, 3R-ß-hydroxyleucine **1c**.



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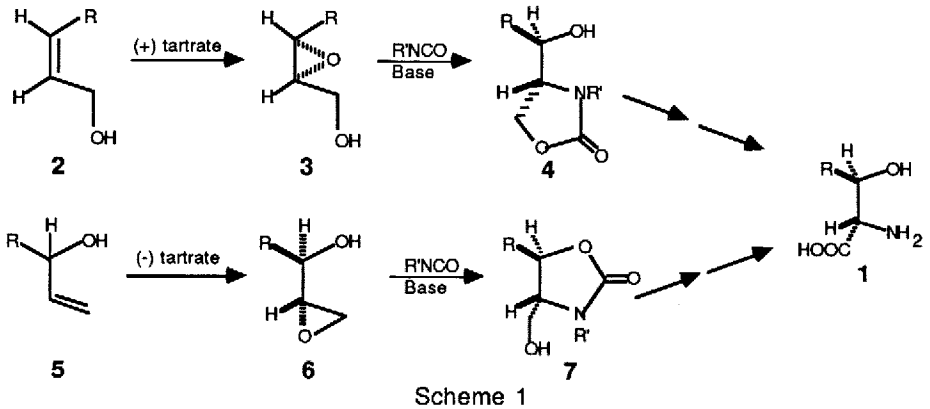
a R=CH_3
b R=C_6H_5
c R=$CH(CH_3)_2$

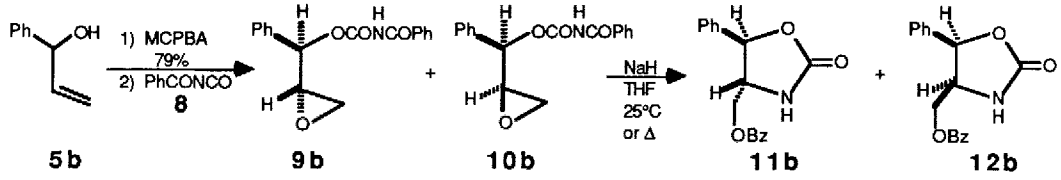
There are two potential applications of the excellent epoxidation technology of the Sharpless group[9] to the synthesis of **1abc**, as shown in Scheme 1. Asymmetric epoxidation of the Z-allylic alcohol **2** with (+)-tartrate would produce the epoxide **3** which on reaction with an isocyanate should afford the oxazolidinone **4**[10] and thence **1**. The second approach involves kinetic resolution-epoxidation of the opposite allylic alcohol **5** with (-)-tartrate to give the epoxide **6** which would again be transformed into the isomeric oxazolidine **7** on treatment with an isocyanate and thence into **1**. We chose the second route since the conversion of **2** into **3** is reported to proceed with low enantiomeric excess (~65% ee) when R is phenyl or any other large group,[9a] and thus would be inappropriate for the two compounds substituted with bulky groups **1bc**. However there was a serious question of whether kinetic resolution during the epoxidation of **5** where R is phenyl would proceed well, since Sharpless has reported that this epoxidation is slow and the ratio of the fast to the slow rates of epoxidation (k_{rel}) is only 4-10 (generally k_{rel} is >15 for successful kinetic resolutions). As we report herein, this kinetic resolution can be carried out with quite high ee (90-95%).

We initially investigated some of the chemistry in the racemic series. Treatment of 1-phenylprop-2-en-1-ol **5b**[11] with MCPBA gave a 79% yield of a mixture of the erythro and threo epoxyalcohols which were treated with



Scheme 1

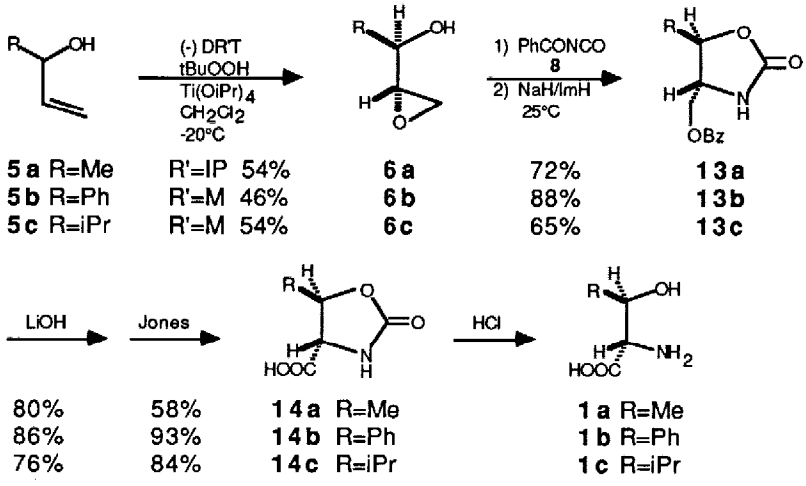
benzoyl isocyanate **8**[12] to give in 91% yield the corresponding erythro and threo epoxy carbamates **9b** and **10b** in a 53:47 ratio (determined by integration of the benzylic proton in each - **9b**: δ 5.88, d, *J*=3.87 Hz; **10b**: δ 5.55, d, *J*=6.36 Hz). Treatment of a solution of the mixture of **9b** and **10b** in THF with NaH (from 0.2 eq to 1.0 eq) at 25°C or at reflux caused the erythro isomer **9b** to cyclize to the trans oxazolidinone **11b** (in which the benzoyl group has shifted from N to O) while the threo isomer **10b** generally remained unchanged under the mild conditions and was



converted to a mixture of easily separated unknown byproducts (not the cis oxazolidinone **12b**) under the more vigorous conditions.[13] The structure of the trans oxazolidinone **11b** was assigned by comparison of ^{1}H NMR data, especially the coupling constants, to that reported in the literature for the corresponding acid,[8a,14] and thus permitted the assignment of stereochemistry to **9b** and **10b**. Flash chromatographic separation (3:1 hexane/ethyl acetate) gave purified samples of **9b** and **10b**. Heating a solution of **10b** with sodium hydride in THF for 18h produced the cis oxazolidinone **12b**, as reported by Knapp.[8b] Also the mixture of erythro and threo isomer **9b** and **10b** give an easily separable mixture of **11b** and **12b** on standing without added base at 25°C for an extended period of time.

Having first tested this chemistry in the racemic series, we then turned to the enantiomerically pure materials (Scheme 2). Treatment of the allylic alcohols **5abc** with 0.5 eq *t*-butyl hydroperoxide and 1 eq titanium tetraisopropoxide in CH_2Cl_2 at -20°C for several days in the presence of 1.2 eq of (-)-DIPT (for **5a**) or 1.5 eq of (-)-DMT (for **5bc**) afforded the desired epoxyalcohols **6abc** in good yields.[15] The enantiomeric purities of **6abc** were shown to be >95%, 90%, and 93%, respectively, by integration of the relevant peaks in the ^{1}H NMR of each in the presence of 0.4 eq of Eu(hfc)$_3$.[16] Treatment with benzoyl isocyanate **8** gave the corresponding carbamates which were not isolated but directly converted into the crystalline oxazolidinones **13abc** in good yield by reaction with sodium hydride and imidazole in THF at 25°C. Again a facile N to O migration of the benzoyl group is observed. Basic hydrolysis of the benzoate preceded well in all cases to give the primary alcohols which were oxidized to the acids **14abc**[17] in excellent yields. The optical purity of all of these acids were determined to be >95% ee by integration of the relevant peaks in the ^{1}H NMR with 1.0 eq Eu(hfc)$_3$.[18] Hydrolysis of the oxazolidinones **14abc** under the acidic conditions described in the literature then afforded the desired amino acids **1abc**. Thus all three of these important amino acids can be prepared by this general short route in high optical purity. The application of this

sequence using (+) tartrate would provide the 2R, 3S diastereomer, while the use of an analogous sequence using the *E*-isomer of 2[8b] should allow one to prepare the remaining two diastereomers [2S, 3S from (+) tartrate and 2R, 3R from (-) tartrate]. Thus all four diastereomers of these ß-hydroxy-α-amino acids should be available in high enantiomeric purity by epoxy *N*-benzoylcarbamate cyclization chemistry.[19]



5a R=Me	R'=IP 54%	**6a**	72%	**13a**
5b R=Ph	R'=M 46%	**6b**	88%	**13b**
5c R=iPr	R'=M 54%	**6c**	65%	**13c**

80%	58%	**14a** R=Me	**1a** R=Me
86%	93%	**14b** R=Ph	**1b** R=Ph
76%	84%	**14c** R=iPr	**1c** R=iPr

Scheme 2

Acknowledgement. We thank the National Institutes of Health (GM-31349) for their generous financial support and Prof. Knapp of Rutgers University for helpful suggestions concerning the cyclization of **10b**.

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11. The allylic alcohols **5bc** were prepared by addition of vinylmagnesium bromide to the corresponding aryl aldehyde. All compounds exhibited spectroscopic data (500 MHz ^{1}H NMR, ^{13}C NMR, IR, HRMS or elemental analysis) in full accord with their assigned structures.
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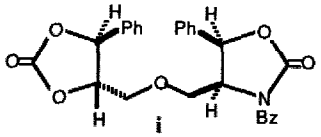
13. Based on a suggestion of Knapp (private communication), we believe the unknown byproducts to be a mixture of pseudo dimeric products **i** (only one of several possible isomers shown), formed by attack of the alkoxide (generated by cyclization of the epoxy carbamate) on another molecule of the epoxy carbamate, followed by cyclic carbonate formation.



i

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15. Compound **6a** has been prepared in this manner before. White, J. D.; Kang, M.; Sheldon, B. G. *Tetrahedron Lett.* **1983**, *24*, 4539.
16. The racemic form of each was prepared by mixing equimolar amounts of **6abc** with the corresponding enantiomers prepared by epoxidation of **1abc** with the corresponding (+)-tartrate. The diastereomeric excess (erythro:threo) was >95% in each case.
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18. Again racemic material was prepared in order to identify non-overlapping peaks of the enantiomers. The enantiomers of **14bc** were prepared by the same route starting from the enantiomers of **6bc**,[16] while the enantiomer of **14a** was made from commercially available d-threonine by treatment with phosgene and base.[14,17]
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