Efficient Enantioselective Synthesis of (2S,3R) Methyl β-Hydroxytyrosinate from Achiral Starting Materials

Michael E. Jung*[1] and Young H. Jung[2]

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, USA

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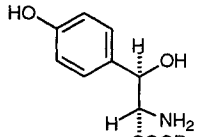
Dedicated to my mentor and friend Gilbert Stork.

Abstract: Kinetic resolution-epoxidation of the allylic alcohol **4** followed by internal opening of the epoxy *N*-benzoyl carbamate derived from the epoxide **5** led, after several functional group transformations, to the desired β-hydroxy tyrosine derivative **1b** and the useful selectively protected derivatives **12-15**.

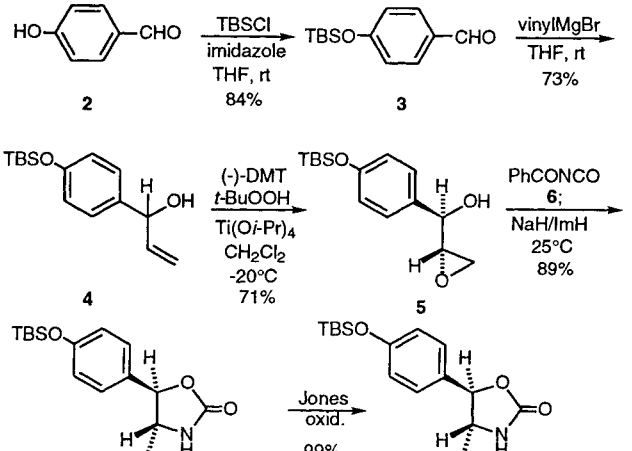
The modified amino acid, β-hydroxytyrosine, **1a**, is found as a component in several naturally occurring antibiotics, e.g., bouvardin, vancomycin (as the chloro derivative) and others.[3] For this reason several syntheses of various diastereomers of β-hydroxytyrosine and their derivatives have appeared.[4] We now report an efficient total synthesis of (2S,3R) methyl β-hydroxytyrosinate, **1b**, which proceeds with high enantioselectivity from inexpensive achiral starting materials.



1a R = H
1b R = Me

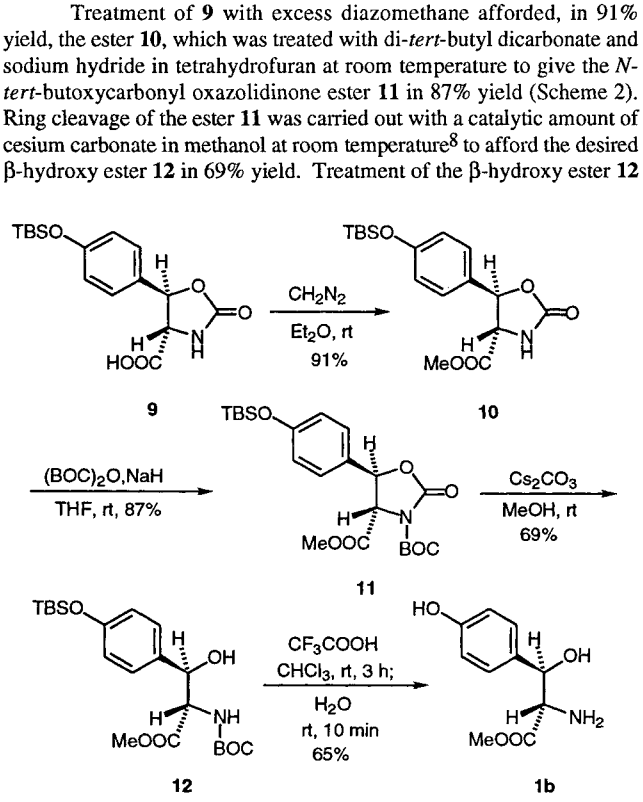
We recently reported the facile synthesis of β-hydroxy-α-amino acids by the use of a Sharpless kinetic resolution-epoxidation process followed by intramolecular ring opening.[5] The application of this chemistry to methyl β-hydroxytyrosinate would seem to be straightforward. However, this turned out not to be the case due to problems with protecting groups, especially the one on the aromatic hydroxyl group. Several routes were examined, only to fail at various stages of the synthesis. For example, use of a benzyl ether as the protecting group led to problems in its deprotection at both the oxazolidinone acid stage and in compounds where the ring was opened, since there also exists benzylic oxygen functionality in these substrates. Likewise protection of the phenol as an allyl ether was successful to give the allyloxy oxazolidinone acid but we were unable to cleanly deprotect this ether under various conditions. Therefore we chose to use the *t*-butyldimethylsilyl (TBS) ether as the protecting group for the phenol, a strategy that ultimately proved successful.

Protection of *p*-hydroxybenzaldehyde **2** with TBSCl afforded in 84% yield the aldehyde **3**,[6] which was treated with vinylmagnesium bromide to give the allylic alcohol **4** in 73% yield (Scheme 1). Treatment of the allylic alcohol **4** with 0.6 eq of *tert*-butyl hydroperoxide and 1 eq of titanium tetraisopropoxide in methylene chloride at -20°C for several days in the presence of 1.0 eq of (-)-dimethyl tartrate (DMT) afforded the desired epoxyalcohol **5** in 71% yield. The enantiomeric purity of **5** was shown 88% by integration of the relevant peaks in the ^{1}H NMR spectrum in the presence of 0.4 eq of Eu(hfc)$_3$. The racemic form of **5** was used as a reference; it was prepared by mixing an equimolar amount of **5** with the corresponding enantiomer prepared by epoxidation of **4** with the corresponding (+)-tartrate. The diastereomeric excess (*erythro:threo*) of the epoxyalcohol **5** was more than 95%. The epoxyalcohol **5** was treated with benzoyl isocyanate **6**[7] to give the corresponding carbamate which was not isolated but directly converted into the crystalline oxazolidinone **7** in 89% yield by reaction with sodium hydride and imidazole in tetrahydrofuran at 25°C without formation of any byproducts. A facile N to O migration of the benzoyl group was observed. Basic hydrolysis of the benzoate in the oxazolidinone **7** with alcoholic ammonia proceeded in 72% yield to give the primary alcohol **8**, which was oxidized to the corresponding acid **9** in 99% yield by Jones reagent. Strong base, e.g., lithium hydroxide, could not be used for the hydrolysis of the benzoate since the TBS ether was not stable under these conditions. However other amine bases worked as well, e.g., Et_3N in aqueous methanol afforded **8** in 61% yield.



Scheme 1

Treatment of **9** with excess diazomethane afforded, in 91% yield, the ester **10**, which was treated with di-*tert*-butyl dicarbonate and sodium hydride in tetrahydrofuran at room temperature to give the *N*-*tert*-butoxycarbonyl oxazolidinone ester **11** in 87% yield (Scheme 2). Ring cleavage of the ester **11** was carried out with a catalytic amount of cesium carbonate in methanol at room temperature[8] to afford the desired β-hydroxy ester **12** in 69% yield. Treatment of the β-hydroxy ester **12**



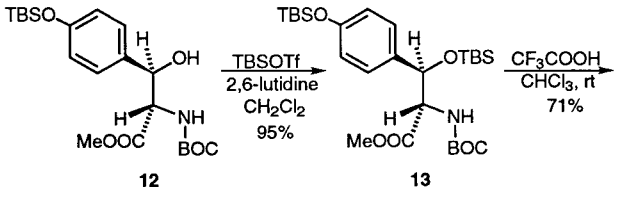
Scheme 2

with trifluoroacetic acid in chloroform followed by adding water afforded 65% of the desired β-hydroxytyrosine ester **1b**, along with cyclized products as a side reaction. The formation of cyclized products

(oxazolidinones) can be explained by an attack of the β-hydroxy moiety on the *N*-BOC group before deprotection.[9] Thus this ester **1b**, the protected form of β-hydroxytyrosine **1a**, can be prepared in only 10 steps from 4-hydroxybenzaldehyde in 10% overall yield. It and its precursors, e.g., **12**, may be used for the synthesis of the naturally occurring peptide antibiotics.

We have also prepared several other derivatives which may be of value in the synthesis of natural products, especially the silylated compounds **13-15** (Scheme 3). Thus treatment of **12** with TBSOTf and 2,6-lutidine in methylene chloride afforded a 95% yield of **13**, which was treated with trifluoroacetic acid in chloroform to give the amino ester **14** in 71% yield. Deprotection of the *tert*-butyldimethylsilyl groups was carried out using tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran at room temperature. The aryl *tert*-butyldimethylsilyl group was deprotected very quickly to give **15** in 95% yield. Thus five different protected derivatives of **1a**, namely **1b** and **12-15**, are available in high optical purity in only 10-14 steps from **2**.[10]

In conclusion, we have developed an efficient route for the preparation of several β-hydroxytyrosine derivatives, including selectively protected compounds in high overall yield from inexpensive



Scheme 3

achiral starting materials for use in the synthesis of the natural peptide antibiotics.

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References and Notes

(1) American Chemical Society Arthur C. Cope Scholar, 1995; UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching Award recipient, 1992.

(2) Current address: Department of Pharmaceutical Chemistry, Sung Kyun Kwan University, Seoul, Korea.

(3) a) Bouvardin: Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040. b) Vancomycin: Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364; Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915. c) Several other cyclic peptides have been shown to contain β-hydroxy-α-amino acids: ristocetin, avoparcin, teicoplanin, actaplanin (A-4696), antibiotic A35512, parvodicin, actinoidin, chloropolysporin.

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(9) The oxazolidinone byproducts (nearly exclusively the trans isomer) could also be formed by protonation and loss of the benzylic hydroxyl (aided by the *p*-hydroxy group), internal trapping by the *t*-butylcarbamate oxygen, and loss of the *t*-butyl cation.[4a]

(10) Since none of our synthetic compounds **12-15** and **1b** have been prepared previously, their structures were assigned based on the characteristic[11] small coupling constant between the vicinal protons in the ^{1}H NMR of the threo isomers, e.g., **15**, J = 2.1 Hz, **14**, J = 3.1 Hz.

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