Communications

An Enantiomeric Synthesis of *allo*-Threonines and *β*-Hydroxyvalines

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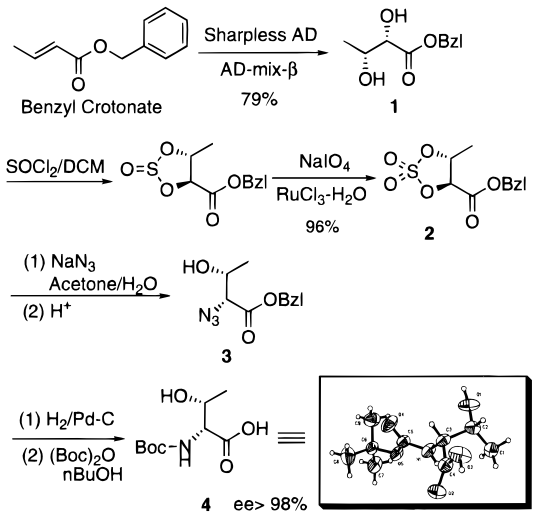
In conjunction with current efforts to design and synthesize enantioselectively peptidomimetic building blocks on a large scale, we require an efficient route to *β*-hydroxy α-amino acids, such as *allo*-threonines and *β*-hydroxyvalines. The *allo*-threonines, the diastereomers of threonine, represent one of the most common families of nonproteinogenic amino acid building blocks. In recent years, L- and D-*allo*-threonines (*a*Thr) have been found as important constituents in an increasing family of bioactive peptides, such as antibiotic hormaomycin,[1] antitumor astins,[2] antiviral viscosin,[3] and phytotoxic syringopeptins.[4] More interestingly, *allo*-threonines are the key building blocks in glycopeptides which are associated with biological recognition and selectivity.[5] The glycopeptidolipids present on the cell wall surface of C-mycosides are characterized by a variable oligosaccharide chain attached directly to the *β*-hydroxy group of the D-*allo*-threonine.[6] It has also been shown that substitution of threonines by *allo*-threonines in peptide sequences can render the molecules more resistant to proteolysis under physiological conditions.[7] Similarly, chiral *β*-hydroxyvalines are important components in biologically active molecules, such as potent anti-HIV luzopeptins[8] and the antibiotics aureobasidin A and tigemonam.[9,10]

In spite of their biological significance, the use of these building blocks has been hampered by cost and scale up problems. Most synthetic routes to these important amino acids are based on the alkylation of enolates from bis-lactims, oxazinones, or imidazolidinones or other procedures,[11,12] which involve multistep stoichiometric preparation and careful purification of each corresponding chiral auxiliary. We wish to describe an effective method for the catalytic asymmetric synthesis of these building blocks in high enantiomeric purity.

Scheme 1



In order to prepare D-*allo*-threonine starting with benzyl crotonate (Scheme 1), the Sharpless AD reaction was carried out on this *trans*-disubstituted alkene with AD-mix-*β* in the presence of methanesulfonamide. The reaction proceeds smoothly to give diol **1** with excellent optical purity.[13−15] The diol **1** is converted to its 2,3-cyclic sulfite with $SOCl_2$ and oxidized to cyclic sulfate **2** in a one-pot synthesis. It is reported that the cyclic sulfate acts as an excellent leaving group with good regioselec-

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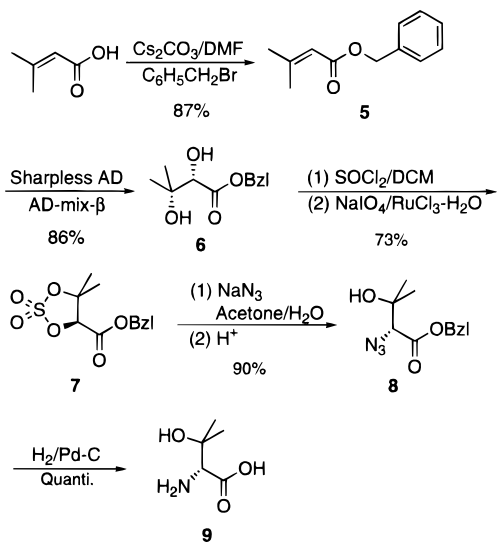
Scheme 2



tivity.[16] Nucleophilic displacement by NaN_3 at the α-C of cyclic sulfate **2** occurs with clean inversion of chirality, and acidic hydrolysis provides the desired α-azido ester **3**.[16] Compound **3** readily undergoes catalytic hydrogenation to generate the optically pure (2*R*,3*R*)-*allo*-threonine. The X-ray diffraction analysis of (2*R*,3*R*)-Boc-*allo*-threonine **4** proves the correct structure of the final product. In the large scale synthesis starting from the Sharpless AD reaction (60 mmol and up), only one silica gel chromatographic purification is necessary to purify **3** before hydrogenation to provide the final product in an overall 68% yield. By changing the Sharpless chiral catalytic ligand, the (2*S*,3*S*)-*allo*-threonine was also obtained by a similar manner in a 60% yield and 98% enantiomeric excess.

For the synthesis of β-hydroxyvaline, conventional benzylation of 3,3-dimethylacrylic acid provided benzyl 3,3-dimethylacrylate **5** which was subjected to the Sharpless AD reaction. Using a very similar strategy, optically pure (2*R*)-3-hydroxyvaline **9** can be obtained on a large scale and in 98% enantiomeric excess (Scheme 2).

In summary, we present an efficient route to prepare *allo*-threonines and β-hydroxyvalines on a large scale and in high enantiomeric excess. Most reagents involved are inorganic salts and easily removed by simple aqueous workup, and the crude form of intermediates can be used for the next step without further purification. Purification of the azido alcohol intermediate before hydrogenation is recommended, however, to obtain highly pure building blocks. Currently, we are extending this method to synthesize other β-hydroxy α-amino acids using appropriate α,β-unsaturated esters. This will allow us access to a variety of new building blocks for peptidomimetic drug design.

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Supporting Information Available: The experimental procedures and copies of ^{1}H NMR spectra for compounds **7**−**9** (7 pages).

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