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The Preparation of L-(2*S*, 3*S*)-4,4,4-[$^2H_3$] Valine

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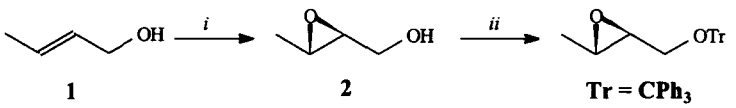
Abstract: Isotopically labeled amino acids are important for protein structure determination and in biosynthetic studies. We report now on the synthesis of (2*S*, 3*S*)-4,4,4-[$^2H_3$] valine (**9**) using a short, versatile, enzyme-free procedure. The deuterium label is introduced *via* an organocuprate opening of a chiral epoxide. © 1997 Elsevier Science Ltd.

The synthesis of isotopically labeled amino acids of unambiguous stereochemistry is important in several contexts. Labeled amino acids are used in protein structure determination and as tracers in biosynthetic studies determining metabolic pathways. Using ^{13}C NMR and infrared spectroscopy, stereoselective isotopic enrichment can help deconvolute very complex and overlapping spectral signals. The utility of these labeled compounds continues to make new and improved stereospecific syntheses desirable.

While there are several synthetic methods in the literature for preparing deuterium labeled valine,[1-5] they suffer from a combination of low yields, lack of versatility, and reliance on a multi-enzyme system for stereoselectivity. Our synthetic route to (2*S*, 3*S*)-4,4,4-[$^2H_3$] valine involves a method used by Aberhard and Lin,[4,5] namely use of a labeled organometallic reagent for the opening of a chiral epoxide. This methodology is highly stereoselective for the desired L-valine, makes possible the synthesis of a variety of labeling patterns in amino acids, and avoids enzymatic reactions.

The widely used and well-studied Sharpless asymmetric epoxidation was chosen as the most versatile route for synthesis of the required epoxide with high enantioselectivity. Choosing the appropriate tartrate in assembling the Sharpless catalyst can provide both enantiomers of a desired epoxide, adding an extra degree of flexibility to the placement of an isotopic label.

The commercially available crotyl alcohol (**1**), (*E*)-2-buten-1-ol (Fluka), was used as the starting material for the Sharpless epoxidation.[6] The catalyst was made from L-(+)-diisopropyl tartrate and titanium isopropoxide. The product, epoxy crotyl alcohol (**2**), was obtained in 84% yield and in 93% enantiomeric excess (**Scheme 1**),[7] in good agreement with previous reports.[6] The degree of enantiomeric purity was determined by NMR analysis of the Mosher ester derived from commercially available (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA chloride). The synthesis of **2** has been reported in the literature[8-10] in 50-58% yield. Using slightly more catalyst than is suggested in the published procedure[6] and a longer reaction time seemed to improve the yield significantly.



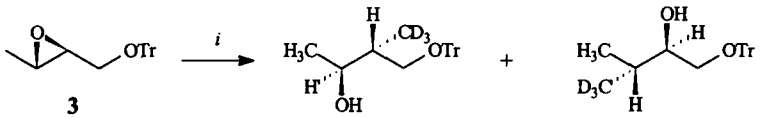
1 2 **Tr = CPh_3** 3

Reaction Conditions : *i.* $Ti(OiPr)_4$, (+)-DIPT, tBuOOH; *ii.* Trityl chloride, triethylamine, DMAP.

Scheme 1

White and co-workers[10] showed that treatment of **2** with lithiocyanomethylcuprate afforded a 1:1 mixture of the 1,2- and 1,3-diols in 46% yield for each. We hoped that preparation of the trityl ether of **2** would serve to bias the epoxide opening reaction. Treatment of **2** with trityl chloride, triethylamine, and DMAP gave trityl ether **3** in 81% yield (**Scheme 1**).[11,12] (Hoagland mentions that several recrystallizations of **3** can lead to optically pure material if higher enantiomeric excess is essential.)

While Aberhard and Lin used methyllithium to open an epoxide,[4,5] Lipshutz *et al.* reported that higher-order mixed organocuprates of the formula $R_2Cu(CN)Li_2$ give high yields in reaction with epoxides.[13] Using commercially available deuteriated methyllithium-lithium iodide complex (Aldrich) to make the organocuprate reagent according to White's procedure,[10] epoxy trityl ether **3** was opened to give alcohols **4** and **5** in a 1:5 ratio (**Scheme 2**). Purification by flash chromatography gave pure **5** in 65% yield.

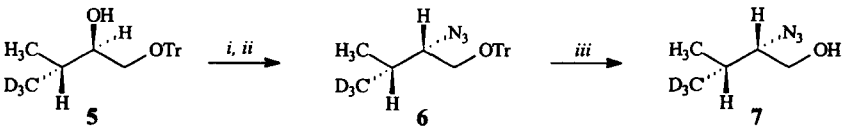


3 4 5

Reaction Conditions : *i.* CuCN, $CD_3Li \cdot LiI$, THF.

Scheme 2

Treatment of **5** with mesyl chloride and triethylamine in methylene chloride[14] gave an unstable mesylate which, when treated with sodium azide, provided azido ether **6** in 84% yield (**Scheme 3**).[15-18] Deprotection of **6** was achieved with refluxing 80% acetic acid for 1.5 hours to afford alcohol **7** in 78% yield.

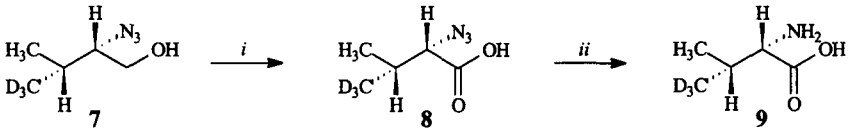


5 6 7

Reaction Conditions : *i.* mesyl chloride, triethylamine; *ii.* NaN_3, DMF, Δ; *iii.* 80% HOAc, Δ.

Scheme 3

Oxidation of azido alcohol **7** with pyridinium dichromate in DMF[19] gave azido acid **8** in 70% yield.[20] Hydrogenation of **8** with 10% palladium on carbon in glacial acetic acid[21] gave amino acid **9** (**Scheme 4**).



Reaction Conditions : *i*. PDC, DMF; *ii*. H_2, 10% Pd/C, HOAc.

Scheme 4

Purification with ion-exchange chromatography using Dowex 50WX2-200 resin gave pure **9** in 52% yield. Derivatization of **9** to make the pentafluoropropyl isopropyl ester[22] followed by GC analysis with an Alltech Chirasil-Val column revealed a 93% enantiomeric excess of L-valine **9**. In the ^{1}H NMR spectrum, only one methyl doublet was observed at 0.92 ppm. This is the downfield methyl signal of L-valine corresponding to the *pro-R* methyl group, as expected. The ^{13}C NMR spectrum showed an intense peak at 12.99 ppm (the *pro-R* methyl) and a very weak multiplet at 12.00 ppm (the *pro-S* methyl). The carbon signal of the *pro-S* methyl group is split into a weak multiplet because of the deuterium substitution.

This seven step procedure has several advantages over other reported routes to (2*S*, 3*S*)-4,4,4-[$^2H_3$] valine. It gives complete stereocontrol at the 2-position as well as good stereoselectivity (93% ee) at the 3-position, while several literature methods control only the 3-position configuration.[4,5] Kluender's procedure affords 78% deuterium incorporation while our method gives complete label incorporation.[2] Finally, the use of possibly temperamental multi-enzyme reactions is unnecessary in our procedure.[1,3]

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