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SYNTHESIS AND ABSOLUTE CONFIGURATION OF (+)-2,3,3-TRIMETHYL-2-HYDROXYBUTANOIC ACID

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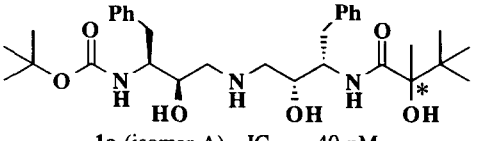
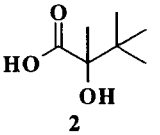
Abstract: The absolute configuration of (+)-2,3,3-trimethyl-2-hydroxybutanoic acid, a key intermediate in the synthesis of the HIV-protease inhibitor **1a** (isomer A), has been confirmed as (*R*) on the basis of X-ray analysis.

During the course of our efforts to prepare potent inhibitors of the HIV-protease, we observed a 22-fold difference in the intrinsic activities of the two diastereomeric α-hydroxyamides **1a** and **1b**.[1] In order to determine the absolute stereochemistry of the more potent isomer **1a**, and to develop a stereoselective synthesis of this compound, we sought to prepare each enantiomer of the intermediate α-hydroxy acid **2**. A search of the chemical literature revealed an enantioselective synthesis of the dextrorotatory enantiomer **(+)-2** *via* a chiral oxathiane auxiliary reported by Eliel and Lynch.[2] The authors assigned the (*R*)-configuration to this compound based on Cram's, Prelog's and Sharpless' rules. However, the dextrorotatory compound had previously been characterized as the (*S*)-enantiomer.[3] While there was strong evidence that this earlier work was in error, some degree of ambiguity remained regarding the optical rotation associated with a particular absolute configuration. In fact, Eliel and Lynch reported that they could not prepare a crystalline intermediate to unequivocally provide the absolute configuration of **(+)-2**. Herein we report an asymmetric synthesis of **(+)-2** *via* Sharpless epoxidation along with a proof for assignment of the (*R*)-configuration from X-ray crystallography.



1a (isomer A) IC_{50} = 40 nM
1b (isomer B) IC_{50} = 900 nM



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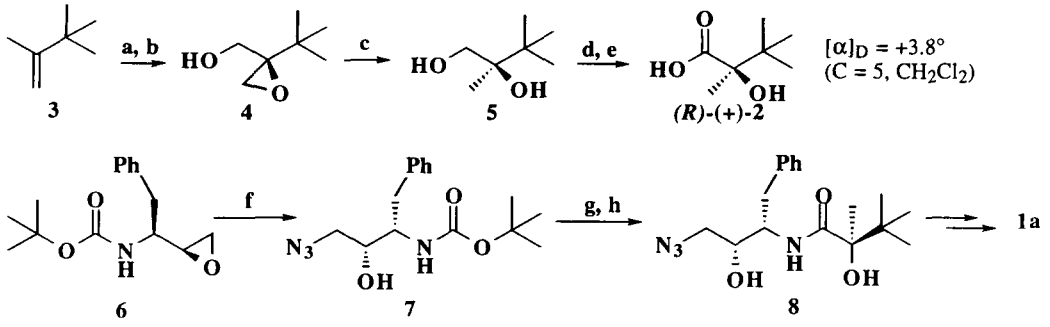
The synthesis of **(+)-2** is outlined in Scheme 1. Allylic oxidation of 2,3,3-trimethyl-1-butene (**3**) using SeO_2 and *t*-BuOOH in the presence of salicylic acid[4] afforded the corresponding allylic alcohol (33% yield) which was converted to the chiral epoxide **4** (73% yield) *via* Sharpless epoxidation with diethyl D-(-)-tartrate.[5] The epoxide **4** was treated with LAH in ether to give the diol **5** in 81% yield.[6] Swern oxidation of **5** afforded the corresponding α-hydroxy aldehyde in quantitative yield which was converted *via* Lindgren oxidation[7] to the hydroxy acid **(+)-2** ($[\alpha]_D$ = +3.8 , C = 5, CH_2Cl_2)[8] in 65% yield after recrystallization from hexane.

Treatment of the L-phenylalanine-derived epoxide **6**[1] with sodium azide gave the azido alcohol **7**, which was converted in two steps to the α-hydroxyamide **8** *via* acid catalyzed removal of the Boc group followed by amide coupling of the resulting amine with **(+)-2**. A single crystal X-ray analysis (Figure 1) of **8** unambiguously confirmed that the dextrorotatory enantiomer **(+)-2** has the (*R*)-configuration as predicted by Eliel and Lynch.

Scheme I.



a) SeO_2/t-BuOOH/salicylic acid, 33%; b) diethyl D-(-)-tartrate/Ti(i-PrO)$_4$/4Å molecular sieves/t-BuOOH, 73%; c) LAH/ether, 81%; d) oxalyl chloride/DMSO/Et_3N/CH_2Cl_2; e) $NaClO_2$/NH_2SO_3H/THF-H_2O, 65%; f) NaN_3/MeOH/NH_4Cl, 92%; g) HCl/EtOAc, 100%; h) ***(R)*-(+)-2**/BOP reagent/NMM/DMF, 45%

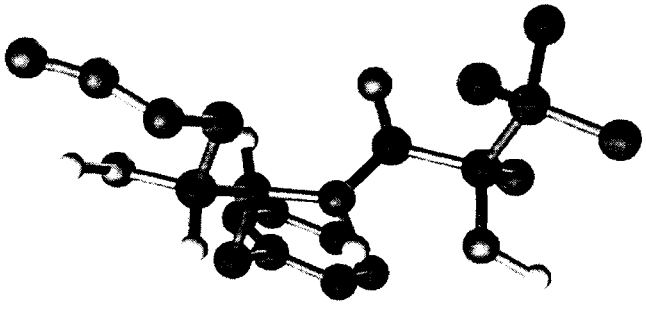


Figure I. The Solid State Conformation of **8** as Determined by X-Ray Analysis.

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6) Eliel and Lynch (see ref. 2, footnote 13) reported that compound **5** has been synthesized *via* a similar approach by Prof. W. Baldwin.
7) Lindgren, B. O.; Nilsson, T. *Acta. Chem. Scand.* **1973**, *27*, 888.
8) The enantiomeric excess of this material was found to be 96% as determined by chiral HPLC analysis of the corresponding 4-nitrophenyl ester (Daicel CHIRALCEL OD column/hexane-ether-ethanol 80:19:1).

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