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A Short Enantioselective Synthesis of *N*-Boc-α-Amino Acids from Epoxy Alcohols

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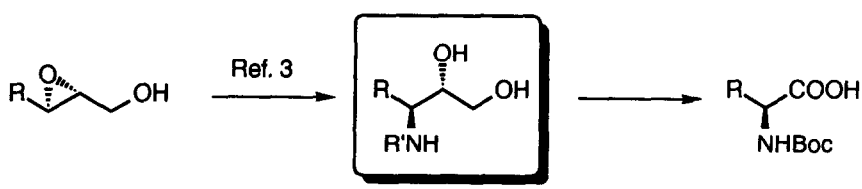
Abstract: *A new and efficient enantioselective synthesis of Boc-α-amino acids has been developed. Starting from an enantiomerically enriched epoxy alcohol the sequence involves a regioselective nucleophilic epoxide opening by diphenylmethylamine (benzhydrilamine), hydrogenolysis/protection of the amino group, and oxidation of the diol moiety.*

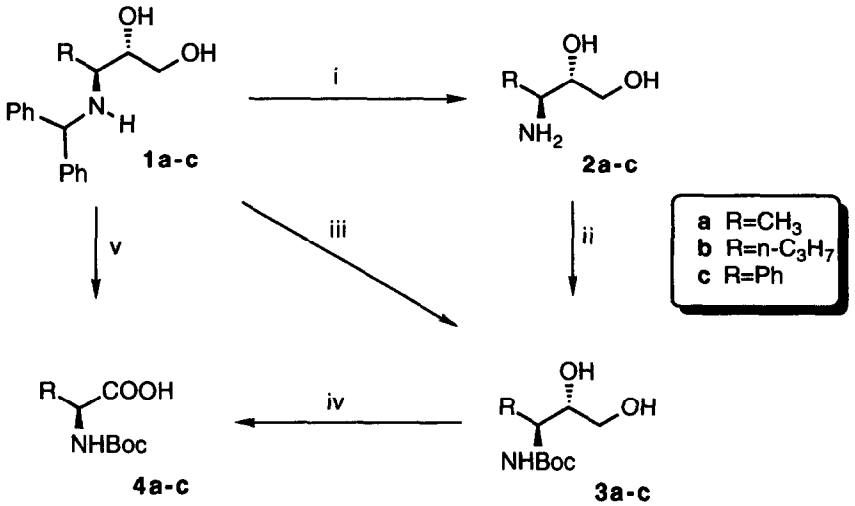
Optically pure α-amino acids are the subject of enormous interest both at the academic and industrial levels[1]. Accordingly, and in spite of much previous research, synthetic methodology allowing the preparation of either enantiomer of both natural and unnatural α-aminoacids is still actively pursued[2].

We disclose in the present communication a new and simple solution to this problem, based on the oxidative cleavage of enantiomerically enriched 3-amino-1,2-diols arising from a recently developed regioselective ring opening of chiral epoxy alcohols by primary amines[3].



Some important characteristics that make *a priori* this approach attractive are: a) complete control of the stereochemistry of the target amino acid -by simple selection of the tartrate enantiomer used in the Sharpless epoxidation- and b) broad applicability given the great variety of (*E*)-allyl alcohols which have been efficiently converted into chiral epoxy alcohols[4].

3-Diphenylmethylamino-1,2-diols (**1**), readily available in high regio-, diastereo-, and enantiomeric purity[3], were selected as starting materials for the projected synthesis. The sequences allowing the conversion of **1** into *N*-Boc protected amino acids (**4**) are summarized in Scheme I.



Scheme 1. *Reagents: i)* H_2, $Pd(OH)_2/C$, MeOH; *ii)* $(Boc)_2O$, Na_2CO_3, MeOH,))); *iii)* $(Boc)_2O$, H_2, $Pd(OH)_2/C$, CH_3COOEt; *iv)* $RuCl_3$, $NaIO_4$, Na_2CO_3,CH_3CN,CCl_4, H_2O; *v)* steps *iii* and *iv* without purification of **3.**

Thus, hydrogenation of **1a-c**, preferably as their hydrochlorides, on 20% palladium hydroxide on carbon (Pearlman's catalyst) in methanol took place readily leading to **2a-c** in 88-100% yield (see Table 1). Conversion of aminodiols **2** into the corresponding *N*-Boc derivatives **3a-c** was most conveniently performed with $(Boc)_2O$ in methanol, in the presence of Na_2CO_3, under ultrasonic irradiation[5]. The preparation of **3** from **1** has also been performed as a one-pot procedure, by simply treating a solution of **1** in ethyl acetate with H_2 and $(Boc)_2O$ in the presence of Pearlman's catalyst, with greatly improved overall yields[6]. (Table 1). Interestingly, Boc-aminodiols **3** are highly crystalline materials, thus offering the opportunity of enantiomeric enrichment by crystallization if required.

Table 1. Yields of the individual steps in the synthesis of amino acids **4a-c** according to Scheme 1.

Entry	R (configuration)	Conditions (step)				
		i (1→2)	ii (2→3)	iii (1→3)	iv (3→4)	v (1→4)
a	CH_3(2*S*,3*S*)	100%	71%	85%	90%	71%
b	n-C_3H_7(2*R*,3*R*)	100%	68%	91%	82%	62%
c	C_6H_5(2*R*,3*R*)	88%	65%	90%	79%	-

Final oxidative cleavage of the 1,2-diol moiety was readily performed with $RuCl_3/NaIO_4$ in $CH_3CN/CCl_4/H_2O$[6b,7]. The yields of the *N*-Boc aminoacids **4** proved to be highly dependent on the concentration at which the reactions were performed. The best results (Table 1) were obtained at a 0.06 M substrate concentration.

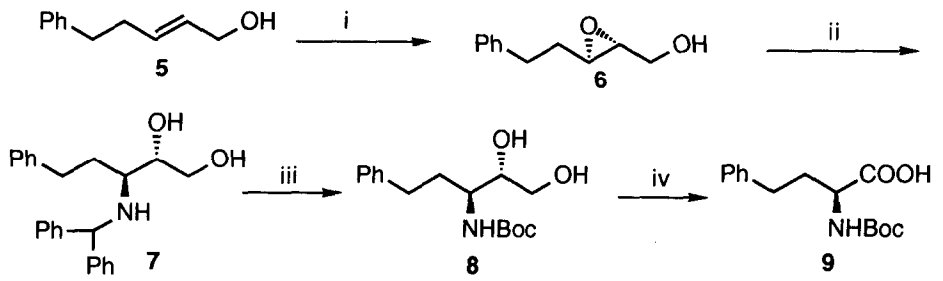
If desired, the whole synthetic sequence **1**→**4** can be carried out without isolation of the intermediates. This possibility, which has been tested for Boc-L-alanine (**4a**) and Boc-D-norvaline (**4b**), is characterized by an slightly lower yield with respect to the optimum two-step sequence[8].

The enantiomeric purities of **4a-c** were determined by derivatization and HPLC analysis of the diastereomeric mixtures. For Boc-L-alanine **4a**, the following dipeptides were synthetized: Boc-DL-Ala-L-Tyr and Boc-L-Ala-L-Tyr and subsequently analyzed by HPLC on a Nucleosil 100 column eluting with CH_3OH/H_2O. By this procedure, it could be established that the prepared Boc-L-Ala was of >98% ee.

Boc-D-Nva **4b** and Boc-D-Pgl **4c**, in turn, were converted into the corresponding methyl esters (CH_2N_2/ether) and studied by HPLC on a Chiracel OD-R column. In both cases, the stereochemical purity was determined to be greater than 98% since only one enantiomer could be observed[9].

The result obtained with D-phenylglycine is of primordial importance since it clearly shows that our procedure is racemization free even when labile intermediates are involved. In this context, it is important to recall that Sharpless and co-workers[10] had previously converted 3-azido-3-phenyl-1,2-propanediol into phenylglycine through an oxidation/hydrogenation sequence. In that case, significant racemization occurred in the oxidation stage, probably due to the lability of the presumed α-azidoaldehyde intermediate.

As a further illustration of the potential of the present methodology, we have developed a short enantioselective synthesis of Boc-homophenylalanine[11] (**9**), a key component of most commercially important ACE inhibitors[12] (Scheme 2). (2*R*,3*R*)-2,3-Epoxy-5-phenylpentan-1ol (**6**) was obtained in 77% yield (90% ee)[13] by Sharpless epoxidation[14,15] of the readily available 3-phenyl-2-penten-1-ol (**5**). Regioselective nucleophilic ring opening of **6** with diphenylmethylamine in the presence of titanium tetraisopropoxide afforded aminodiol **7** as a readily separable 9:1 mixture of regioisomers in 74% yield. Hydrogenolysis followed by treatment with Boc_2O under Luche[5] conditions led in 72% yield to *N*-Boc protected aminodiol **8**. Final oxidation with ruthenium tetroxide under usual conditions[6b,7] afforded (+)-**9** in the same enantiomeric purity as epoxide **6** in 52% yield.



Scheme 2. *Reagents: i)* Bu^tOOH, $Ti(O^iPr)_4$, (-)-DIPT, 4Å sieves, -32°C, CH_2Cl_2;
ii) Ph_2CHNH_2, $Ti(O^iPr)_4$, CH_2Cl_2; *iii)* a) H_2, $Pd(OH)_2/C$, MeOH; b) $(BOC)_2O$, $NaHCO_3$, MeOH,))) *iv)* $RuCl_3$, $NaIO_4$, CH_3CN,CCl_4, H_2O.

In summary, we have developed a short and efficient enantioselective synthesis of α-aminoacids through a nucleophilic amination/oxidation sequence. To the inthrinsic characteristics of predictability of absolute stereochemistry, wide applicability, and use of a safe and inexpensive reagent as the -NH_2 source, the additional bonus of stereochemical integrity during the oxidation step has also to be added.

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15.- It has been reported (Nuñez, M.T.; Martín, V.S. *J. Org. Chem.* **1990**, *55*, 1928) that **6** can be prepared in >95% ee by the stoichiometric version of the Sharpless epoxidation using 4.5M TBHP and DET at -20°C. Accordingly, it is feasible to obtain enantiomerically pure amino acid **9.**

Typical Experimental Procedure.

(2*R*,3*R*)3-*tert*-butoxycarbonylamino-3-phenyl-1,2-diol (**3c**).

To a stirred suspension of 20% wt. $Pd(OH)_2/C$ (24 mg) in 0.4 mL ethyl acetate, under H_2 at 1 atm, was added a solution of (2*R*,3*R*)-3-diphenylmethylamino-3-phenyl-1,2-diol (0.29 g, 0.9 mmol) (prepared according to ref. 3) and $(Boc)_2O$ (0.24 g, 1.1 mmol) in ethyl acetate (1.6 mL). The reaction was monitored by TLC (50% hexanes/ethyl acetate). After 24-48 h, the solution was filtered and evaporated. The resulting crude was crystallized from hexane/ether yielding 190 mg of (2*R*,3*R*)-3-*tert*-butoxycarbonylamino-3-phenyl-1,2-diol (**3c**) as a white solid. The mother liquor was evaporated and the residue was chromatographed (SiO_2, 2.5% NEt_3, eluting with hexanes/ethyl acetate) to afford a further 20 mg of the product as a white solid (total yield: 90%, $[\alpha]_D$=-52.7 (c=1, $CHCl_3$)).

N-Boc-D-phenylglycine (**4c**).

To a vigorously stirred mixture of (2*R*,3*R*)-3-*tert*-butoxycarbonylamino-3-phenyl-1,2-diol (**3c**) (337 mg, 1.26 mmol) in 6.3 mL CCl_4, 6.3 mL CH_3CN and 9.5 mL H_2O, at room temperature under nitrogen, were added $NaIO_4$ (1.1 g, 0.52 mmol) and $RuCl_3$ (6.3 mg, 0.03 mmol). Stirring was allowed to continue for 2 hours. Then, 25 mL CH_2Cl_2 were added and the mixture was extracted with 1M $NaHCO_3$. The aqueous solution was washed with ether, carefully acidified with sat $KHSO_4$ and extracted with ether. The organic solution was dried and evaporated to afford 317 mg of *N*-Boc-D-phenylglycine (79% yield).

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