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First One-Pot Copper-Catalyzed Synthesis of α-Hydroxy-β-Amino Acids in Water. A New Protocol for Preparation of Optically Active Norstatines

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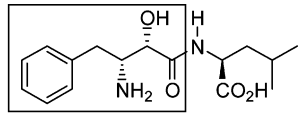
α-Hydroxy-β-amino acids were synthesized with excellent yields for the first time in water and by a simple procedure based on a copper catalytic cycle, which included the recovery and reuse of the catalyst and is possible to realize by using only water as reaction medium.

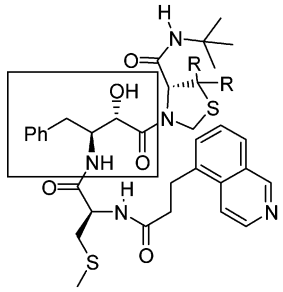
Introduction

Nonproteinogenic α-hydroxy-β-amino acids (isoserine derivatives) are probably the most important members of the β-amino acid family. They are the essential moiety of a large number of well-known, naturally occurring products that are endowed with powerful biological activity.[1] The most striking examples are the Taxol derivatives,[2] the immunological response modifier bestatin,[3] and a number KNI protease inhibitors (Figure 1).[1c] (+)-(2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutanoic acid (**1**) [(+)-phenylnorstatine] is one of the two amino acids that constitute the dipeptide bestatin, and its (2*S*,3*S*) C-3 epimer **2** [(−)-allophenylnorstatine] is contained in two tripeptides, the kynostatins (KNI)-227 and (KNI)-272, which are highly potent HIV-1 protease inhibitors (Figure 2).[4]

As a result of the importance of the isoserine moiety, several procedures have been developed to synthesize α-hydroxy-β-amino acids in optically active form. These methods include asymmetric catalytic synthesis, enzymatic kinetic resolution, and the use of chiral auxiliaries and chiral building blocks.[2b,5]



Bestatin



(KNI)-227, R = Me; (KNI)-272, R = H

FIGURE 1. Biologically active molecules containing α-hydroxy-β-amino acid units.

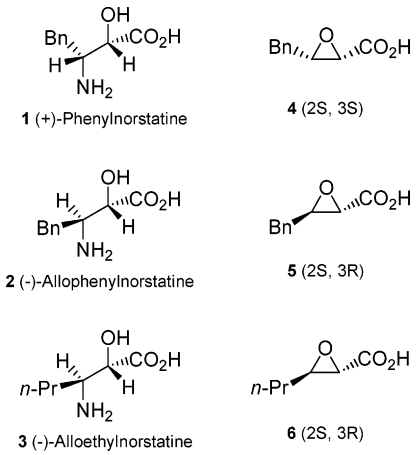


FIGURE 2. Some α-hydroxy-β-amino acids of biological interest and their 1,2-epoxide precursors.

Among these procedures, the synthetic approach that employs the nucleophilic ring opening of an appropriate

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1,2-epoxide[5b] is, in principle, a very simple route that has the advantage of using starting materials that are readily available with high ee by using the Sharpless or the Jacobsen epoxidation of allylic alcohols[6,7] or α,β-unsaturated carboxylic esters,[8] respectively. On the other hand, this approach has the disadvantage that the ring opening of the oxirane ring is generally not completely β-regioselective. With alkyl substituents at C-β, a satisfactory β-regioselectivity can be obtained by using a large amount of catalyst (150−500%).[9] All of the procedures are carried out in organic solvents and have multiple steps because, after the ring opening of the 1,2-epoxide, further reactions are necessary to obtain the desired α-hydroxy-β-amino acids, such as the oxidation of the primary hydroxy group, the hydrolysis of the carboxylic ester, or other transformations that require the isolation and purification of all intermediates.

An efficient catalytic one-pot synthesis of β-alkyl and β-arylisoserines starting from α,β-epoxycarboxylic acids is to date not known and would be of interest for the potential large-scale production of these compounds. In addition, the pharmaceutical industry is showing enormous interest in environmentally responsible procedures that would allow simple and cost-effective syntheses of target molecules.[17]

We believe that the use of water as reaction medium instead of an organic solvent optimizes the preparation of the important family of α-hydroxy-β-amino acids and is in perfect accord with the Click Chemistry principles that were recently pointed out by Sharpless.[18]

In this paper we report the first one-pot metal-catalyzed synthesis of α-hydroxy-β-amino acids by azidolysis of α,β-epoxycarboxylic acids and the in situ reduction of the resulting β-azido-α-hydroxycarboxylic acids intermediate, where the same metal catalyst catalyzes both the oxirane ring opening by NaN_3 and the azido group reduction processes. To maximize the efficiency of the procedure, the whole process was performed (i) solely in water without using any organic solvents, (ii) on a gram scale, with (iii) recovery and (iv) reuse of the catalyst.

To develop this idea, we needed a metal salt that, in water, would be able (i) to catalyze *anti*-stereo- and β-regioselectively the ring opening of a α,β-epoxycarboxylic acid by NaN_3, (ii) to chemoselectively catalyze the reduction of azido group to amino by $NaBH_4$ in high yields, (iii) to form a boride complex[20] that could be quantitatively separated from the reaction mixture and (iv) then be reused without loss in efficiency, and (v) to make the procedure as simple as possible in view of automating the process.

For several years we have been studying organic reactions in water, and we have showed the advantages related to its use as reaction medium and contributed to the development of a benign organic synthesis.[19] In all cases, we have pointed out the crucial role that the pH of the reaction medium plays in controlling the efficiency of the processes.

Recently we have become engaged in a project aimed at defining a new, environmentally friendly one-pot protocol for synthesizing α-hydroxy-β-amino acids starting from α,β-epoxycarboxylic acids. We began to study the azidolysis of alkyl and aryl-1,2-epoxides and α,β-epoxycarboxylic acids in water, showing that the pH of the reaction medium directs the regioselectivity of the reactions.[12]

Metal salts such $Cu(NO_3)_2$, $InCl_3$ and even $AlCl_3$, once believed to be unusable in water,[12d] were efficient catalysts for a totally β-regio- and *anti*-stereoselective azidolysis of α,β-epoxycarboxylic acids in aqueous medium,[12] carried out with 5.0 molar equiv of NaN_3 at pH 4.0, kept constant for the entire reaction time. $CoCl_2$, $Zn(NO_3)_2$, and $Ni(NO_3)_2$ also gave good results but were not able to completely control the regioselectivity of the process.[12b]

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(9) Racemic β-alkyl-α,β-epoxycarboxylic acids and their ester derivatives give azidolysis at C-β with LiN_3 or NaN_3 in organic medium in the presence of an excess of $Ti(i\text{-}OPr)_4$ (1.5 molar equiv),[10] $LiClO_4$ (5.0 molar equiv),[11] or $Mg(ClO_4)_2$ (2.5 molar equiv).[11] When the reaction is carried out in water, the regioselectivity depends on the pH and on the presence of a Lewis acid.[12] Nonaromatic isoserines have been prepared with excellent enantiomeric purity by the β-lactam synthon method developed by Ojima,[13] by using L-aspartic acid[14] and Boc-L-leucine[15] as chiral building blocks, and by adding lithium (*S*)-(α-methylbenzyl)benzylamide and (+)-camphorsulphonyl oxaziridine to the *tert*-butyl cinnamate derivative.[16]

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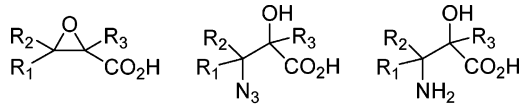
(20) Combination of a metal salt of Cu, Ni, Co, Zn, Fe, etc. with aqueous $NaBH_4$ produces a finely divided black precipitate of the metal boride.[21,22] Borides can be dissolved in acidic water or in basic ammoniac solution in the presence of oxygen. Because they actively catalyze the decomposition of borohydrides, these borides have been used as a practical source of H_2.[22c−e] The role of the metal boride has been studied, and it is generally thought that the metal boride acts as a true catalyst, coordinating and activating the substrates towards the reduction.[22d,e]

CHART 1. α,β-Epoxycarboxylic Acids Utilized and Corresponding Azido Acids and Amino Acids Prepared



7 **8** **9**

	a	b	c	d	e	f	g
R_1	H	H	H	H	H	Me	H
R_2	Me	*n*-Pr	Ph	$(CH_2)_4$	Et	Me	Ph
R_3	H	H	H		Me	H	Me

TABLE 1. Metal-Salt-Catalyzed Reductions of Azide 8b to Amine 9b in Water

entry	catalyst	*T* (°C)	*t* (h)	*C* (%)[a]
1	none	25	18	<1
2	$AlCl_3$	25	24	
3	$InCl_3$	25	0.5	26
4	$CoCl_2$	25	0.5	>99
5	$Cu(NO_3)_2$	0	0.5	>99

[a] Conversion based on GC analyses of the methyl ester derivative.

Results and Discussions

To investigate the reduction step, β-azido-α-hydroxyhexanoic acid (**8b**) was chosen as reference compound and was reduced to β-amino-α-hydroxyhexanoic acid (**9b**) (Chart 1), by using the catalysts that gave the best results in the azidolysis process.[12] The results obtained by using 10 mol % of catalyst and 2.0 molar equiv of $NaBH_4$ are presented in Table 1.

As can be seen, $AlCl_3$ was ineffective, $InCl_3$ was not efficient, and furthermore the indium boride could not been quantitatively recovered. At 25 °C, $CoCl_2$ was a good catalyst for the azido reduction to amino by $NaBH_4$,[19f] but it did not ensure a complete β-regioselectivity (84%) in the azidolysis reaction of **7b**.[12b]

The catalyst of choice for the reduction step was $Cu(NO_3)_2$, which in aqueous medium and in the presence of $NaBH_4$ (pH > 10) allowed *anti*-α-hydroxy-β-aminohexanoic acid (**9b**) to be obtained exclusively in 0.5 h at 0 °C with a 93% yield (Table 1, entry 5), isolated in pure form by simple ion-exchange resin purification thereby avoiding the use of any organic solvents. Because the $Cu(NO_3)_2/NaBH_4$ system had not been previously used for the reduction of azides,[23] this protocol was extended to a number of α-hydroxy-β-azidocarboxylic acids (Table 2).

The reductions of **8** were fast (30 min at 0 °C), and the amino-derivatives **9** were isolated in excellent yields

TABLE 2. Copper-Catalyzed Reduction of β-Azido-α-hydroxycarboxylic Acids 8 in Water[a]

entry	azido acid	amino acid	yield (%)[b]
1	**8a**	**9a**	88
2	**8b**	**9b**	93
3	**8b**	**9b**	93[c]
4	**8c**	**9c**	93
5	**8c**	**9c**	94[c]
6	**8d**	**9d**	87
7	**8e**	**9e**	90
8	**8f**	**9f**	85
9	**8g**	**9g**	96

[a] $Cu(NO_3)_2$ (10 mol %), $NaBH_4$ (2.0 mol/eq), 0 °C, 30 min. [b] Yield of the isolated product. [c] Yield obtained using the recovered catalyst.

TABLE 3. Azidolysis of 1,2-Epoxide 7b in Water with NaN_3 at 65 °C for 1.5 h

expt	catalyst[a]	pH	NaN_3 (mol/eq)	α/β ratios	*C* (%)[b]
1	$Cu(NO_3)_2$	4.0[c]	5.0	<1/>99	>99
2		4.0[c]	1.5		<1
3	$Cu(NO_3)_2$	4.0[c]	1.5	<1/>99	>99
4	$Cu(NO_3)_2$	*d*	5.0	10/90	>99
5	$Cu(NO_3)_2$	*d*	1.5	<1/>99	>99

[a] 10 mol %. [b] Conversion based on the GC analyses of the methyl ester derivative. [c] Maintained fixed for all of the reaction time. [d] pH obtained by mixing the reagents and not regulated during the reaction.

without using any organic solvents. In all cases Cu(B) was recovered by simple Büchner filtration of the mother liquors and reused without problems for a further reduction of an azidocarboxylic acid in aqueous medium (Table 2, entries 3 and 5). According to our plan to recycle the catalyst we recovered Cu(B) and showed that is possible to reconvert the solid to Cu^{2+} in water at pH 4.0. This copper(II) aqueous solution was then used for the azidolysis of **7b** carried out under the above-mentioned conditions (NaN_3 5.0 molar equiv, pH fixed at 4.0, 65 °C, 1.5 h) followed by in situ reduction ($NaBH_4$ 2.0 molar equiv, 0 °C, 0.5 h) of intermediate **8b**. The whole process worked well, and α-hydroxy-β-aminohexanoic acid (**9b**) was isolated in 86% yield, but the excess of NaN_3 used in the azidolysis step hampered the recovery of Cu(B).

Indeed under basic conditions, the $Cu^{2+}/NaBH_4$ system reduces NaN_3 to NH_3. Ammonia greatly lowers the Cu^0/Cu^{II} redox potential, making possible the oxidation of Cu(B) to Cu^{2+} under air atmosphere and its dissolution in water as $Cu(NH_3)_4^{2+}$,[24] thereby preventing its recovery as a solid. In principle, Cu^{2+} could be recovered as an amino complex, but this would require a longer procedure.

We needed to go back and reinvestigate the azidolysis of α,β-epoxycarboxylic acids in water, decreasing the amount of NaN_3.

By using only 1.5 molar equiv of NaN_3, at 65 °C and after 1.5 h, the results of the azidolysis of **7b** were the following (Table 3): (i) At fixed pH 4.0 the reaction works only in the presence of the catalyst (Table 3, entries 2 and 3) and is again completely regio- and stereoselective (Table 3, entry 3 vs 1). (ii) If the reaction was performed at the pH obtained by simply mixing the reagents (pH

(21) The stoichiometry of boride does not conform to the ordinary concepts of valence. In the case of copper boride, the molecular formula strongly depends on the preparation temperature, and it is generally reported as Cu(B).[22a,b]

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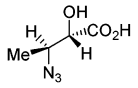
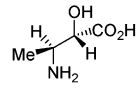
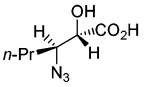
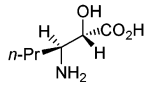
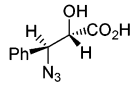
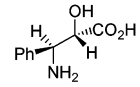
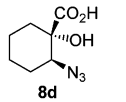
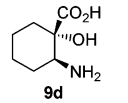
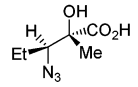
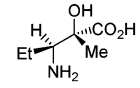
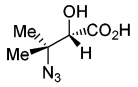
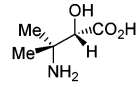
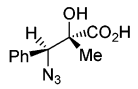
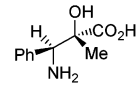
TABLE 4. Azidolysis of Oxiranes 7 in Water Catalyzed by $Cu(NO_3)_2$ (10 mol %) and Using NaN_3 (1.5 molar equiv)

1,2-epoxide	*T* (°C)	*t* (h)	azido-acid[a]	yield (%)[b,c]
7a	65	2	**8a**	96
7b	65	1.5	**8b**	95
7c	30	0.25	**8c**	95
7d	30	0.25	**8d**	94
7e	65	0.25	**8e**	96
7f	30	3	**8f**	94
7g	65	4	**8g**	96

[a] Only *β*-azido-α-hydroxy carboxylic acid was formed. [b] Isolated yield of ≥98% pure azido acid after workup. [c] In the absence of catalyst no conversion was observed.

TABLE 5. One-Pot $Cu(NO_3)_2$-Catalyzed Synthesis in Water of (±)-α-Hydroxy-*β*-amino Acids[25]

1,2-Epoxide	Azidolysis[a] T (°C)	t (h)	Azido acid	Reduction[a] 0 °C, 0.5 h	Amino acid	Yield[b] (%)
7a	65	2	 **8a**		 **9a**	80
7b	65	1.5	 **8b**		 **9b**	86
7c	30	0.25	 **8c**		 **9c**	83
7d	30	0.25	 **8d**		 **9d**	80
7e	65	0.25	 **8e**		 **9e**	83
7f	30	3	 **8f**		 **9f**	79
7g	65	4	 **8g**		 **9g**	91

[a] See experimental procedure.[25] [b] Yield of isolated product.

4.3) and not regulated during the reaction, the conversion was quantitative, and again a complete *β*-regioselectivity was found (Table 3, entry 5 vs 4). This last result is very important in view of an automation of the process.

This simplified azidolysis protocol was extended to a variety of α,*β*-epoxycarboxylic acids **7**; high yields and a complete *β*-regioselectivity were always obtained (Table 4).

The definitive one-pot protocol was defined and extended to a variety of oxiranes (Table 5). The copper catalytic cycle[25] (Scheme 1) started when 10 mol % of $Cu(NO_3)_2$ catalyzed the azidolysis of a α,*β*-epoxycarboxylic acid in the presence of 1.5 molar equiv of NaN_3. At the end of this step (30 or 65 °C, 0.25−4 h), 2.0 molar equiv of $NaBH_4$ was added at 0 °C with the immediate formation of black Cu(B), followed by the azido group reduction (30 min). Copper is then quantitatively recovered by filtering the aqueous heterogeneous mixture. The aqueous layer was charged on an ion-exchange resin to furnish the final α-hydroxy-*β*-amino acid without using any organic solvent. The fine black Cu(B) precipitate was redissolved in water at pH 4.0 under air atmosphere (Scheme 1), and this solution was reused by adding the oxirane **7** and NaN_3 to repeat the cycle again. The catalyst was used for five cycles on a 1-, 10-, and 100-mmol scale without loss of its efficiency and was always completely recovered. The final amino acids were analyzed by Atomic Absorption Spectrophotometry before and after ion exchange purification, and no traces of

SCHEME 1. Copper Catalytic Cycle

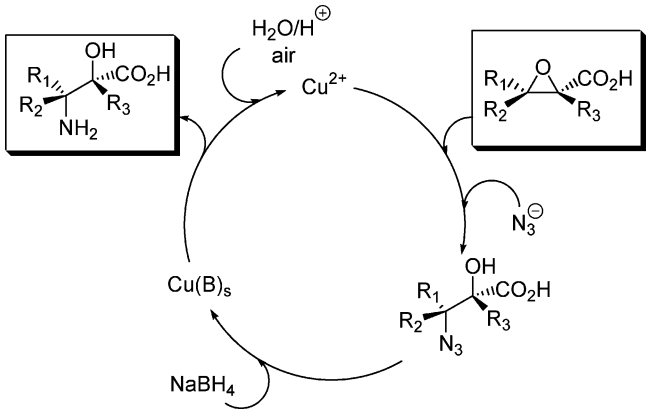
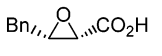
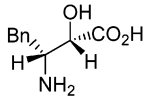
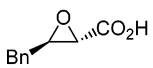
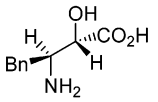
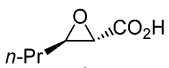
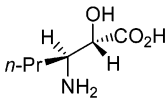


TABLE 6. One-Pot Preparation of Optically Active Norstatines

1,2-Epoxide	a / b → Amino acid	Yield (%)[c]
 **4**	 **1**	72[d]
 **5**	 **2**	75[d]
 **6**	 **3**	83[d]

[a] 65 °C, 1.5 h.[25] [b] 0 °C, 0.5 h.[25] [c] Yield of isolated product. [d] Optical purity of the 1,2-epoxide starting material (**4** = 90% ee; **5** = 95% ee; **6** = 93% ee).

(25) In a typical procedure, 1.300 g (10.0 mmol) of an α,*β*-epoxyhexanoic acid (**7b**) was dissolved in water (10 mL). Powdered NaN_3 (0.975 g, 15 mmol) and 10 mL of an aqueous solution 0.1 M of $Cu(NO_3)_2$ were added under stirring (resulting pH 4.3−4.5), and the mixture was warmed to 65 °C. After 1.5 h (ca. pH 5.5) the reaction mixture was cooled to 0 °C, and $NaBH_4$ was added portion-wise (0.757 g, 20 mmol). After 30 min at 0 °C the reaction mixture was filtered, and the copper boride was separated quantitatively. The aqueous mother liquors were acidified to red (indicator paper) with a few drops of concentrated HCl and charged on an ion-exchange resin Dowex 50WX8-400. Eluting with NH_4OH 0.1 M, the 2-hydroxy-3-aminohexanoic acid (**9b**) was isolated in 86% yield as a white crystalline solid. Recovered Cu(B) was dissolved in 20 mL of a water solution at pH 4.0, and the procedure was repeated. The catalyst was used four times without decreasing its efficiency. The structures of the products were confirmed by usual analyses; see Supporting Information.

copper were found (sensitivity > 0.5 ppm), confirming the complete recovery of the catalyst.

Finally, the procedure was applied to the synthesis of optically active alkylisoserines of biological interest: (+)-phenylnorstatine (**1**), (−)-allophenylnorstatine (**2**), and (−)-alloethylnorstatine (**3**) starting from the corresponding optically active α,β-epoxycarboxylic acids **4**,[26] **5**,[29] and **6**,[32] respectively (Table 6).

The optically active norstatines **1**,[33] **2**,[35] and **3**[32] were isolated in 72−83% overall yields, and the enantiomeric excesses (90−95%) were found to be consistent with those of the corresponding starting materials. These results proved, as expected, that the process proceeds with the preservation of the purity of the chiral centers.

Conclusions

In conclusion, *anti*- and syn-α-hydroxy-β-amino acids were synthesized in excellent yields from α,β-epoxycarboxylic acids using for the first time a one-pot copper-catalyzed azidolysis−reduction process that includes the recovery and reuse of the catalyst. The whole process has been performed solely in water, and considering that it plays an essential role in the recovery of copper boride and in its reconversion into Cu^{2+} at pH 4.0, water is the only reaction medium in which the process here presented can be carried out.

Acknowledgment. The Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), the Consiglio Nazionale delle Ricerche (CNR), and the Università degli Studi di Perugia are thanked for financial support.

Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) *Z*)-4-Phenyl-2-buten-1-ol, used to prepare **4**, was synthesized according to the procedure advised by Nicolaou.[27] Sharpless asymmetric epoxidation of the alcohol followed by $RuCl_3$/periodic acid Sharpless oxidation[28] allowed **4** to be obtained with 90% ee (measured by HPLC analysis on a chiral stationary phase and ^{1}H NMR analysis of the Mosher ester; see Supporting Information) (comparable to those obtained in the original procedures).[6c,d]

(27) Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Yoshimitsu, N.; De Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467−494.

(28) Carlsen, P. H.; Katsuki, T.; Martín, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(29) *E*)-4-Phenyl-2-buten-1-ol, used for preparing **5**, was synthesized by standard DIBAL-reduction of the corresponding α,β-unsaturated ethyl ester,[30] which was prepared following the recently reported procedure[31] where carboethoxymethyltriphenylphosphonium bromide (1.0 equiv) was added to a THF mixture of phenylacetaldehyde (1.0 equiv) and sodium acetate (1.2 equiv) and refluxed for 2 h (93% yield, after silca gel column chromatography). Sharpless asymmetric epoxidation[6c,d] and $RuCl_3$/periodic acid oxidation[28] of the alcohol then allowed **5** to be obtained with 95% ee (measured by HPLC analysis on a chiral stationary phase and ^{1}H NMR analysis of the Mosher ester; see Supporting Information) (comparable to that obtained in the original procedures).[6c,d]

(30) Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627−630.

(31) Hon, I.-S.; Lee, I.-F. *Tetrahedron* **2000**, *56*, 7893−7902.

(32) Epoxycarboxylic acid **6** was prepared by Sharpless asymmetric epoxidation[6c,d] and $RuCl_3$/periodic acid oxidation[28] of *trans*-2-hexenol with 93% ee (measured by ^{1}H NMR analysis of the Mosher ester) (comparable to that obtained in the original procedures).[6c,d] Compound **3**: mp > 230 °C (dec) and $[\alpha]_d^{20} = -11.7$ ($c = 0.52$ in 1 N HCl).

(33) Mp = 236−237 °C and $[\alpha]^{20}_D = +29.6$ ($c = 0.25$ in 1 N HCl) [lit.[14] mp = 235−237 °C and $[\alpha]^{20}_D = +29.9$ ($c = 0.214$ in 1 N HCl; lit.[34] mp = 236−237 °C and $[\alpha]^{20}_D = 29.2$ ($c = 0.25$ 1 N HCl). HPLC analysis on a chiral stationary phase, performed on the *N*-acetyl-methylester derivative, confirmed the enantiomeric purity of the starting epoxyalcohol **4** (Supporting Information).

(34) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853−1868.

(35) Mp = 236−237 °C and $[\alpha]^{20}_D = -5.2$ ($c = 0.56$ in 1 N HCl) [lit.[16] $[\alpha]^{20}_D = -5.4$ ($c = 0.51$ in 1 N HCl). HPLC analysis on a chiral stationary phase, performed on the *N*-acetyl-methylester derivative, confirmed the enantiomeric purity of the starting epoxyalcohol **5** (Supporting Information).