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Chemoenzymatic Synthesis of Both Enantiomers of *cis*-6-Hydroxymethylpipecolic Acid

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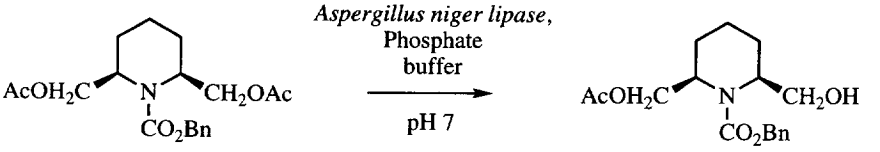
Abstract: Both enantiomers of *cis*-6-hydroxymethylpipecolic acid, a piperidine-based non-proteinogenic amino acid, have been synthesized in high enantiopurity (ee ≥ 98%) via an enzymatic desymmetrization procedure.

Peptides and proteins are critical to the proper functioning of all organisms. Peptides and their analogues are employed as therapeutic agents for medical problems exemplified by a disruption of communication between enzyme substrates or messenger molecules and the enzymes or receptors acting as their targets. Unmodified peptides are easily degraded by proteases and their mimetics can have superior efficacy, bioavailability and stability than peptides.[1] An important part of the design and synthesis of peptidomimetics is the availability of enantiopure, non-natural amino acids. They can be used to replace certain natural amino acids in the original peptide in order to create a peptidomimetic. Also, the incorporation of non-standard amino acids with well defined stereochemical and structural properties is a useful tool to study peptide conformation and protein folding. More recently, biosynthetic methods have been developed for the site-specific incorporation of unnatural amino acids into proteins.[2] This expansion of the genetic code is a powerful means to probe protein structure and function. This importance is reflected in the number of recent original and review publications in the literature concerning the synthesis of amino acids.[3]

We report here the synthesis of both enantiomers of *cis*-6-hydroxymethylpipecolic acid starting from alcohol **2**, a synthon made using an enzymatic desymmetrization procedure (Scheme 1) we have recently developed.[4] Biocatalysts such as lipases are frequently used in the synthesis of biologically active compounds.[5]

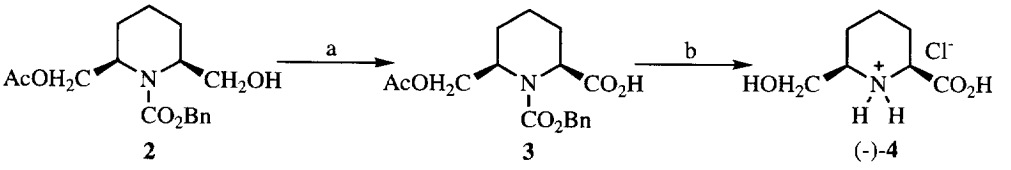
Scheme 1



1 **2**

Alcohol **2** (ee ≥ 98%), of known absolute configuration (2R, 6S), was obtained by enzymatic desymmetrization of diester **1a** in the presence of *Aspergillus niger* lipase.[4] Alcohol **2** was oxidized[6] with $RuCl_3$ and $NaIO_4$ in CH_3CN, CCl_4 and H_2O to give the carboxylic acid **3** (Scheme 2). Acid **3** was hydrogenated (10% Pd on carbon) in acidic water, which not only freed the amino group but also hydrolysed the acetate, to afford the desired amino acid hydrochloride, (−)-2S, 6R-**4** [$[\alpha]_D^{23}$ = − 33.6 (c 1.14, H_2O)].[7,8]

Scheme 2



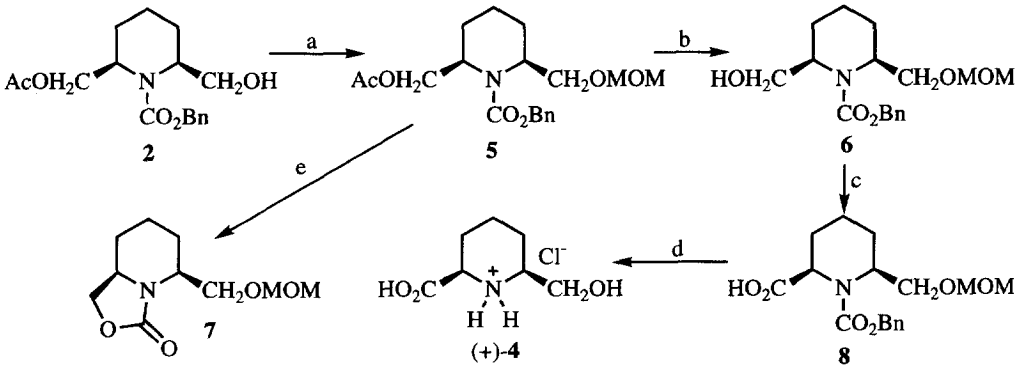
2 **3** (-)-**4**

Reagents and Conditions: a) $RuCl_3$ (0.022 eq), $NaIO_4$ (4.1 eq), CH_3CN (2mL/mmol alcohol), CCl_4 (2mL/mmol alcohol), H_2O (3mL/mmol alcohol), overnight, 68%;
b) H_2 (35 psi),10% Pd-C (25% w/w), 3N HCl (100 eq), 50°C, 15 hrs, 71%.

The synthesis of the opposite enantiomer, (+)-**4**, is reported in Scheme 3. Protection of the hydroxy group of **2** with chloromethyl methyl ether (MOM) in the presence of diisopropyl ethyl amine followed by the hydrolysis of the acetate **5** with pig liver esterase (PLE) gave **6** in high yield. The use of PLE was necessary, because base-catalyzed hydrolysis gave the oxazolidinone **7**, and acid-catalyzed hydrolysis would have yielded the corresponding meso diol. Oxidation of **6** by the method mentioned above provided the carboxylic acid **8** which was hydrogenated in an acidic aqueous solution, thus provoking the removal of the benzyl carbamate as well as the MOM protecting group to afford enantiopure (+)-2R, 6S-**4** [$[\alpha]_D^{23}$ = + 34.5 (c 1.14, H_2O)].[7,8]

The synthesis of racemic **4** by hydrogenation of 6-(hydroxymethyl)pyridine-2-carboxylate has been reported[9] but as far as we know there is no report on the enantioselective synthesis of this compound.

Scheme 3



Reagents and Conditions: a) MOM-Cl (2 eq), DiPEA (3 eq), CH_2Cl_2 (6mL/mmol), overnight, 95%;
b) PLE (560 units/mmol substrat), phosphate buffer pH 7 (25 mL), 24 hrs, 98%;
c) $RuCl_3$ (0.022 eq), $NaIO_4$ (4.1 eq), CH_3CN (2mL/mmol alcohol), CCl_4 (2 mL/mmol alcohol), H_2O (3 mL/mmol alcohol), overnight, 79%;
d) H_2 (35 psi),10% Pd-C (25% w/w), 3N HCl (100 eq), 50°C, 12 hrs, 63%;
e) 0.2N NaOH (1.5 eq), THF, H_2O, MeOH, 2.5:1:1, 1 hr, 98%.

Thus, the enzymatic desymmetrization of meso piperidines reported on Scheme 1 could lead to the synthesis of several enantiopure, non-standard amino acids. Both enantiomers of these molecules would be attainable. A hint of the possibilities of this process can be observed in the synthesis of both enantiomers of *cis*-6-hydroxymethylpipecolic acid hydrochloride. Extension of this method to the 2,4,6-trisubstituted pipecolic acids is under progress.

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7. All new compounds gave satisfactory spectral and combustion data. Compound **4** : m.p. 225-230°C (decomposition); IR (KBr) 3420-3360, 3250-2760, 1740, 1545, 1385, 1190 cm^{-1}; ^1H NMR (D_2O) δ 1.41 (m, 1H), 1.62 (m, 2H), 1.88 (m, 2H), 2.26 (m, 1H), 3.24 (m, 1H), 3.60 (dd, J_1 = 12.6 Hz, J_2 = 7.2 Hz), 3.77 (dd, J_1 = 12.6 Hz, J_2 = 3.8 Hz), 3.89 (dd, J_1 = 12.3 Hz, J_2 = 3.3 Hz). ^{13}C NMR (H_2O) δ 24.02, 26.39, 28.28, 60.20, 60.91, 64.19, 174.22. Anal. Calcd for $C_7H_{14}O_3Cl$: C, 42.97; H, 7.21; N, 7.14. Found: C, 42.76; H, 7.19; N, 6.80. (2S, 6R)-**4**: $[\alpha]_D^{23}$ = −33.6 (c 1.14, H_2O); (2R, 6S)-**4**: $[\alpha]_D^{23}$ = +34.5 (c 1.14, H_2O).
8. Absence of epimerisation/racemisation has been confirmed by NMR analysis of Mosher's esters of N-benzylmethyl esters of (+) and (−)-**4**.
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