Chemoenzymatic Synthesis of Both Enantiomers of *cis*-6-(Hydroxymethyl)- and *cis,cis*-4-Hydroxy-6-(hydroxymethyl)pipecolic Acids

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Both enantiomers of *cis*-6-(hydroxymethyl)- and *cis,cis*-4-hydroxy-6-(hydroxymethyl)pipecolic acids, piperidine-based nonproteinogenic amino acids, have been synthesized from starting materials obtained from enzymatic desymmetrizations.

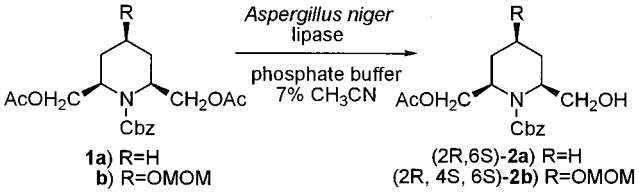
Introduction

Peptides of potential therapeutic value are easily degraded by proteases, and their mimetics can have superior efficacy, bioavailability, and stability. An important part of the design and synthesis of peptidomimetics is the availability of enantiopure, nonstandard amino acids. They can be used to replace certain natural amino acids in the original peptide in order to create a peptidomimetic.[1] Also, the incorporation of nonstandard amino acids with well-defined stereochemical and structural properties is a useful tool to study peptide conformation and protein folding.[2] More recently, biosynthetic methods have been developed for the site-specific incorporation of unnatural amino acids into proteins.[3] 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 enantioselective synthesis of amino acids.[4] We report here the synthesis of both enantiomers of *cis*-6-(hydroxymethyl)-pipecolic acid (**4a**) and *cis,cis*-4-hydroxy-6-(hydroxymethyl)pipecolic acid (**4b**) starting from alcohols **2a**,**b**, synthons obtained by an enzymatic desymmetrization procedure we have recently developed.[5,6]

Results and Discussion

Alcohols **2a**,**b** (ee ≥ 98%), of known absolute configuration (**2a**: 2*R*,6*S*; **2b**: 2*R*,4*S*,6*S*), were obtained by enzymatic desymmetrization of diesters **1a**,**b** in the presence of *Aspergillus niger* lipase[5] (Scheme 1). Alcohols **2a**,**b** were oxidized[7] with $RuCl_3$ and $NaIO_4$ in $CH_3CN-CCl_4-H_2O$ to give carboxylic acids **3a**,**b** (Scheme 2). Acids **3a**,**b** were hydrogenated (10% Pd on carbon) in acidic water, which not only freed the amino group but also hydrolyzed the acetate (and the MOM protecting group in the case of **3b**), to afford the amino acid hydrochlorides, (2*S*,6*R*)-**4a** ($[\alpha]^{23}_D$ −33.6 (*c* 1.14, H_2O)) and (2*S*,4*R*,6*R*)-**4b** ($[\alpha]^{23}_D$ −18.2 (*c* 1.22, H_2O)).

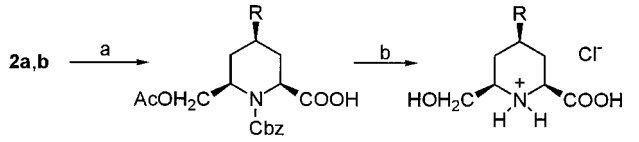
Scheme 1



1a) R=H
b) R=OMOM

(2R,6S)-**2a**) R=H
(2R, 4S, 6S)-**2b**) R=OMOM

Scheme 2[a]



3a) R=H
b) R=OMOM

(2S,6R)-**4a**) R=H
(2S,4R,6R)-**4b**) R=OH

[a]Reaction conditions: (a) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O; (b) H_2, Pd/C, 6N HCl

The opposite enantiomers were synthesized from the same starting materials **2a**,**b** (Scheme 3). Protection of the 6-hydroxy group of **2a**,**b** with chloromethyl methyl ether (MOM) in the presence of diisopropylethylamine followed by the hydrolysis of the acetates **5a**,**b** with pig liver esterase (PLE) gave **6a**,**b** in high yields. The use of an hydrolase was necessary because base-catalyzed hydrolysis gave an oxazolidinone from the attack of the alcoholate on the *N*-benzyloxycarbonyl group. Oxidation of **6a**,**b** by the method mentioned above provided the carboxylic acids **7a**,**b** which were hydrogenated in an acidic aqueous solution, thus provoking the removal of the benzyl carbamate as well as the MOM groups to

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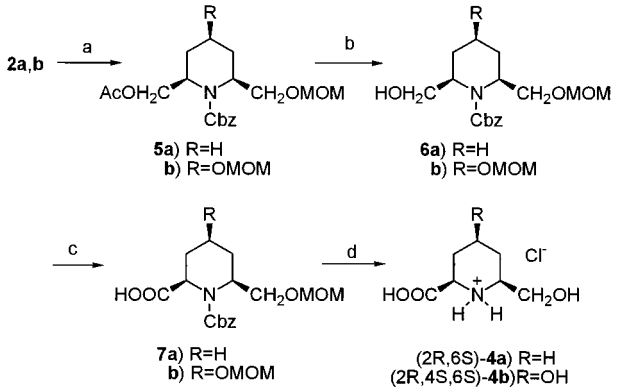
Scheme 3[a]



[a]Reaction conditions: (a) MOMCl, diisopropyl ethyl amine, CH_2Cl_2; (b) PLE, phosphate buffer; (c) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O; (d) H_2, Pd/C, 6N HCl

afford enantiopure amino acid hydrochlorides, (2*R*,6*S*)-**4a** ($[\alpha]^{23}_D$ +34.5 (*c* 1.14, H_2O)) and (2*R*,4*S*,6*S*)-**4b** ($[\alpha]^{23}_D$ +17.4 (*c* 1.32, H_2O)).

Both enantiomers of substituted pipecolic acids **4a**,**b** have been prepared from the same starting materials **2a**,**b**, which were obtained by enzymatic desymmetrization of meso compounds **1a**,**b**. These nonproteinogenic amino acids could be incorporated into peptidomimetics for their secondary structure-promoting effects and increased proteolytic stability. Pipecolic acid derivatives **4a**,**b** possess a set of characteristics which makes them attractive scaffolds[8] for combinatorial synthesis: they are enantiomerically pure and conformationally rigid; they provide a three-dimensional spatial arrangement of orthogonally manipulable functional groups for the generation of molecular diversity. Also, the piperidine ring is a common structural subunit in natural products or bioactive synthetic compounds. The interest in these compounds is well-displayed by the wealth of published material detailing their sources, biological activities, and syntheses.[9]

Experimental Section

General. NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C). Melting points are uncorrected. Flash column chromatography was carried out using 230−400 mesh silica gel. Pig liver esterase was from Sigma or Amano.

General Procedure for O-Protection of Alcohols 2a and 2b. To a solution of **2a** or **2b** (6 mmol) and 3.5 equiv of diisopropyl ethylamine in 20 mL of anhydrous CH_2Cl_2 at 0 °C under N_2 were added 3 equiv of MOM-Cl dropwise with stirring. After 30 min, the ice bath was removed, and the reaction was stirred for 15 h. The reaction mixture was diluted with 200 mL of EtOAc and washed successively with 1 N HCl (3 × 25 mL), saturated aqueous $NaHCO_3$ (3 × 25 mL), and brine (50 mL). The organic phase was dried ($MgSO_4$) and evaporated.

(−)-*N*-(Benzyloxycarbonyl)-*cis*-2(*R*)-(acetoxymethyl)-6(*S*)-[(methoxymethoxy)methyl]piperidine (5a). Flash chromatography with 25% EtOAc/75% petroleum ether afforded **5a** in 94% yield as a colorless oil. $[\alpha]^{25}_D = -11.6$ (*c* 1.0, $CHCl_3$); IR (neat) 3025, 2925, 1745, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.35−7.23 (m, 5H), 5.12 (AB system, J = 12.4 Hz, 2H), 4.70 (s, 2H), 4.55−4.36 (m, 2H), 4.13 (dd, J_1 = 10.5 Hz, J_2 = 8.4 Hz, 1H), 3.85 (dd, J_1 = 10.6 Hz, J_2 = 6.4 Hz, 1H), 3.52−3.39 (m, 2H), 3.28 (s, 3H), 1.94 (s, 3H), 1.86−1.45 (m, 6H); ^{13}C NMR ($CDCl_3$) 170.5, 155.9, 136.5, 128.3, 127.8, 127.7, 96.2, 67.9, 67.1, 64.1, 55.1, 49.3, 48.2, 24.8, 24.7, 20.6, 14.2; HRMS (EI) calcd for $C_{19}H_{27}NO_6$ (M^+) 366.1916 found 366.1920 ± 0.0011.

(−)-*N*-(Benzyloxycarbonyl)-*cis*,*cis*-2(*R*)-(acetoxymethyl)-4(*S*)-(methoxymethoxy)-6(*S*)-[(methoxymethoxy)methyl)]-piperidine (5b). Flash chromatography with 40% EtOAc/60% petroleum ether afforded **5b** in 95% yield as a colorless oil. $[\alpha]^{25}_D = -6.15$ (*c* 2.02, $CHCl_3$); IR (neat) 3025, 2910, 1740, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.37−7.27 (m, 5H), 5.13 (AB system, J = 12.4 Hz, 2H), 4.66−4.53 (m, 5H), 4.45−4.42 (m, 1H), 4.29 (dd, J_1 = 7.0 Hz, J_2 = 10.7 Hz, 1H), 4.11 (dd, J_1 = 7.7 Hz, J_2 = 10.7 Hz, 1H), 3.96−3.92 (m, 1H), 3.75 (t, J = 9.0 Hz, 1H), 3.60 (dd, J_1 = 5.6 Hz, J_2 = 9.2 Hz, 1H), 3.33 (s, 3H), 3.31 (s, 3H), 1.92 (s, 3H), 1.87−1.74 (m, 4H); ^{13}C NMR ($CDCl_3$) 170.5, 155.9, 136.5, 128.3, 127.9, 127.8, 96.3, 94.2, 69.7, 67.9, 67.2, 66.3, 55.3, 55.1, 48.8, 47.6, 29.2, 28.5, 20.6; HRMS (EI) calcd for $C_{21}H_{31}NO_8$ (M^+) 426.2128, found 426.2133 ± 0.0013.

General Procedure for Enzymatic Hydrolysis of Acetates 5a and 5b. The acetate (0.8 mmol) was suspended in 20 mL of phosphate buffer at pH 7.0. To this mixture was added PLE (100 mg), and the reaction mixture was stirred at room temperature. The pH of the solution was maintained at its initial value by addition of 0.1 N NaOH. After the addition of 1 equiv of base (∼24 h), the aqueous mixture was saturated with NaCl and extracted three times with EtOAc. The combined EtOAc fractions were dried ($MgSO_4$) and evaporated.

(−)-*N*-(Benzyloxycarbonyl)-*cis*-2(*S*)-[(methoxymethoxy)-methyl]-6(*R*)-(hydroxymethyl)piperidine (6a). Flash chromatography with 50% EtOAc/50% petroleum ether gave **6a** in 85% yield as a colorless oil. $[\alpha]^{25}_D = -5.7$ (*c* 1.1, $CHCl_3$); IR (neat) 3680−3140, 3030, 2930, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.34−7.27 (m, 5H), 5.13 (AB system, J = 12.4 Hz, 2H), 4.55−4.52 (m, 2H), 4.41−4.33 (m, 2H), 3.56−3.44 (m, 4H), 3.27 (s, 3H), 2.92 (br s, 1H), 1.76−1.44 (m, 6H); ^{13}C NMR ($CDCl_3$) 156.9, 136.5, 128.3, 127.8, 127.7, 96.2, 67.9, 67.2, 64.3, 55.2, 51.7, 49.3, 24.8, 24.4, 14.5; HRMS (EI) calcd for $C_{17}H_{25}NO_5$ (M^+) 326.1603, found 326.1607 ± 0.0010.

(+)-*N*-(Benzyloxycarbonyl)-*cis*,*cis*-2(*S*)-[(methoxymethoxy)methyl]-4(*R*)-(methoxymethoxy)-6(*R*)-(hydroxymethyl)piperidine (6b). Flash chromatography with 75% EtOAc/25% petroleum ether gave **6b** in 92% yield as a colorless oil. $[\alpha]^{25}_D = +5.6$ (*c* 1.24, $CHCl_3$); IR (neat) 3620−3120, 3020, 2930, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.33−7.26 (m, 5H), 5.13 (AB system, J = 12.3 Hz, 2H), 4.62−4.54 (m, 4H), 4.47−4.41 (m, 2H), 3.90−3.84 (m, 1H), 3.79−3.61 (m, 4H), 3.33 (s, 3H), 3.28 (s, 3H), 3.01 (br s, 1H), 1.96−1.80 (m, 4H); ^{13}C NMR ($CDCl_3$) 156.6, 136.4, 128.3, 127.9, 127.8, 96.1, 94.7, 79.8, 69.6, 68.8, 67.3, 65.6, 55.3, 55.2, 51.5, 49.2, 29.1; HRMS (EI) calcd for $C_{19}H_{29}NO_7$ (M^+) 384.2022, found 384.2018 ± 0.0011.

General Procedure for Oxidation of Alcohols 2a, 2b, 6a, 6b. The alcohol (0.6 mmol) was dissolved into a mixture of acetonitrile (1.2 mL), CCl_4 (1.2 mL), and water (1.8 mL). $RuCl_3 \cdot 3H_2O$ (0.022 equiv) and $NaIO_4$ (4.1 equiv) were successively added, and the mixture was stirred overnight at room temperature. Brine (10 mL) was added to the mixture, and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography with silica gel neutralized with Et_3N (3% w/w).

(−)-*N*-(Benzyloxycarbonyl)-*cis*-6(*R*)-(acetoxymethyl)-piperidine-2(*S*)-carboxylic Acid (3a). Flash chromatography with $CHCl_3$−EtOAc−MeOH (14:1:1) gave acid **3a** in 73% yield as a colorless oil. $[\alpha]^{25}_D = -17.7$ (*c* 1.0, $CHCl_3$); IR (neat) 3640−3310, 3030, 2930, 1745, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) 10.35 (br s, 1H), 7.34−7.26 (m, 5H), 5.19 (m, 2H), 4.93−4.84 (m, 1H), 4.46 (s, 1H), 4.17 (m, 2H), 2.32 (m, 1H), 1.98 (s, 3H), 1.75−1.56 (m, 5H); ^{13}C NMR ($CDCl_3$) 176.3, 170.8, 156.4, 136.7,

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128.2, 127.6, 127.5, 67.0, 63.3, 54.1, 49.1, 26.4, 24.8, 20.8, 15.8; HRMS (EI) calcd for $C_{17}H_{21}NO_6$ (M^+) 336.1447, found 336.1451 ± 0.0010.

(+)-*N*-(Benzyloxycarbonyl)-*cis,cis*-4(*R*)-(methoxymethoxy)-6(*R*)-(acetoxymethyl)piperidine-2(*S*)-carboxylic Acid (3b). Flash chromatography with $CHCl_3$−EtOAc−MeOH (10:1:1) gave acid **3b** in 75% yield as a colorless oil. $[\alpha]^{25}_D = +28.1$ (*c* 2.4, $CHCl_3$); IR (neat) 3650−3300, 3035, 3030, 1750, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) 7.78 (br s, 1H), 7.27−7.19 (m, 5H), 5.09 (s, 2H), 4.73 (s, 1H), 4.55−4.53 (m, 1H), 4.42−4.40 (m, 2H), 4.32 (s, 2H), 3.91 (s, 1H), 3.26 (s, 3H), 2.57−2.53 (m, 1H), 1.87 (s, 3H), 1.75−1.63 (m, 3H); ^{13}C NMR ($CDCl_3$) 176.8, 170.8, 156.4, 136.1, 128.4, 127.9, 127.8, 93.7, 67.7, 65.9, 65.8, 55.2, 49.8, 48.0, 29.1, 28.7, 20.7; HRMS (EI) calcd for $C_{19}H_{25}NO_8$ (M^+) 396.1658, found 396.1666 ± 0.0012.

(+)-*N*-(Benzyloxycarbonyl)-*cis*-6(*S*)-[(methoxymethoxy)-methyl]piperidine-2(*R*)-carboxylic Acid (7a). Flash chromatography with $CHCl_3$−EtOAc−MeOH (14:1:1) gave acid **7a** in 81% yield as a colorless oil. $[\alpha]^{25}_D = +15.4$ (*c* 1.6, $CHCl_3$); IR (neat) 3450, 3060, 2940, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) 10.89 (br s, 1H), 7.32−7.26 (m, 5H), 5.17 (AB system, $J = 11.1$ Hz, 2H), 4.95−4.88 (m, 1H), 4.58−4.48 (m, 2H), 4.35 (m, 1H), 3.68−3.45 (m, 2H), 3.28 (d, $J = 16.9$ Hz, 3H), 2.31 (m, 1H), 1.93 (m, 1H), 1.69−1.53 (m, 4H); ^{13}C NMR ($CDCl_3$) 176.3, 156.8, 136.2, 128.3, 127.9, 127.8, 96.1, 67.7, 66.7, 54.9, 52.9, 50.1, 25.9, 24.5, 15.6; HRMS (EI) calcd for $C_{17}H_{23}NO_6$ (M^+) 338.1603, found 338.1608 ± 0.0010.

(−)-*N*-(Benzyloxycarbonyl)-*cis,cis*-4(*S*)-(methoxymethoxy)-6(*S*)-[(methoxymethoxy)methyl]piperidine-2(*R*)-carboxylic Acid (7b). Flash chromatography with $CHCl_3$−EtOAc−MeOH (10:1:1) gave acid **7b** in 78% yield as a colorless oil. $[\alpha]^{25}_D = -30.8$ (*c* 3.6, $CHCl_3$); IR (neat) 3380, 3040, 2940, 1740, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) 9.97 (br s, 1H), 7.33−7.25 (m, 5H), 5.22−5.18 (m, 2H), 4.83 (s, 1H), 4.62−4.59 (m, 3H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.37 (s, 1H), 4.00 (m, 1H), 3.86−3.78 (m, 2H), 3.31 (s, 6H), 2.60 (d, $J = 12.4$ Hz, 1H), 2.09 (d, $J = 14.1$ Hz, 1H), 1.87−1.72 (m, 2H); ^{13}C NMR ($CDCl_3$) 176.8, 156.3, 136.2, 128.4, 127.9, 127.8, 96.2, 93.6, 69.0, 67.7, 66.2, 55.2, 55.0, 50.5, 48.9, 29.1, 28.2; HRMS (EI) calcd for $C_{19}H_{27}NO_8$ (M^+) 398.1815, found 398.1822 ± 0.0012.

General Procedure for Hydrogenation of 3a, 3b, 7a, and 7b. To a suspension of the amine (0.25 mmol) in 6 N HCl (25 mL) was added 75 mg of Pd/C, and the mixture was hydrogenated at 45 psi at 50 °C for 15 h. After filtration of the mixture through a pad of Celite, water was evaporated. Column chromatography on Sephadex G-10 (40−120 μm) with MeOH as eluant gave the amino acid as a white solid. The product was recrystallized in H_2O−EtOH.

***cis*-6-(Hydroxymethyl)piperidine-2-carboxylic Acid (4a).** (2*S*,6*R*)-**4a**: $[\alpha]^{25}_D = -33.6$ (*c* 1.14, H_2O); (2*R*,6*S*)-**4a**: $[\alpha]^{25}_D = +34.5$ (*c* 1.14, H_2O). Spectroscopic data are identical for both enantiomers: mp 225−230 °C (dec); IR (KBr) 3400, 3250−2500, 1780 cm^{-1}; ^1H NMR (D_2O) 3.89 (dd, $J_1 = 12.3$ Hz, $J_2 = 3.3$ Hz, 1H), 3.77 (dd, $J_1 = 12.6$ Hz, $J_2 = 3.8$ Hz, 1H), 3.60 (dd, $J_1 = 12.6$ Hz, $J_2 = 7.2$ Hz, 1H), 3.24 (m, 1H), 2.26 (m, 1H), 1.88 (m, 2H), 1.62 (m, 2H), 1.41 (m, 1H); ^{13}C NMR (D_2O) 174.2, 64.2, 60.9, 60.2, 28.3, 26.4, 24.1; HRMS (EI) calcd for $C_7H_{14}ClNO_3$ (M^+) 160.0974, found 160.0976 ± 0.0005.

***cis,cis*-4-Hydroxy-6-(hydroxymethyl)piperidine-2-carboxylic Acid (4b).** (2*S*,4*R*,6*R*)-**4b**: $[\alpha]^{25}_D = -18.2$ (*c* 1.22, H_2O); (2*R*,4*S*,6*S*)-**4b**: $[\alpha]^{25}_D = +17.02$ (*c* 1.32, H_2O). Spectroscopic data are identical for both enantiomers: mp 205−208 °C (dec); IR (KBr) 3420, 3275−2520, 1770 cm^{-1}; ^1H NMR (D_2O) 3.97 (d, $J = 12.5$ Hz, 2H), 3.81−3.78 (m, 1H), 3.67−3.61 (m, 1H), 3.37−3.26 (m, 1H), 2.51 (d, $J = 12.7$ Hz, 1H), 2.09 (d, $J = 12.9$ Hz, 1H), 1.60 (dd, $J_1 = 12.6$, $J_2 = 12.1$, 1H), 1.43 (dd, $J_1 = 12.5$ Hz, $J_2 = 12.2$ Hz, 1H); ^{13}C NMR (D_2O) 174.5, 67.8, 63.9, 59.0, 36.4, 35.1; HRMS (EI) calcd for $C_7H_{14}ClNO_4$ (M^+) 176.0923, found 176.0928 ± 0.0005.

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Supporting Information Available: Spectrometric information (^1H NMR) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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