



## Synthesis of Enantiomerically Pure (2R, 5S)- and (2R, 5R)-5-Hydroxypipicolinic Acid from Glycinate Schiff Bases.

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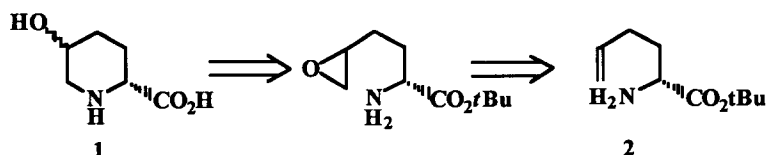
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**Abstract:** An asymmetric synthesis of *cis*- and *trans*- 5-hydroxy-(D)-pipicolinic acid, starting from glycinate Schiff bases is described. The approach involves the stereoselective alkylation to generate an unsaturated side chain which on cyclisation leads to the desired *trans*- or *cis*- 5-hydroxy-(D)-pipicolinic acid. Copyright © 1996 Elsevier Science Ltd

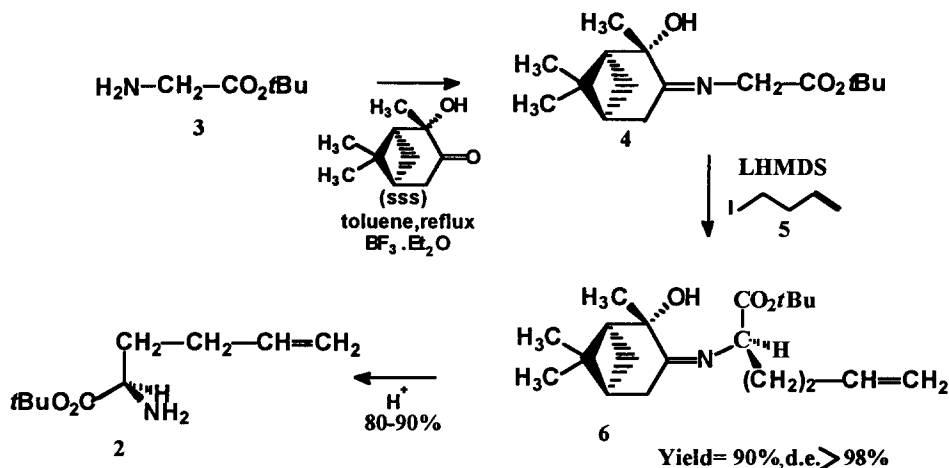
The aminoacid 5-hydroxy-(L)-pipicolinic acid **1**<sup>1</sup> is present in various plants such as dates and acacia, and in microorganisms such as *Pseudomonas fluorescens*.<sup>2</sup> The hydroxyiminoacid has been described as a powerful inhibitor of platelet aggregation and it is suspected to be involved in the biological effects of *Xylia xylocarpa* extracts,<sup>3</sup> a plant used in Indian medicine for the treatment of leprosy. All naturally occurring pipicolinic acid derivatives are L enantiomers. We were interested in the asymmetric synthesis of both the D- and L-enantiomers of **1**, with the aim of introducing them into various peptides as replacements of the homologs D- or L-4-hydroxyproline. Modification of the size of the ring structure is expected to lead to peptides with new properties<sup>4</sup>. While the replacement of proline by pipicolinic acid derivatives has already been studied in at least two compound classes<sup>5</sup>, that of 4-hydroxyproline by 5-hydroxypipicolinic acid seems not to have been described so far.

We have explored a short diastereoselective route to 5-hydroxypipicolinic acid **1**<sup>6</sup>. For the *cis*- or *trans*- 5-hydroxypipicolinic acids, a retrosynthetic analysis suggested that the configuration of carbon 2 should be fixed first (Scheme 1).



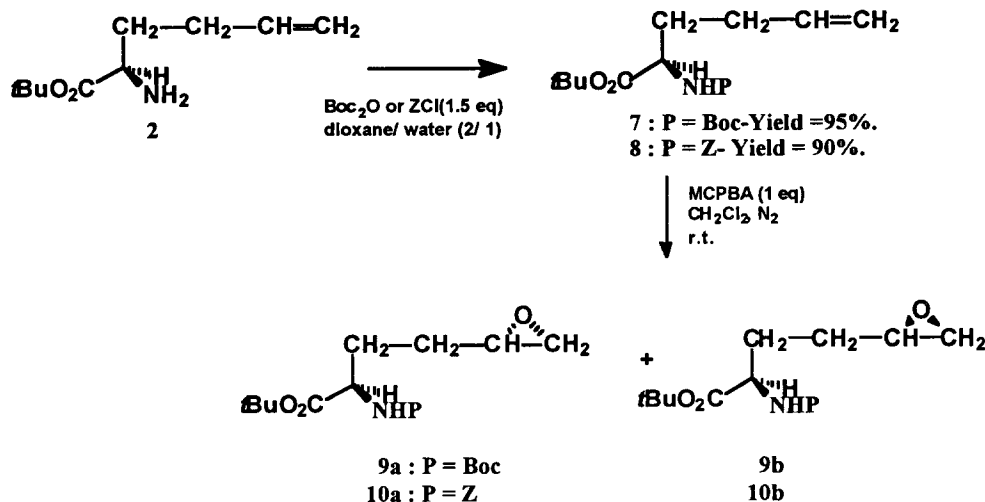
Scheme 1.

For this purpose, we have used the alkylation of chiral Schiff bases (prepared from glycine ester and (SSS)-2-hydroxypinan-3-one) to obtain 2R-aminoacids. Basing on several results from our laboratory,<sup>7</sup> we chose the *tert*-butyl ester group which gave better diastereoisomeric excesses than the methyl ester (Scheme 2).



Scheme 2.

The iodide **5** obtained by conversion of the corresponding bromide or alcohol using standard methods was used as alkylating agent. Several bases [lithium-diisopropylamide (LDA), potassium and lithium hexamethyldisilazide (KHMDs and LHMDs)] were studied for the alkylation of the glycine *t*-butyl ester Schiff bases. The best diastereoisomeric excess was obtained with LHMDs (Scheme 2). Keeping this chiral inducer, we first tried a direct epoxidation of compound **6**, but this reaction involved the C=N bond instead of the C=C bond. We decided to hydrolyse the Schiff base **6**. The resulting aminoester **2** had to be protected before epoxidation of the double bond. We chose the *tert*-butoxycarbonyl (Boc) and the benzyloxycarbonyl groups (Z), both easily introduced and cleavable, and prepared **7** and **8** (Scheme 3). Treatment of **7** and **8** with metachloroperbenzoic acid (MCPBA) in methylene chloride under nitrogen afforded the epoxy-aminoesters **9** and **10** respectively, each as a mixture of two unseparated isomers, the two epoxides of the 2R-aminoester. Direct cyclisation of the epoxide mixtures **9** or **10** was carried out by  $\text{K}_2\text{CO}_3$  in EtOH at 80°C and led unfortunately to pyrrolidine derivatives according to structural assignments mainly based on Mass and  $^1\text{H}$ -NMR data.<sup>8</sup> At this point, we opened the epoxide **9** (or **10**) with  $\text{LiBr}^\circ$  and tested the following strategy starting from **9** or **10**, the best results being obtained with Z, as the protecting group. (Scheme 4, only Z described). All steps of the reaction sequence occurred with complete retention of configuration at C<sub>2</sub>.



Scheme 3.

Protection of the alcohol **11a, b** was achieved with *t*-butyldimethylsilyl chloride (*t*BDMSCl). To form the piperidine ring, we attempted different reaction conditions ( $\text{Et}_3\text{N}$ / MeCN at r.t.;  $\text{K}_2\text{CO}_3$ / DMF reflux; NaH / THF or DMF at r.t.; NaH / THF reflux). Finally, cyclisation was achieved with NaH in DMF at  $85^\circ\text{C}$ ,<sup>6c</sup> leading to the fully protected 5-hydroxyproline derivatives **13a** and **13b**.

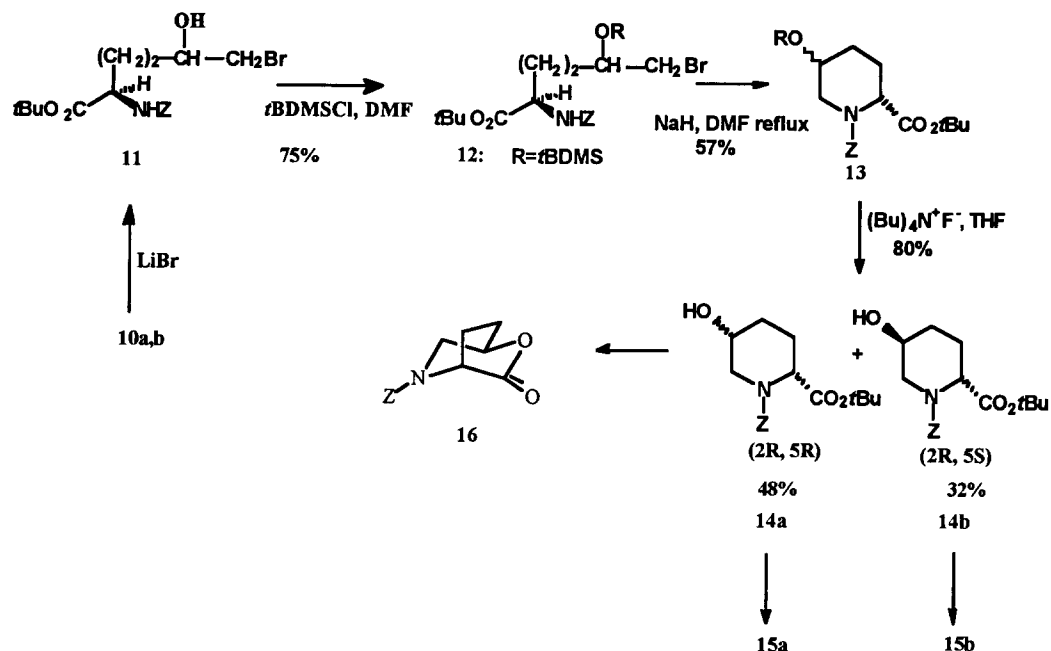
The mixture of *cis*- and *trans*- isomers **13a** and **13b** was first deprotected. The resulting diastereomers **14a** and **14b** could then be separated by column chromatography. In addition, the *cis*-diastereoisomer (2*R*, 5*R*) **14a** could be identified via lactonisation achieved by refluxing in benzene with a catalytic amount of *p*-toluene sulfonic acid to give **16**.<sup>10</sup> As expected, no similar lactone could be obtained with **14b**. We observed for each component the presence of rotamers by  $^1\text{H}$ -NMR spectroscopy at  $20^\circ\text{C}$ . Finally, hydrogenolysis of each carbamate **14a** and **14b** followed by hydrolysis of *tert*-butyl ester gave the free aminoacid hydrochloride **15a** and **15b**, the physicochemical properties of which compared well with literature values (Scheme 4).

In summary, we have reported a new route to (2*R*, 5*S*) and (2*R*, 5*R*) hydroxyproline acids in 17% overall yield. Our method is versatile and can lead to each of the four isomers.

## Experimental

### General

Thin layer chromatography was performed on Merck precoated silica gel 60F<sub>254</sub> plates and spots were visualized by ultraviolet light or by iodine vapour. Melting points uncorrected were obtained on a Büchi 510 apparatus. Optical rotations were determined with a Perkin-Elmer model 141 polarimeter.  $^1\text{H}$  NMR Spectra



Scheme 4

were recorded on a Bruker spectrometer AC 250. Mass spectra were measured on Jeol JMS DX 100 and DX 300 apparatus. Diastereomeric purity was checked by reverse phase HPLC on C-18 Nucleosyl.

**Glycine *tert*-butyl ester 3:**<sup>11</sup> This compound was prepared from *tert*-butyl bromoacetate (22.73g, 155mmol), by addition in dry ether (25ml) of a large excess of  $NH_3$  (l) at  $-40^\circ C$ . Yield : 14.2g (70%).

**Glycinate Schiff base 4:** A solution of glycine *tert*-butylester (2.23g, 17mmol) and of (SSS) 2-hydroxypinan-3-one<sup>12</sup> (1.85g, 11mmol) was refluxed for  $2\frac{1}{2}$  h in toluene in the presence of a catalytic amount of  $BF_3 \cdot Et_2O$ . After evaporation of the solvent, the oil was purified on silica gel (petroleum ether / ether: 1 / 2). Yield : 2.32g (75%). faint yellow oil.-  $R_f$ : 0.46 (ether / petroleum ether: 3 / 1). -  $^1H$ -NMR ( $C_6D_6$ ):  $\delta$  (ppm) = 0.87 (3H, s, Me), 1.30 (3H, s, Me), 1.40 (3H, s, Me), 1.45 (9H, s, *t*Bu), 1.60-2.60 (6H, m), 3.00 (1H, s), 4.00 (2H, s,  $CH_2$ ).

**4-iodo-1-butene 5:** Two methods have been used:

a)- Compound 5 was first prepared from 3-buten-1-ol following Lange's procedure<sup>13</sup>. To dry dichloromethane (473ml) triphenylphosphine, imidazole and iodine (104mmol, each) were added. A solution of 3-buten-1-ol (69.4mmol) in dry dichloromethane (79ml) was then slowly introduced and the mixture was stirred at room temperature under argon for 5h. The disappearance of the alcohol was followed by TLC. When the reaction was completed, most of the solvent was cautiously removed by distillation under reduced pressure (15mm) because of the volatility of 5. Yield = 5g (40%).

b)- Alternatively, 4-bromo-1-buten (2.25ml, 22.2mmol) was dissolved in dry acetone (165ml), sodium iodide (6.66g, 44.4mmol) was added and the mixture refluxed for 3h. After filtration, the solvent was removed by distillation. After addition of water to the remaining oil, the aqueous layer was extracted with ether (3.30ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by distillation. Yield = 2.02g (50%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ (ppm) = 2.5-2.7 (2H, m, -CH<sub>2</sub>-CH<sub>2</sub>I), 3.1-3.22 (2H, t, J = 7.15Hz, -CH<sub>2</sub>I), 5-5.2 (2H, m, -CH<sub>2</sub>), 5.54-5.8 (1H, m, -CH=).

**2-[(*SSS*)-2-hydroxypinan-3-imino]-2'-(1-buten-4-yl)-*t*butylacetate 6:** A solution of *n*-butyllithium in ether or hexane<sup>14</sup> (13.7ml, 2.3mmol) was prepared under nitrogen and mixed to the solution of hexamethyldisilazane (HMDS) (4.77ml, 2.5mmol) in anhydrous THF (40ml) at -10°C. After 20min, the mixture was cooled to -100°C; then, the Schiff base 4 (2.57g, 9.14mmol) dissolved in a minimum of THF (3ml), and after 20min, the alkylating agent 5 (3.66g, 2.2mmol) were added. The mixture was stirred at -100°C for 4h, then allowed to reach slowly -30°C (20h). Washing with a saturated solution of NH<sub>4</sub>Cl and extraction of the aqueous phase with ether (3.20ml) followed. The organic layer was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The faintly brown oil was purified by chromatography on silica gel. Yield= 2.75g (90%).- R<sub>f</sub>= 0.65 (ether / hexane: 2 / 1). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ (ppm) = 0.85 (3H, s), 1.31 (3H, s), 1.43 (9H, s), 1.49 (3H, s), 2-2.8 (10H, m), 4.1 (1H, m), 5 (2H, m), 5.7-5.9 (1H, m). HPLC (C-18 Nucleosyl): t<sub>r</sub> = 5.79mn (acetonitrile / water : 65 / 35, isocratic).

**H-(*D*)-norleucine -δ-ene-*Or*Bu 2:** The pure Schiff base 6 could be hydrolysed by two methods:

a)- Aqueous citric acid (15%) was added to a solution of 6 (2.85g, 8.51mmol) in THF (16ml). The mixture was stirred at r.t. for 84h, then, the solvent removed in vacuo. The aqueous layer was extracted with ethyl acetate (3.20ml). The organic layer was discarded and the aqueous layer brought to pH = 8 with sodium carbonate. After several extractions with ethyl acetate, the organic phase was dried (MgSO<sub>4</sub>) and evaporated. 1.40g (yield = 89%). [α]<sub>D</sub> = -25.2 (c = 1.03; MeOH).- <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ (ppm) = 1.46 (9H, s, C<sub>4</sub>H<sub>9</sub>), 1.54-1.77 (4H, m, CH<sub>2</sub>-CH<sub>2</sub>), 2.15 (2H, dd, J<sub>1</sub> = 15.08Hz, J<sub>2</sub> = 8.10Hz, NH<sub>2</sub>), 3.31 (1H, m, N-CH), 5 (2H, m, -CH=CH<sub>2</sub>).

b)- Compound 6 (0.335g, 1mmol) was dissolved in acetonitrile (6ml). Then, an aqueous solution of boric acid (6ml) at pH=6.2 (with phosphate buffer) was added slowly. The mixture was stirred for 20h. After removal of acetonitrile, the solution was brought to pH = 1.5 with KHSO<sub>4</sub>. Then isolation of 2 followed as described under a). Yield = 148mg (60-80%).

**Boc-(*D*) norleucine-δ-ene-*Or*Bu 7:** Compound 2 (0.42g, 2.27mmol) was dissolved in a mixture of dioxane (6ml) and water (3ml). Boc<sub>2</sub>O (0.74g, 3.4mmol) was added at 0°C. The mixture was stirred at r.t. for 2½ h.

After the disappearance of **2**, the dioxane was removed in vacuo, the aqueous layer extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate; then, the solvent was eliminated under reduced pressure. The oil was purified by chromatography on silica gel in petroleum ether / ether (4/1). Yield = 0.615g (95%).-  $R_f$  = 0.85 (ether / hexane).-  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 1.45 (9H, s,  $\text{C}_4\text{H}_9$ ), 1.55 (9H, s,  $\text{C}_4\text{H}_9$ ), 1.6-2.3 (4H, m,  $-\text{CH}_2-\text{CH}_2-$ ), 4.05-4.5 (4H, m,  $-\text{N-CH}$ ), 4.95-5.3 (2H, m,  $\text{CH}_2=\text{CH}$ ), 5.6-6.1 (1H, m,  $-\text{CH}=\text{CH}_2$ ).

**Z-(D) norleucine- $\delta$ -ene-OtBu **8**:** Compound **2** (0.25g, 1.35mmol) was dissolved in a solution of dioxane (5ml) and water (2.5ml) at  $0^\circ\text{C}$ .  $\text{NEt}_3$  (0.25ml, 1.75mmol) and  $\text{ZCl}$  (0.29ml, 2.02mmol) were added. The mixture was stirred for  $2\frac{1}{2}$  h. Dioxane was removed in vacuo and the aqueous phase extracted with ethyl acetate. The organic layer was dried ( $\text{MgSO}_4$ ), concentrated in vacuo and the residue chromatographed on silica gel in petroleum ether / ether (4/1). Yield: 0.39g (90%).-  $R_f$  = 0.69 (ether / petroleum ether).-  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  (ppm) : 1.38 (9H, s,  $\text{CO}_2\text{tBu}$ ), 1.5-2.15 (4H, m,  $-\text{CH}_2-\text{CH}_2-$ ), 4.2 (1H, m,  $-\text{CH-N}$ ), 4.9 (2H, m,  $-\text{CH}=\text{CH}_2$ ), 5.05 (2H, s,  $-\text{CH}_2\text{Ph}$ ), 5.3 (1H, d, NH), 5.65-5.8 (1H, m,  $-\text{CH}=\text{CH}_2$ ), 7.3 (5H, s, Ph).

**Boc-(D) norleucine- $\delta$ -epoxy-OtBu (mixture of epoxy isomers **9a** and **9b**) and Z-(D) norleucine- $\delta$ -epoxy-OtBu (mixture of epoxy isomers **10a** and **10b**):** The N-protected aminoester **7** (or **8**) (4.35mmol) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (26ml). MCPBA (0.75g, 4.35mmol) was added in one portion. The mixture was stirred at r.t. under nitrogen for 19h. After washing several times in ether (10ml) and 10%  $\text{NaHCO}_3$  (5ml), the organic layer was dried ( $\text{MgSO}_4$ ) and concentrated. The product was purified by chromatography on silica gel. The two isomers **9a** and **9b** (respectively **10a** / **10b**) appeared as a single peak in the chromatogram.

**9a, b:** Yield = 1.25g (86%).-  $R_f$  = 0.66 (ether / hexane : 2 / 1).-  $[\text{M}+\text{H}]^+ = 302$  ( $\text{FAB}^+ / \text{NBA}$ ).-  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 1.45 (9H, s,  $\text{C}_4\text{H}_9$ ), 1.47 (9H, s, Boc), 1.5-2 (4H, m,  $-\text{CH}_2-\text{CH}_2-$ ), 2.49 and 2.77 (2H, 2 $\times$  m,  $\text{CH}_2\text{O}$ ), 2.9 (1H, m, CHO), 4.22 (1H, m,  $\text{HN-CH}$ ). NH : 5.05 (1H, d,  $J = 8.9\text{Hz}$ ) and 5.11 (1H, d,  $J = 8.9\text{Hz}$ ).  
**10a, b:** Yield = 1.41g (97%).-  $R_f$  = 0.71 (ether / petroleum ether = 2 / 1).-  $[\text{M}+\text{H}]^+ = 336$ .-  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 1.39 (9H, s,  $\text{CO}_2\text{tBu}$ ), 1.47-2 (4H, m,  $\text{CH}_2-\text{CH}_2$ ), 2.4 and 2.7 (2H, m,  $\text{CH}_2\text{O}$ ), 2.85 (1H, m, CHO), 4.2 (1H, m,  $\text{N-CH}$ ), 5.02 (2H, s,  $\text{OCH}_2\text{C}_6\text{H}_5$ ), 7.27 (5H, s,  $\text{C}_6\text{H}_5$ ). NH : 5.31 (1H, d,  $J = 8.37\text{Hz}$ ) and 5.7 (1H, d,  $J = 8.37\text{Hz}$ ).

**Z-[5-(R,S)-hydroxy-6-bromo-norleucine]-OtBu **11**:** This compound was prepared from **10** following Bajwa's procedure<sup>9</sup>. Anhydrous  $\text{LiBr}$  (0.56g, 6.4mmol) was added to a solution of **10a** / **10b** (1.34g, 4mmol) and acetic acid (0.68, 12mmol) in dry THF (40ml) and the reaction mixture was stirred at room temperature for 12h. When the reaction was completed, the mixture was diluted with water and extracted with ether. The organic layer was washed with 5%  $\text{KHCO}_3$ , dried ( $\text{MgSO}_4$ ) and concentrated. Yield: 1.64g (99%). -  $R_f$  = 0.56 (ether / petroleum ether : 2 / 1).-  $[\text{M}+\text{H}]^+ = 416$  ( $\text{FAB}^+ / \text{NBA}$ ).-  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 1.4 (9H, s,

$C_4H_9$ ), 1.5-2.05 (4H, m,  $-CH_2-CH_2$ ), 3.2-3.45 (2H, m,  $-CH_2Br$ ), 3.7-3.85 (1H, m,  $-CHOH$ ), 4.25 (1H, m,  $-N-CH-CO$ ), 5.05 (2H, s,  $-CH_2C_6H_5$ ). NH: 5.35 (1H, d,  $J = 7.76\text{Hz}$ ) and 5.45 (1H, d,  $J = 7.76\text{Hz}$ ). OH: 2.3 (1H, d,  $J = 4.3\text{Hz}$ ) and 2.6 (1H, d,  $J = 5\text{Hz}$ ).

**Z-[5-(*R,S*)-*t*-butyldimethylsilyl-6-bromo-norleucine]-*O**t*Bu 12a, b:** The alcohol **11** (0.30g, 0.72mmol) was dissolved in dry DMF (0.7ml) and added slowly to a solution of imidazole (0.122g, 1.8mmol) and tBDMSCl (0.14g, 0.94mmol) in DMF (0.4ml). After stirring for 18h at r.t., DMF was removed in vacuo. The residue was washed with water, concentrated and chromatographed on silica gel, the mixture of **12a** / **12b** was obtained. Yield : 0.285g, (75%).-  $R_f = 0.8$  (ether / petroleum ether : 1 / 2).-  $[M+H]^+ = 530$  (FAB<sup>+</sup> / NBA).- <sup>1</sup>H-NMR ( $C_6D_6$ ):  $\delta$  (ppm) = - 0.01 and 0 (6H, s, SiMe<sub>2</sub>), 1.32 (9H, s, CO<sub>2</sub>*t*Bu), 1.4-2.1 (4H, m,  $-CH_2-CH_2$ ), 2.9-3.1 (2H, m,  $-CH_2Br$ ), 3.5-3.65 (1H, m,  $-CHOR$ ), 4.35-4.55 (1H, m,  $-CH-N$ ), 5.05 and 5.1 (2H, s,  $-CH_2C_6H_5$ ), 5.36 and 5.4 (1H, d,  $J = 8.21\text{Hz}$ , NH), 7.05-7.3 (5H, m,  $C_6H_5$ ).

**N-Z-2-*t*-butyloxycarbonyl-5-(*R,S*)-*t*-butyldimethylsilyl-piperidine 13a, b:** Compound **12** (0.682g, 1.9mmol) was added to a suspension of NaH (3mmol), in dry DMF (3mmol). The mixture was refluxed under nitrogen for 24h. DMF was removed in vacuo. Dry ether was added to the residue and the mixture was filtered in order to eliminate sodium bromide. After concentration in vacuo, compound **13** was purified by chromatography on silica gel. The two diastereoisomers could not be separated. Yield = 0.486g (57%).-  $[M+Na]^+ = 472$  (FAB<sup>+</sup> / GT).- <sup>1</sup>H-NMR ( $CDCl_3$ ):  $\delta$  (ppm) = 0 (6H, m, SiMe<sub>2</sub>), 0.85 (9H, m, Si*t*Bu), 1.36 and 1.4 (9H, s, CO<sub>2</sub>*t*Bu), 1.5-2 (2H, m,  $\beta_a$  and  $\gamma_a$ ), 2.1-2.3 (1H, m,  $\gamma_e$ ), 2.6-2.9 (1H, m,  $\beta_e$ ), 3-3.6 (2H, m,  $\epsilon_e$  and  $\epsilon_a$ ), 3.8-4.1 (1H, m, N-CH), 3.9-4.5 (1H, m,  $\delta$ ), 5.1 (2H, m,  $CH_2Ph$ ), 7.24-7.34 (5H, m, Ph).

**N-Z-2-*t*-butyloxycarbonyl-5-hydroxy-piperidine 14a / 14b:** The mixture of **13** (2g, 4.45mmol), was dissolved in freshly distilled THF (25 ml). Tetra-*n*-butylammonium fluoride (2.33g, 8.9mmol) in THF (1.5ml), was added dropwise at 0°C. The solution was stirred for 5h under nitrogen at r.t. Then, a saturated aqueous solution of NH<sub>4</sub>Cl was added. After three extractions with ether, the organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The two diastereoisomers **14a** (yield : 0.72g, 48%) and **14b** (yield : 0.48g, 32%) were separated by chromatography in ether.

**14a:**  $R_f = 0.63$  (ether).-  $[M+H]^+ = 336$  (FAB<sup>+</sup> / NBA).-  $[\alpha]_D = +58.48$  ( $c = 0.684$ , MeOH).- A mixture of rotamers : <sup>1</sup>H-NMR ( $CDCl_3$ ) :  $\delta$  (ppm) = 1.1-1.25 (1H, m,  $\gamma_e$ ); 1.35 and 1.4 (9H, both s, CO<sub>2</sub>*t*Bu); 1.5-2.4 (4H, m,  $\beta_e$ ,  $\gamma_a$ ,  $\beta_a$ , and OH); 2.6-2.9 (1H, m,  $\epsilon_e$ ); 3.45-3.65 (1H, m,  $\epsilon_a$ ); 3.9-4.2 (1H, m,  $\delta_e$ ); 4.5-4.7 (1H, m,  $\alpha_a$ ); 4.95-5.2 (2H, m,  $-CH_2Ph$ ); 7.15 and 7.3 (5H, m, Ph).

**14b:**  $R_f = 0.49$  (ether).-  $[M+H]^+ = 336$  (FAB<sup>+</sup> / NBA).-  $[\alpha]_D = +10.7$  ( $c = 0.82$ ,  $CHCl_3$ ).- A mixture of rotamers : <sup>1</sup>H-NMR ( $CDCl_3$ ) :  $\delta$  (ppm) = 1.2-1.35 (1H, m,  $\gamma_e$ ); 1.45 and 1.49 (9H, both s, CO<sub>2</sub>*t*Bu); 1.65-2.5

(4H, m,  $\beta_e$ ,  $\gamma_a$ ,  $\beta_a$ , and OH); 3.1-3.35 (1H, m,  $\epsilon_e$ ); 3.9-4.15 (1H, m,  $\epsilon_a$ ,  $\delta_a$ ); 4.7-4.9 (1H, m, aa); 5-5.3 (2H, m, -CH<sub>2</sub>Ph); 7.35 (5H, m, Ph). (Assignments confirmed by selective decoupling experiments).

**5-hydroxypipelicolic acid hydrochloride 15a and 15b:** **14a** (respectively, **14b**) (0.84g, 2.5mmol) was added to the suspension of Pd(OH)<sub>2</sub> / C-20% (0.12g) in methanol (respectively, dichloromethane, 15ml). The solution was stirred under hydrogen pressure at 1atm for 20h and then filtered. The solvent was evaporated. The product (0.43g, 2.14mmol) was dissolved in dioxane/ water (1/ 1) (7.7ml) and refluxed with 3M HCl (15ml) for 20h. After evaporation of the solvent, the aminoacid hydrochloride was recrystallized from methanol / acetone and dried.

*(2R, 5R)-5-hydroxypipelicolic acid hydrochloride 15a* : Yield: 0.25g, (98%). m.p. 180-182°C.  $[\alpha]_D = +17.2$  (c= 0.85, H<sub>2</sub>O) [Litt <sup>2a</sup>:  $[\alpha]_D = +18.5$  (c = 1,3, MeOH)] <sup>1</sup>H-NMR (CD<sub>3</sub>OD) :  $\delta$  (ppm) = 1.75-2.2 (4H, m,  $\beta$ ,  $\gamma$ ); 3.15-3.3 (2H, m,  $\epsilon$ ); 3.9-4 (1H, m, -N-CH); 4.05-4.1 (1H, m,  $\delta$ ); - C<sub>6</sub>H<sub>12</sub>ClNO<sub>3</sub>. H<sub>2</sub>O (199.5) Calc. : C 36.12 H 7.07 N 7.02 found : C 35.92 H 6.85 N 6.90.

*(2R, 5S)-5-hydroxypipelicolic acid hydrochloride 15b* : Yield : 0.110 g, (94%). m.p =210-215°C.

$[\alpha]_D = +8.07$  (c= 1.425, H<sub>2</sub>O) [Litt <sup>2a</sup>:  $[\alpha]_D = +8.6$  (c = 1, H<sub>2</sub>O)]. <sup>1</sup>H- NMR (D<sub>2</sub>O) :  $\delta$  (ppm) = 1.65 (1H, m,  $\gamma_a$ ); 1.85 (1H, m,  $\beta_a$ ); 2.08 (1H, m,  $\gamma_b$ ); 2.4 (1H, m,  $\beta_b$ ); 2.9 (1H, dd,  $J_{ab} = 12.29, 9.63\text{Hz}$ ,  $\epsilon_a$ ); 3.5 (1H, m,  $\epsilon_b$ ); 3.95 (2H, m,  $\alpha$  and  $\delta$ ).

## References and Notes

1. The configuration of the 5-hydroxypipelicolic acid derivatives is indicated in one of the following ways: position 5: *cis*- and *trans*- hydroxy or 5R and 5S, respectively; position 2 : D and L-aminoacid or 2R and 2S, respectively.
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