Pergamon

*Tetrahedron*, Vol. 52, No. 18, pp. 6409-6420, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00282-7

# Diastereoselective Synthesis of (2*S*,5*S*)-and (2*R*,5*S*)-5-Hydroxyhomopipecolic Acid from *S*-Glutamic Acid. An Entry to Streptolutine Stereoisomers.

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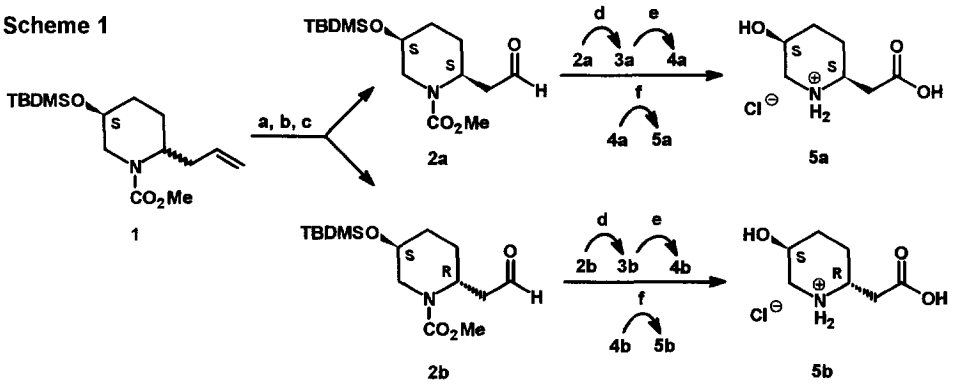
**Abstract**: Starting from readily available methyl (2*RS*,5*S*) 5-(t-butyldimethylsilyloxy)-2-(2'-propenyl)-piperidine-carboxylate (**1**), a diastereoselective synthesis of homopipecolic acids **5a** and **5b** and of di-epistreptolutine derivative **10** is decribed. Copyright © 1996 Elsevier Science Ltd

In our continuing studies of chiral nonracemic 5-substituted pipecolic acids with interesting biological activities,[1] we now report the first diastereoselective synthesis of (2*S*,5*S*)-and (2*R*,5*S*)-hydroxyhomopipecolic acid (**5a,b**) and di-epistreptolutine derivative **10**.

The starting substrate for the synthesis of the desired compounds was the readily available piperidine derivative **1** (*cis*:*trans* = 25:75), prepared from *S*-glutamic acid,[2] which was treated with ozone in dichloromethane/methanol 1:1, alternatively in methanol, to provide the dimethylacetal of **2a,b** in 77% isolated yield. Several attempts were made to cleave this acetal to the aldehyde **2a,b** but this was not successful because partial deprotection of the t-butyldimethylsilyloxy group ocurred. Ozonisation in dichloromethane furnished **2a,b** only in 30-40% yield. After a series of experiments we found that in the presence of glacial acetic acid the yield of **2a,b** increased to acceptable 65% overall yield and the amount of side products were minimised. The diastereomeric mixture of the aldehydes **2a,b** were separated by repeated column chromatography on silicagel. Treatment of **2a** and **2b** respectively with $Br_2$/MeOH/$NaHCO_3$[3] furnished the methyl esters **3a** (78%) and **3b** (83%) as colourless oils (Scheme 1). After desilylation of **3a** and **3b** with 5 M methanolic HCl, the urethane and ester group of **4a** and **4b** was removed with 6 M HCl under reflux, to afford (2*S*,5*S*) 5-hydroxyhomopipecolic acid (**5a**) (m.p. 180°C, $[\alpha]_D^{20}$ = +20.8, c=0.3, MeOH) and (2*R*,5*S*) 5-hydroxyhomopipecolic acid (**5b**) (m.p. = 90°C, $[\alpha]_D^{20}$ = -21.3, c=1.7, MeOH).

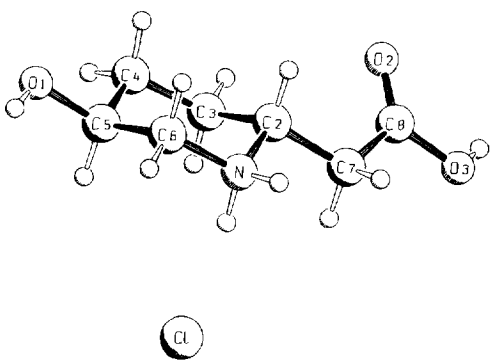
**Scheme 1**



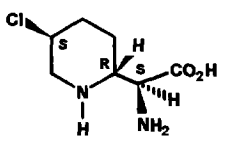

**a: $CH_2Cl_2$, AcOH, -78 °C, $O_3$; b: $Me_2S$; c: CC, silicagel, EtOAc; d: MeOH, $H_2O$, $NaHCO_3$, $Br_2$; e: 5 M HCl/MeOH; f: 6 M HCl, reflux**

A suitable crystal for X-ray crystallography of **5b** was provided by diffusion controlled crystallisation from MeOH/acetone/diethyl ether. As expected the X-ray structure of **5b** reveals the diequatorial position for both substituents.[4a]

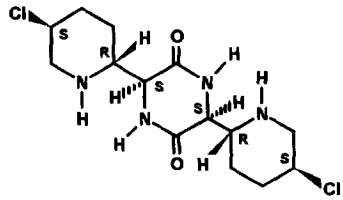
**X-ray structure of 5b (Schakal plot[5])**




With the enantio-and diastereopure ß-amino ester **3b**, which can be prepared in gram quantities, we anticipated that the enolate of **3b** might be an attractive precursor for the synthesis of one diastereomer of the still unknown amino acid streptolutine. Streptolutine is the monomer of cyclo-streptolutine (antibiotic 593A)[6a,b] which was isolated from *Streptomyces griseolutus*[7], and synthesized in racemic form.[6c,d] It possesses strong antiviral and antineoplastic activities.



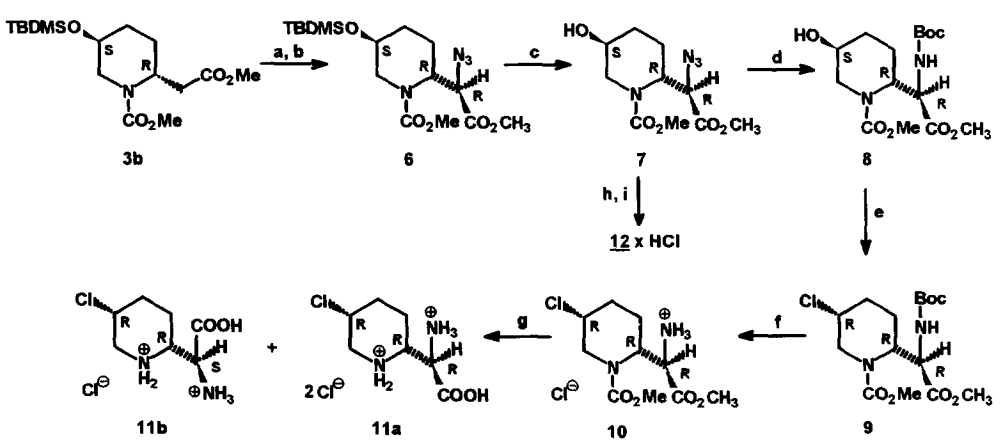
streptolutine



cyclostreptolutine

To introduce the amino group in the methoxycarbonyl methyl side chain at C-7 of **3b**, we decided to use the electrophilic azidation reaction following the procedure of Evans.[8a] Therefore the ester enolate of **3b** was generated by the treatment with potassium hexamethyldisilazide (KHMDS), followed by the addition of 2,4,6-triisopropylbenzenesulfonyl azide.[8b] Quenching with glacial acetic acid provided compound **6** (d.e >90%, determined by NMR). **6** was desilylated with 5 M methanolic HCl to give azide **7** (73% with reference to **3b**), which was hydrogenated in the presence of $Boc_2O$ to afford the fully protected amino acid **8**. The conversion of the OH function into Cl was carried out as previously described by us[1c] with inversion of the configuration at C-5, using the $CCl_4/PPh_3$ system, to obtain **9** in 65 % yield.[9] The Boc-group of **9** was removed with 5 M methanolic HCl to give the protected di-epi-streptolutine derivative **10**. Unfortunately more drastic conditions (6 M HCl, reflux), to remove the ester and urethane protecting groups, lead to complete epimerisation at C-7 to give the diastereomeric mixture of **11a,b**. All attempts to get suitable crystals of compound **10** to determine the configuration of the newly created stereogenic centre at C-7 by X-ray crystallographic analysis were fruitless. Therefore we decided to hydrogenate **7** and to transform the resulting amine with methanolic HCl to the amino acid hydrochloride **12** ($[\alpha]_D^{20}$ = -25.7, c=0.9, MeOH). Fortunately **12** gave suitable crystals for X-ray analysis (Scheme 2).

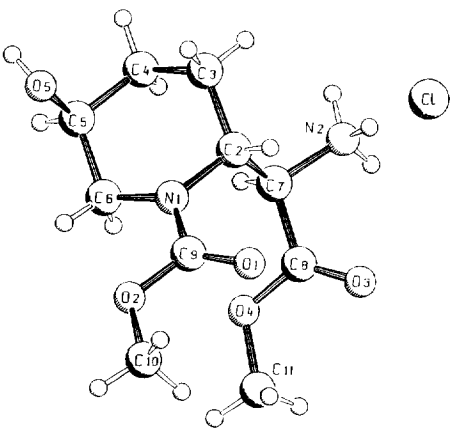
**Scheme 2**



**a: THF, KHMDS, $TrisN_3$, -78 °C; b: AcOH; c: 5 M HCl/MeOH; d: Pd/C, $H_2$, MeOH, $Boc_2O$; e: $PPh_3$, $CCl_4$, reflux; f: 5 M MeOH/HCl; g: 6 M HCl, reflux; h: Pd/C, $H_2$, MeOH; i: MeOH, HCl**

The X-ray structure[4b] of compound **12** shows axial orientation of the substituents in 2 ($A^{1,3}$-allylic strain[10]) and in 5 position and R-configuration at C-7 atom. The high diastereoselective azidation of the enolate of **3b** can be rationalised by the axial disposition of the ester enolate. The Si-side of the enolate is shielded by the piperidine moiety. As we have reported previously in the synthesis of (2*R*,5*R*) 5-chloropipecolic acid,[1c] the Appel reaction of **8** provided **9** with complete inversion of the configuration in 5-position.

**X-ray structure of 12 (Schakal plot[5])**




In summary, an efficient synthesis of (2*S*,5*S*) 5-hydroxyhomopipecolic acid (**5a**) and its 2*R*,5*S* diastereomer was developed. Furthermore compound **3b** is an ideal substrate for the synthesis of a streptolutine diastereomer. Pharmacological test results will be published elsewhere in due course.

## Experimental

**General**: All reactions were carried out under nitrogen atmosphere in Schlenk tube technique. Solvents were dried according to common methods and distilled before use. TLC: Merck precoated silica gel 60 F-254 plates; detection with iodine vapour or UV light. Column chromatography : silica gel Merck 60 (0.063-0.2 mm). M.p. are corrected by differential thermo analysis (DTA). Optical rotations: Perkin Elmer 241 spectrometer. IR spectra (KBr): Perkin Elmer 681. Ozonisation: Fischer Ozonisator, Model 502. Mass spectra: Finnigan Mat 8200 spectrometer. $^1H$ NMR (200 MHz) and $^{13}C$ NMR (50 MHz) spectra: Bruker AC 200 spectrometer; chemical shifts in ppm relative to the solvent as internal standard, coupling constants in Hz. Data are reported on the major diastereomers.

**Methyl (2*S*,5*S*)-5-(t-Butyldimethylsilyloxy)-2-formylmethyl-piperidine-1-carboxylate (2a) and Methyl (2*R*,5*S*)-5-(t-Butyldimethylsilyloxy)-2-formylmethyl-piperidine-1-carboxylate (2b)**

A solution of **1** (4.81 g, 15.34 mmol) in dichloromethane (150 ml) was cooled (-78°C) and glacial acetic acid (1.5 ml, 25.0 mmol) was added. The mixture was ozonised and then nitrogen was passed through the solution for 2 min to remove excess ozone. Dimethyl sulfide (10 ml) was added and stirring was continued for 30 min at -78°C then at room temperature for 1h. The solution was washed with sat. ammonium chloride (80 ml) and with sat. ammonium hydrogen carbonate solution (2x 70 ml). The organic layer was dried over sodium sulfate, filtered and evaporated. The pale yellow oil was purified by column chromatography on silica gel and the diastereomers were separated with petroleum ether/EtOAc (2:1). Yield: **2a** 300 mg (6%), $R_f$ = 0.33; **2a/b** 1.45 g (30%); **2b** 1.39 g (29%); total yield: 3.14 g (65%), colourless oils.- **2a**: $^1$H-NMR ($CDCl_3$, 330K): δ (ppm) = 9.67 (t, $J_{8,7}$ = 2.3 Hz, 1H, 8-H), 4.85-4.60 (m, 1H, 2-H), 4.15-3.89 (m, 1H, 5-H), 3.68 (s, 3H, $OCH_3$), 3.70-3.45 (m, 1H, 6-$H_e$), 2.76-2.41 m, 3H, 6-$H_a$, 7-H), 1.88-1.37 (m, 4H, 4-H, 3-H), 0.88 (s, 9H, $SiCMe_3$), 0.07 (s, 6H, $SiMe_2$).- $^{13}$C-NMR ($CDCl_3$): δ (ppm) = 199.73 (C=O, aldehyde), 155.0 (C=O, urethane), 67.26 (C-5), 52.53 ($OCH_3$), 45.86 (C-6), 44.91 (C-2), 43.84 (C-7), 29.0 (C-4), 26.86 (C-3), 25.51 ($SiC\underline{Me}_3$), 17.82 ($Si\underline{C}Me_3$), -4.96, -5.01 ($SiMe_2$).- IR (neat): ν ($cm^{-1}$) = 2940-2850 (C-H), 2730, 1730-1600 (C=O, aldehyde and urethane).- MS (70 eV): m/z (%) = 258 (19) [$M^+$–t-Bu], 170 (21) 215 (16), 214 (100) [$M^+$– $CH_2CHO$, $-CO_2CH_2$], 140 (25), 126 (49), 89 (65), 75 (36), 73 (40), 59 [$CO_2CH_3^+$].- $[\alpha]_D^{20}$ = - 4.5 (c = 0.4, EtOH).

**2b**: $^1$H-NMR ($CDCl_3$): δ (ppm) = 9.58 (dd, $J_{7anti,8}$ = 3.2 Hz, $J_{7syn,8}$ = 2.0 Hz, 1H, 8-H), 4.86-4.80 (m, 1H, 2-$H_e$), 3.86 (d, $J_{6e,6a}$ = 13.8 Hz, 1H, 6-$H_e$), 3.80 ($m_c$, 1H, 5-$H_e$), 3.54 (s, 3H, $OCH_3$), 2.85 (dd, $J_{6a,6e}$ = 13.9 Hz, $J_{6a,5e}$ = 1.3 Hz, 1H, 6-$H_a$), 2.70-2.55 (ddd, $J_{gem}$ = 15.6 Hz, $J_{7anti,\ 2e}$ = 8.7 Hz, $J_{7anti,8}$ = 3.2 Hz, 1H, 7-$H_{anti}$), 2.49-2.37 (ddd, $J_{gem}$ = 15.6 Hz, $J_{7syn,2e}$ = 6.5 Hz, $J_{7syn,8}$ = 2.0 Hz, 1H, 7-$H_{syn}$), 2.20-2.00 (m, 1H, 3-$H_a$), 1.65-1.49 (m, 2H, 4-H), 1.24-1.13 (m, 1H, 3-$H_e$), 0.86 (s, 9H, $SiCMe_3$), 0.04 (s, 6H, $SiMe_2$).- $^{13}$C-NMR ($CDCl_3$): δ (ppm) = 200.54 (s, C=O, aldehyde), 156.43 (s, C=O, urethane), 64.24 (d, C-5), 52.39 (q, $OCH_3$), 45.68 (d, C-2), 45.47 (dd, C-6), 44.07 (t, C-7), 26.54 (t, C-4), 25.49 (q, $SiC\underline{Me}_3$), 22.32 (t, C-3), 17.84 (s, $Si\underline{C}Me_3$), -5.12, -5.23 (q, q, $SiMe_2$).- IR (neat): ν($cm^{-1}$) = 2940, 2880, 2850 (C-H), 2720 (aldehyde), 1720-1610 (C=O, aldehyde and urethane).- MS (70 eV): m/z (%) = 315 (0.2) [$M^+$], 258 (90) [$M^+$–t-Bu], 214 (34), 140 (21), 89 (100), 82 (32), 81 (18), 75 (58), 73 (37), 59 (34), 55 (22). $[\alpha]_D^{20}$ = + 20.1 (c = 1.4, EtOH).

**Methyl (2*S*,5*S*)-5-(t-Butyldimethylsilyloxy)-1-methoxycarbonyl-2-piperidinyl acetate (3a)**

To a suspension of **2a** (980 mg, 3.11 mmol) and $NaHCO_3$ (2.04 g, 24.3 mmol) in 20 ml $MeOH/H_2O$ (9:1), a solution of bromine (0.54 ml, 10.02 mmol) in 10 ml $MeOH/H_2O$ (9:1) was added over a period of 1 h. Stirring was continued over night and excess bromine was reduced with sodium thiosulphate. After addition of water (70 ml) the mixture was extracted with ether (3x 80 ml) and the combined organic layers were dried over sodium sulfate, filtered and evaporated. The oily rsidue was purified by column chromatography on silica gel with petroleum ether/EtOAc (2:1). Yield 840 mg (78%), colourless oil. $R_f$ = 0.54 (PE/EtOAc 2:1).

$^1$H NMR ($CDCl_3$): δ (ppm) = 4.70-4.45 ($m_c$, 1H, 2-H), 4.10-3.75 ($m_c$, 1H, 6-$H_e$), 3.57, 3.55 (s, s, 2 x $OCH_3$), 3.55-3.35 ($m_c$, 1H, 5-H), 2.59-2.40 (m, 1H, 6-$H_a$), 2.45 (d, $J_{7,2}$ = 7.2 Hz, 2H, 7-H), 1.76-1.25 (m, 4H, 4-H, 3-H), 0.75 (s, 9H, $SiCMe_3$), -0.06 (s, 6H, $SiMe_2$).- $^{13}$C NMR ($CDCl_3$): δ (ppm) = 171.09 (s, C=O, ester), 155.42 (s, C=O, urethane), 67.31 (d, C-5), 52.35 (q, $OCH_3$), 51.30 (q, $OCH_3$), 46.82 (d, C-2), 45.59 (dd, C-6), 34.38 (t, C-7), 28.89 (t, C-4), 26.34 (t, C-3), 25.46 (q, $SiC\underline{Me}_3$), 17.73 (s, $Si\underline{C}Me_3$), -5.04 (q, $Si\underline{Me}_2$).- IR (neat): ν($cm^{-1}$) = 2950, 2980, 2890, 2860 (C-H), 1740 (C=O, ester), 1700 (C=O, urethane).- MS (70 eV): m/z (%) = 314 (2) [$M^+$-$OCH_3$), 288 (36) [$M^+$-t-Bu], 215 (15), 214 (100), 170 (22), 140 (24), 89 (75), 75 (16), 73 [$CH_2CO_2Me^+$], 59 (19) [$CO_2Me^+$].- $[\alpha]_D^{20}$ = + 13.1 (c = 0.5, $CHCl_3$). Calcd. C 55.62 H 9.04 N 4.05 found C 55.42 H 9.16 N 4.19.

**Methyl (2*R*,5*S*)-5-(t-Butyldimethylsilyloxy)-1-methoxycarbonyl-2-piperidinyl acetate (3b)**

To a suspension of **2b** (3.16g, 10.02 mmol) and $NaHCO_3$ (6.80g, 80.94 mmol) in 40 ml $MeOH/H_2O$ (9:1), a solution of bromine (1.73 ml, 33.98 mmol) in 10 ml $MeOH/H_2O$ (9:1) was added over a period of 1 h. Stirring was continued over night and excess bromine was reduced with sodium thiosulfate. After addition of water (100 ml) the mixture was extracted with ether (3x 120 ml) and the combined organic layers were dried over sodium sulfate, filtered and evaporated. The oil was purified by column chromatography on silica gel with petroleum ether/EtOAc (2:1). Yield 2.88 g (83%), colourless oil. $R_f$ = 0.44 (PE/EtOAc 2:1). $^1$H NMR ($CDCl_3$): δ (ppm) = 4.72-4.60 (m, 1H, 2-$H_e$), 3.85 (d, $J_{6e,6a}$ = 14.2 Hz, 1H, 6-$H_e$), 3.77 ($m_c$, 1H, 5-$H_e$), 3.54 (s, 6H, 2 x $OCH_3$), 2.85 (dd, $J_{6a,6e}$ = 14.0 Hz, $J_{6a,5e}$ = 1.3 Hz, 6-$H_a$), 2.50 (dd, $J_{gem}$ = 14.3 Hz, $J_{7,2e}$ = 7.7 Hz, 1H, 7-H), 2.39 (dd, $J_{gem}$ = 14.5 Hz, $J_{7,2e}$ = 7.8 Hz, 1H, 7-H), 2.16 (m, 1H, 3-$H_a$), 1.66-1.41 (m, 2H, 4-$H_a$, 4-$H_e$), 1.28-1.17 (m, 1H, 3-$H_e$), 0.77, 0.74 (s, 9H, $SiCMe_3$), -0.04, -0.06, -0.07 (s, 6H, $SiMe_2$) rotamers.- $^{13}$C NMR ($CDCl_3$): δ (ppm) = 171.0 (s, C=O, ester), 155.96 (s, C=O, urethane), 64.14 (d, C-5), 51.86, 51.05 (q, q, 2 x $OCH_3$), 47.31 (d, C-2), 45.14 (dd, C-6), 34.46 (t, C-7), 26.18 (t, C-4), 25.20 (q, $SiC\underline{Me}_3$), 21.59 (t, C-3), 17.51 (s, $Si\underline{C}Me_3$), -5.23, -5.53 (q, q, $Si\underline{Me}_2$).- IR (neat): ν ($cm^{-1}$) = 2950, 2930, 2880, 2850 (C-H), 1760-1640 (C=O, ester and urethane).- MS (70 eV): m/z (%) = 314 (1.7) [$M^+$-$OCH_3$], 288 (36) [$M^+$-t-Bu], 215 (15), 214 (100), 170 (22), 140 (24), 89 (75), 75 (16), 73 (30), 59 (22) [$CO_2CH_3^+$].- $[\alpha]_D^{20}$ = + 6.5 (c = 0.4, EtOH). Calcd. C 55.62 H 9.04 N 4.05 found C 55.80 H 9.01 N 4.19.

**Methyl (2*S*, 5*S*)-5-Hydroxy-1-methoxycarbonyl-2-piperidinyl acetate (4a)**

**3a** (800 mg, 2.32 mmol) was dissolved in 5 M methanolic HCl solution (40 ml) and stirred for 16 h at room temperature. After evaporation of the methanolic HCl, the remaining oil was dissolved in 2-PrOH (25 ml) and evaporated to remove traces of HCl. This procedure was repeated three times. The oil was purified by column chromatography on silica gel with ethyl acetate. Yield: 492 mg (90%), colourless oil. $R_f$ = 0.38 (EtOAc). $^1$H NMR ($CDCl_3$): δ (ppm) = 4.60-4.45 (m, 1H, 2-H), 4.10-3.95 (m, 1H, 5-H), 3.56, 3.54 (s, s, 3H, 3H, 2 x $OCH_3$), 3.55-3.36 (m, 1H, 6-$H_e$), 2.58-2.35 (m, 3H, 6-$H_a$, 7-H), 1.84-1.75 (m, 1H, 3-$H_e$), 1.64-1.55 (m, 2H, 4-$H_e$, 3-$H_a$), 1.47-1.32 (m, 1H, 4-$H_a$).- $^{13}$C NMR ($CDCl_3$): δ (ppm) = 171.36 (s, C=O,

ester), 155.65 (C=O, urethane), 66.26 (d, C-5), 52.67, 51.51 (q, q, 2 x $O\underline{C}H_3$), 46.87 (d, C-2), 45.46 (dd, C-6), 34.43 (t, C-7), 27.87 (t, C-4), 26.51 (t, C-3).- IR (neat): ν ($cm^{-1}$) = 3580-3200 (O-H), 3000, 2950, 2870 (C-H), 1780-1640 (C=O, ester and urethane).- MS (70 eV): m/z (%) = 231 (0.16) [$M^+$], 158 (68), 140 (48), 89 (100), 88 (55), 74 (36), 71 (19), 59 (32) [$CO_2CH_3^+$], 44 (23), 43 (21).- $[\alpha]_D^{20}$ = +10.3 (c = 1.7, EtOH).

**Methyl (2*R*,5*S*)-5-Hydroxy-1-methoxycarbonyl-2-piperidinyl acetate (4b)**

A solution of **3b** (1.1 g, 3.18 mmol ) in 5 M methanolic HCl (50 ml) was stirred for 20 h at room temperature and treated in the same manner as described for **3a**. Yield: 701 mg (95%), colourless oil, $R_f$ = 0.28 (EtOAc). $^1H$ NMR ($CDCl_3$): δ (ppm) = 4.58-4.45 (m, 1H, 2-H), 4.10-3.95 (m, 1H, 5-H), 3.56, 3.54 (s, s, 3H, 3H, 2 x $OCH_3$), 3.53-3.35 (m, 1H, 6-$H_e$), 2.57-2.35 (m, 3H, 6-$H_a$, 7-H), 1.86-1.67 (m, 1H, 3-$H_a$), 1.62-1.54 (m, 2H, 4-$H_a$, 4-$H_e$), 1.48-1.20 (m, 1H, 3-$H_e$).- $^{13}C$ NMR ($CDCl_3$): δ (ppm) = 171.33 (C=O, ester), 156.53 (C=O, urethane), 63.26 (C-5), 52.41, 51.39 (2 x $OCH_3$), 47.62 (C-6), 44.76 (C-2), 34.31 (C-7), 24.87 (C-4), 21.63 (C-3).- IR (neat): ν ($cm^{-1}$) = 3600-3240 (O-H), 3000, 2950, 2870 (C-H), 1740-1630 (C=O, ester and urethane).- MS (70 eV): m/z (%) = 231 (3.6) [$M^+$], 213 (13), 172 (52) [$M^+$-$CO_2CH_3$], 158 (100) [$M^+$-$CH_2CO_2CH_3$], 140 (80), 126 (21), 59 (21) [$CO_2CH_3^+$], 55 (15), 42 (24), 41 (17).- $[\alpha]_D^{20}$ = + 7.7 (c = 2.0, EtOH).

**(2*S*,5*S*) 5-Hydroxyhomopipecolic acid (5a)**

**4a** (330 mg, 1.43 mmol) was dissolved in 6 M HCl solution (40 ml) and refluxed for 16 h. After evaporation of the volatiles the dark brown residue was treated with 2-propanol (20 ml) and evaporated. The remaining brown powder was dissolved in methanol (50 ml), charcoal (500 mg) was added and the mixture was refluxed for 2 h. The charcoal was removed by filtration, the methanol was evaporated and the now pale brown powder was recrystallised from methanol/acetone/ether (diffusion controlled). Yield: 195 mg (70%), M.p. 180°C (DTA). $^1H$ NMR ($D_4$-MeOD): δ (ppm) = 4.12 ($m_c$, 1H, 5-$H_e$), 3.55-3.25 (m, 2H, 2-$H_a$, 1H, 6-$H_e$), 3.19 (dd, $J_{6a,6e}$ = 12.9 Hz, $J_{6a,5e}$ = 1.3 Hz, 6-$H_a$), 2.85 (m, 2H, 7-H), 2.10-1.67 (m, 4H, 3-H, 4-H).- $^{13}C$ NMR ($D_4$-MeOD): δ (ppm) = 173.67 (C=O), 62.38 (C-5), 54.96 (C-2), 51.40 (C-6), 38.02 (C-7), 29.78 (C-4), 24.32 (C-3).- IR (KBr): ν ($cm^{-1}$) = 3430 (O-H), 3280-2500 (C-H, COOH, $NH_2^+$), 1730 (C=O).- $[\alpha]_D^{20}$ = + 20.8 (c = 0.3, MeOH). Calcd. C 42.97 H 7.21 N 7.16 found C 42.87 H 7.45 N 6.90.

**(2*R*,5*S*)-5-Hydroxyhomopipecolic acid (5b)**

**4b** (400 mg, 1.73 mmol) was dissolved in 6 M HCl solution (60 ml) and treated in the same manner as described for **4a**. Yield: 280 mg (83%), colourless monoclinic crystals. M.p. 90°C (DTA). $^1H$ NMR ($D_4$-MeOD): δ (ppm) = 4.05-3.87 (m, 1H, 5-$H_a$), 3.60-3.37 (m, 2H, $2_a$-H, 6-$H_e$), 2.91 (dd, $J_{6a,6e}$ = 10.3 Hz, $J_{6a,5e}$ = 1.5 Hz, 1H, 6-$H_a$), 2.83 (d, $J_{7,2a}$ = 6.5 Hz, 2H, 7-H), 2.17 (m, 2H, 3-$H_e$, 4-$H_e$), 1.77-1.55 (m, 2H, 3-$H_a$, 4-$H_a$).- $^{13}C$ NMR ($D_4$-MeOD): δ (ppm) = 173.56 (s, C=O), 64.83 (d, C-5), 54.22 (d, C-2), 49.74 (t, C-6), 37.08 (t, C-7), 32.00 (t, C-4), 27.50 (t, C-3).- IR (KBr): ν ($cm^{-1}$) = 3470, 3380 (O-H), 3300-2480 (C-H,

COOH, $NH_2^+$), 1720 (C=O).- $[\alpha]_D^{20}$ = - 21.3 (c = 1.7, MeOH). Calcd. C 42.97 H 7.21 N 7.16 found C 42.01 H 7.16 N 6.76.

**Methyl (2'*R*,5'*S*,2*R*)-2-Azido-5'-t-butyldimethylsilyoxy-1'-methoxycarbonyl-2'-piperidinyl acetate (6)**

To a cold solution (-78°C) of **3b** (2.75 g, 7.97 mmol) in THF (60 ml), a solution of potassium hexamethyldisilazide (1.75 g, 8.76 mmol) in toluene (33 ml) was added and stirring was continued for 30 min. Then solution of triisopropylbenzenesulfonyl azide (2.71 g, 8.76 mmol) in toluene (45 ml) was added. The reaction was quenched after 3 min by addition of glacial acetic acid (2.0 ml, 34.97 mmol). The mixture was allowed to reach room temperature and stirring was continued at ambient temp. for an additional hour. Then ether (100 ml) was added and the solution was washed with brine (100 ml). The organic layer was separated, dried over sodium sulfate, filtered and evaporated. The pale yellow oil was purified by column chromatography on silica gel with PE/EtOAc (2:1). The colourless oil contained still ≈10% triisopropylbenzene sulfonyl azide (determined by $^1$H NMR), which could not be removed on this stage. Yield: 3.10 g (, $R_f$ = 0.74 (PE/EtOAc 2:1). $^1$H NMR ($CDCl_3$): δ (ppm) = 4.53-4.47 (m, 1H, 2-$H_e$), 4.03 (d, $J_{7,2e}$ = 7.2 Hz, 1H, 7-H), 4.00-3.81 (m, 2H, 6-$H_e$, 5-$H_e$), 3.67 (s, 3H, $OCH_3$), 3.58 (s, 3H, $OCH_3$), 2.98 (d, $J_{6a,6e}$ = 13.8 Hz, 1H, 6-$H_a$), 2.15-1.91 (m, 1H, 3-$H_a$), 1.76-1.47 (m, 3H, 3-$H_e$, 4-$H_e$), 0.80 (s, 9H, $SiCMe_3$), -0.02, -0.03 (s, s, 6H, $SiMe_2$).- $^{13}$C NMR ($CDCl_3$): δ (ppm) = 169.45 (s, C=O, ester), 156.26 (s, C=O, urethane), 64.02 (d, C-5), 60.22 (d, C-7), 52.44, 52.38 (q, q, 2 x $OCH_3$), 51.28 (d, C-2), 46.40 (dd, C-6), 26.54 (t, C-4), 25.38 (q, $SiC\underline{Me}_3$), 18.52 (t, C-3), 17.72 ($SiC\underline{M}e_3$), -5.23, - 5.35 (q, q, $SiMe_2$).- IR (neat): ν ($cm^{-1}$) = 2950, 2920, 2880 (C-H), 2120 ($N_3$), 1760-1640 (C=O, ester and urethane).- MS (70 eV): m/z (%) = 371 (0.5) [$M^+$-$CH_3$], 329 (26) [$M^+$-t-Bu], 272 (37), 269 (23), 237 (18), 140 (100) [$C_7H_{10}NO_2^+$], 89 (37), 75 (18),73 (20), 59 (22) [$CO_2Me^+$].

**Methyl (2'*R*,5'*S*,2*R*)-2-Azido-5'-Hydroxy-1'-methoxycarbonyl-2'-piperidinyl acetate (7)**

A solution of **6** (3.10 g, 8.02 mmol) in 5 M methanolic HCl (60 ml) was stirred for 16 h at ambient temperature. After evaporation of the solvent the remaining colourless oil was dissolved in 2-propanol (50 ml) and stirred for 30 min in presence of $NaHCO_3$ (1.00 g) to remove traces of HCl. $NaHCO_3$ was removed by filtration and the solvent was evaporated. The remaining pale yellow oil was purified by column chromatography on silica gel with EtOAc. Yield: 1.59 g, (73% depending on **3b**), colourless oil. $R_f$ = 0.33 (EtOAc). $^1$H NMR ($CDCl_3$, 330 K): δ (ppm) = 4.46-4.45 (m, 1H, 2-$H_e$), 4.05 (d, $J_{7,2e}$ = 9.0 Hz, 1H, 7-H), 3.95-3.86 (m, 2H, 6-$H_e$, 5-$H_e$), 3.65 (s, 3H, $OCH_3$), 3.57 (s, 3H, $OCH_3$), 3.25-3.00 (s, 1H, OH), 3.03 (d, $J_{6a,6e}$ = 14.3 Hz, 1H, 6-$H_a$), 2.05-1.85 (m, 1H, 3-$H_a$), 1.73-1.51 (m, 3H, 3-$H_e$, 4-H).- $^{13}$C NMR ($CDCl_3$): δ (ppm) = 169.39 (s, C=O, ester), 156.90 (s, C=O, urethane), 65.51 (d, C-5), 60.11 (d, C-7), 52.71, 52.44 (q, q, 2 x $OCH_3$), 51.56 (d, C-2), 46.04 (dd, C-6), 25.40 (t, C-4), 18.56 (t, C-3).- IR (neat): ν ($cm^{-1}$) = 3540-3220 (O-H), 2940, 2880 (C-H), 2090 ($N_3$), 1760-1590 (C=O, ester and urethane).- MS (70 eV): m/z (%) = 273 (0.1) [$M^+$ + 1], 158

(100) [$M^+$-$N_3CHCO_2Me$], 140 (72) [$C_7H_{10}NO_2$], 126 (19), 82 (10), 81(14), 59 (24) [$CO_2Me^+$], 55 (19), 42 (22) [$N_3^+$], 41 (12).- $[\alpha]_D^{20}$ = + 1.7 (c = 0.6, $CHCl_3$).

**Methyl (2'*R*,5'*S*,2*R*)-2-t-Butoxycarbonylamino-5'-hydroxy-1'-methoxycarbonyl-2'-piperidinyl acetate (8)**

**7** (1.02 g, 3.75 mmol) and di-t-butyldicarbonate (8.16 g, 34.7 mmol) was dissolved in methanol (80 ml) and hydrogenated 21 h in the presence of 100 mg Pd/C (10%) at 50 bar. The catalyst was removed by filtration and the solvent was evaporated. The colourless oil was purified by column chromatography on silica gel with PE/EtOAc (2:1), $R_f$ = 0.16. Yield: 1.16 g (89%), sticky, colourless solid. $^1H$ NMR ($CDCl_3$, 330 K): δ (ppm) = 5.17 ("s", 1H, NH), 4.55 (t, $J_{7,NH} \approx J_{7,2}$ = 9.9 Hz, 1H, 7-H) , 4.21 ($m_c$, 1H, 2-H), 4.02 (d, $J_{6e,6a}$ = 14.6 Hz, 1H, 6-$H_e$) 3.90 ($m_c$, 1H, 5-H), 3.60 (s, 3H, $OCH_3$), 3.13 (d, $J_{6a,6e}$ = 14.6 Hz, 1H, 6-$H_a$), 2.22 (s, 1H, OH), 2.00-1.73 (m, 2H, 3-$H_a$, 4-$H_a$), 1.69-1.51 (m, 2H, 3-$H_e$, 4-$H_e$), 1.34 (s, 9H, $OCMe_3$).- $^{13}C$ NMR ($CDCl_3$, 330K): δ (ppm) = 171.50 (s, C=O, ester), 156.87 (s, C=O, urethane), 155.12 (s, C=O, urethane), 80.19 (s, O<u>C</u>$Me_3$), 63.80 (d, C-5), 53.43 (d, C-2), 52.61 (q, $OCH_3$), 52.06 (q, $OCH_3$), 51.84 (d, C-7), 46.09 (dd, C-6), 28.02 (q, OC<u>Me</u>$_3$), 25.88 (t, C-4), 18.74 (t, C-3).- IR (neat): ν($cm^{-1}$) = 3540-3200 (N-H, O-H), 2950, 3860 (C-H), 1740-1600 (C=O, ester and urethane).- MS (70 eV): m/z (%) = 273 (0.3) [$M^+$-Ot-Bu], 158 (36), 140 (17) [$C_7H_{10}NO_2$], 73 (12) [$OtBu^+$], 70 (14), 61 (14), 59 (7) [$CO_2Me^+$], 45 (16), 43 (100), 41 (7).- $[\alpha]_D^{20}$ = + 1.4 (c = 0.8, $CHCl_3$).

**Methyl (2'*R*,5'*R*,2*R*)-2-t-Butoxycarbonylamino-5'-chloro-1'-methoxycarbonyl-2'-piperidinyl acetate (9)**

A solution **8** (800 mg, 2.31 mmol) and triphenylphosphine (727 mg, 2.77 mmol) in tetrachloromethane (70 ml) was refluxed. The reaction process was monitored by $^{13}C$ NMR spectroscopy. When the $^{13}C$ NMR spectra indicated no further signal for the C-5 OH group (≈ 1 week) the suspension was allowed to reach room temperature. Methanol (2 ml) was added and the mixture was refluxed for 2 h. After evaporation of the solvent, the remaining residue was purified by column chromatography on silica gel with trichloromethane/EtOAc (9:1), $R_f$ = 0.23. Yield: 551 mg (65%), colourless, sticky solid. $^1H$ NMR ($CDCl_3$, 330 K): δ (ppm) = 5.20 (d, $J_{NH,7}$ = 9.4 Hz, 1H, NH), 4.58 (dd, $J_{7,2e}$ = 10.0 Hz, $J_{7,NH}$ = 9.4 Hz, 1H, 7-H), 4.32-4.10 (m, 2H, 6-$H_e$, 2-$H_e$), 3.71-3.45 (m, 1H, 5-$H_a$), 3.61 (s, 6H, 2 x $OCH_3$), 2.99 (dd, $J_{6a,6e}$ = 13.4 Hz, $J_{6a,5a}$ = 11.6 Hz, 1H, 6-$H_a$), 2.12-1.81 (m, 3H, 3-H, 4-$H_e$), 1.78-1.48 (m, 1H, 4-$H_a$), 1.37, 1.36, 1.35 (s, s, s, 9H, $OCMe_3$). rotameres.- $^{13}C$ NMR ($CDCl_3$, 330 K): δ (ppm) = 170.79 (s, C=O, ester), 155.10 (s, C=O, urethane), 154.69 (s, C=O, urethane), 79.98 (s, O<u>C</u>$Me_3$), 53.20, 52.46, 52.23, 51.83, 51.38 (2 x $OCH_3$, C-5, C-2, C-7), 46.63 (dd, C-6), 30.07 (t, C-4), 27.89 (q, OC<u>Me</u>$_3$), 24.80 (t, C-3).- IR (neat): ν ($cm^{-1}$) = 3450-3280 (N-H), 2980, 2960, 2880 (C-H), 1740 (C=O, ester), 1700 (C=O, urethane).- MS (70 eV): m/z (%) = 328 (0.28) [$M^+$-HCl], 178 (30), 176 (100), 140 (74) [$C_7H_{10}NO_2$], 86 (49) 84 (74), 59 (13) [$CO_2Me^+$], 57 (18) [$tBu^+$], 55 (14), 47 (14).- $[\alpha]_D^{20}$ = - 16.3 (c = 0.8, $CHCl_3$).

**Methyl (2'*R*,5'*R*,2*R*)-2-Amino-5'-chloro-1'-methoxycarbonyl-2'-piperidinyl acetate hydrochloride (10)**

A solution of **9** (150 mg, 0.41 mmol) in 5 M methanolic HCl (20 ml) was stirred for 24 h at 20°C. The solvent was evaporated and the solid residue was treated with 2-propanol (30 ml) and evaporated to remove traces of HCl. Yield: 105 mg (85%), colourless powder. M.p.: 216°C (DTA). $^1$H NMR ($D_4$-MeOD): δ (ppm) = 4.86-4.68 (m, 1H, 2-$H_e$), 4.67 (d, $J_{7,2e}$ = 10.4 Hz, 1H, 7-H), 4.52 (d, $J_{6a,6e}$ = 11.5 Hz, 1H, 6-$H_e$), 4.23 ($m_c$, 1H, 5-$H_a$), 3.97, 3.89 (s, s, 3H, 3H, 2 x $OCH_3$), 3.23 (t, $J_{6a,6e} \approx J_{6a,5a}$ = 11.5 Hz, 6-$H_a$), 2.50-1.95 (m, 4H, 3-H, 4-H).- $^{13}$C NMR ($D_4$-MeOD): δ (ppm) = 169.88 (C=O, ester), 157.81 (C=O, urethane), 54.43, 54.34, 54.27 (C-7, C-5, C-2), 51.98, 51.85 (2 x $OCH_3$), 48.17 (C-6), 31.08 (C-4), 26.10 (C-3).- IR (KBr): ν ($cm^{-1}$) = 3100-2580 (C-H, $NH_3^+$), 1750 (C=O, ester), 1685 (C=O, urethane).- $[\alpha]_D^{20}$ = -25.7 (c = 0.9, MeOH). Calcd C 39.75 H 6.34 N 9.27 found C 39.83 H 6.26 N 9.18.

**(2'*R*,5'*R*,2*R*) 2-Amino-5'-chloro-2'-piperidinyl acetic acid dihydrochloride, (Epi-pseudo-streptolutine dihydrochloride) (11a) and (2'*R*,5'*R*,2*S*) 2-Amino-5'-chloro-2'-piperidinyl acetic acid dihydrochloride, (Epi-streptolutine dihydrochloride) (11b).**

**10** (80 mg, 0.26 mmol) was dissolved in 6 M hydrochloric acid (40 ml) and refluxed for 16 h. After evaporation of the solvent, the brown solid was "filtered" with methanol through a RP-18 column (≈ 8 cm). After evaporation of the methanol, the diastereomeric mixture **11a,b** was isolated as an extremely hygroscopic pale yellow solid. Yield 55 mg (70%). $^1$H NMR ($D_4$-MeOD, 330 K): δ (ppm) = 4.65 ($m_c$, 2H, 5-H, 5-H´), 4.25-4.10 ($m_c$, 2H, 2-H, 2-H´), 4.05-3.80 (m, 4H, 7-H, 7-H´, 6-$H_e$, 6-$H_e$´), 3.40-3.15 (m, 2H, 6-$H_a$, 6-$H_a$´), 2.55-1.93 (m, 8H, 3-H, 3-H´, 4-H, 4-H´).- $^{13}$C NMR ($D_4$-MeOD): δ (ppm) = 169.88 (C=O), 57.56, 56.14 (C-7, C-7`), 55.15, 54.69 (C-2, C-2`), 54.56, 53.99 (C-5, C-5`), 52.74, 52.08 (C-6, C-6`), 31.34, 30.17 (C-4, C-4`), 21.22, 18.93 (C-3, C-3`).- IR (KBr): ν ($cm^{-1}$) = 3510-3300 (N-H), 3200-2500 (C-H, COOH), 1740 (C=O).- MS (70 eV): m/z (%) = 194 (23) [$M^+$ - 2 Cl], 164 (9), 163 (100), 135 (28), 119 (5), 104 (6), 103 (13), 76 (7), 75 (7), 50 (6).

**Methyl (2'*R*,5'*S*,2*R*)-2-Amino-5'-hydroxy-1'-methoxycarbonyl-2'-piperidinyl acetate hydrochloride (12)**

A solution of **7** (250 mg, 0.92 mmol) in methanol (50 ml) was hydrogenated in presence of 50 mg Pd/C (10%) at 20 bar for 3 h. The catalyst was removed by filtration, 5 M methanolic HCl (1 ml) was added and the solvent evaporated. To remove traces of HCl, the residue was dissolved 2-propanol (20 ml) and evaporated. Suitable crystals for X-ray analysis were prepared by diffusion controlled crystallisation from MeOH/ether. Yield: 234 mg (90%). Mp.: 195°C (DTA). $^1$H NMR ($D_4$-MeOD): δ (ppm) = 4.85-4.75 (m, 1H, 2-$H_e$), 4.61 (d, $J_{7,2e}$ = 10.0 Hz, 1H, 7-H), 4.23 (d, $J_{6e,6a}$ = 13.8 Hz, 1H, 6-$H_e$), 4.14 ($m_c$, 1H, 5-$H_e$), 3.96, 3.88 (s, s, 3H, 3H, 2 x $OCH_3$), 3.35 (dd, $J_{6a,6e}$ = 13.8 Hz, $J_{6a,5e}$ = 1.8 Hz, 1H, 6-$H_a$), 2.43 (m, 1H, 3-$H_a$), 2.19-2.01 (m, 1H, 4-$H_a$), 1.95-1.68 (m, 2H, 3-$H_e$, 4-$H_e$).- $^{13}$C NMR ($D_4$-MeOD): δ (ppm) = 170.16 (C=O, ester), 158.70 (C=O, urethane), 64.58 (C-5), 54.12, 53.97 (C-2, C-7),

53.00, 51.94 (2 x $OCH_3$), 47.12 (C-6), 26.50 (C-4), 20.31 (C-3).- IR (KBr): ν ($cm^{-1}$) = 3200, 3150 (O-H, $NH_3^+$), 3000, 2950, 2900 (C-H), 1760 (C=O, ester), 1660 (C=O, urethane).- $[\alpha]_D^{20}$ = + 5.7 (c = 0.3, MeOH). Calcd. C 42.48 H 6.77 N 9.91 found C 42.15 H 6.74 N 9.63.

**Acknowledgement**: This work was supported by Deutsche Forschunggemeinschaft, He 1513/2-2(3) and Fonds der Chemischen Industrie. We thank Degussa AG, Hanau, for providing starting materials and Mrs. Anita Betz for experimental assistance.

## References and Notes

**Dedicated to Prof. Dr. G. Seitz on the occasion of his 60th birthday**

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(*Received in Germany* 15 *January* 1996; *revised* 29 *February* 1996; *accepted* 8 *March* 1996)