

## Synthesis of 2S,5S- and 2R,5S-5-Hydroxy-pipecolic Acid via Amide-Methylenation of S-5-Hydroxy-2-piperidone with Dimethyltitanocene.

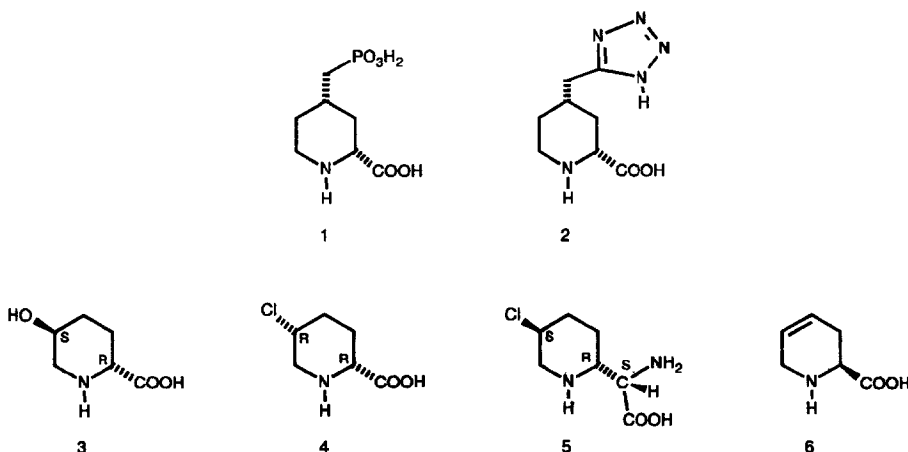
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### Abstract:

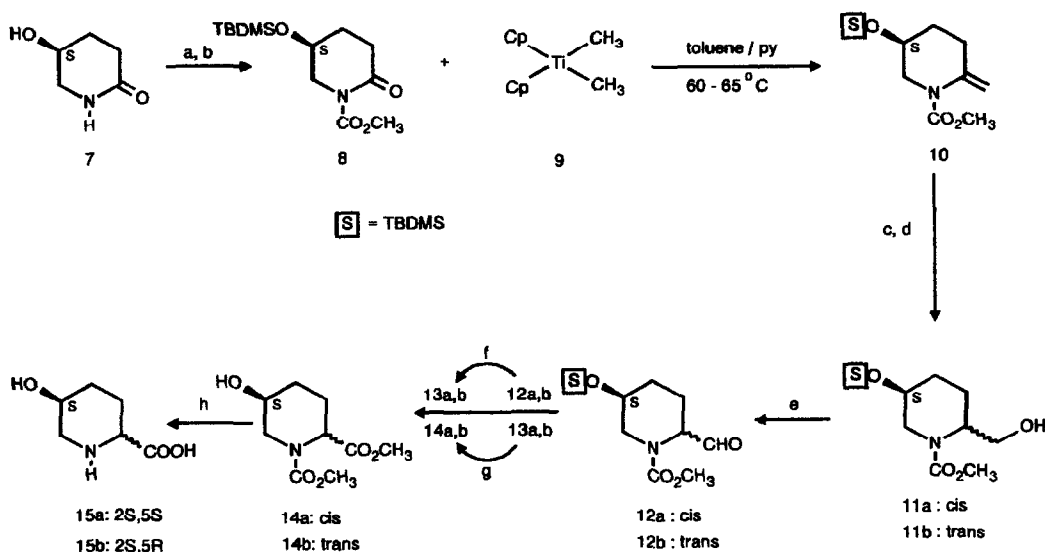
A route to 2S,5S- and 2R,5S-hydroxy-pipecolic acid is presented, starting with the enantiopure 5S-5-hydroxy-piperidone **7**. The key step of this reaction sequence is the chemoselective methylenation of the amide carbonyl group of **8** with dimethyltitanocene **9** to **10**. The transformation of the exocyclic enecarbamate double bond to the carboxylic acid group is best accomplished via hydroboration/oxidation to the alcohol **11a,b**. Separation and oxidation of the diastereomers **11a,b**, to **14a**, and **14b**, and hydrolysis furnishes the diastereomeric pipecolic acids **15a** and **15b** in enantiopure form.

Substituted pipecolic acids are the subject of much current investigation<sup>1</sup>, especially in the field of medicinal Chemistry<sup>2</sup>. Phosphonic amino acids are an important class of competitive N-methyl-D-aspartate (NMDA) antagonists. So CGS 19755 (**1**) is a potent NMDA antagonist and a derivative of pipecolic acid.<sup>3</sup> Replacement of the phosphonic acid functional group by the tetrazole moiety gave the NMDA antagonist **2**.<sup>4</sup>



Previously we synthesized **3**, via a homochiral acyliminium ion<sup>10</sup> and (2R,5R)-5-chloropipelic acid **4**<sup>5</sup>, the first member of a class of enantiopure halogenated pipelic acids. This compound should have interesting pharmacological properties comparable to streptolutin **5**, a compound which was isolated in dimeric form from streptomyces griseolustus<sup>6</sup>. In recent years Baikiain<sup>7</sup> **6** served as a starting material for the synthesis of pipelic acids, substituted in 4- and 6-positions.

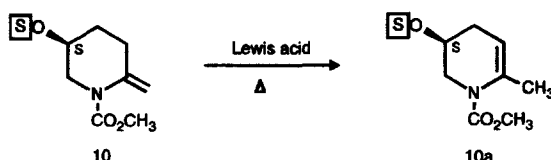
Here we report an alternative method leading to *cis* and *trans* 5-OH-pipelic acid (**15a,b**) with predominant formation of the *cis* diastereomer (2S,5S)-**15a**. In conjunction with our work on the synthesis of **3** and derivatives thereof starting from **8** (derived from **7**), we investigated the reactivity of the amide group of **8** towards various organometallic reagents. We have found that the highly electrophilic, carbamate activated amide carbonyl group of **8**, is readily attacked by metallorganic reagents (e.g. organocuprates) affording ring open products. With the Grubbs-Tebbe reagent<sup>8</sup> we isolated the exocyclic enecarbamate **10** in 40-50% yield.



**a**: TBDMSCl, imidazole, DMF; **b**: BuLi, CNCO<sub>2</sub>CH<sub>3</sub>, THF; **c**: 9-BBN; **d**: 3 M NaOH/H<sub>2</sub>O<sub>2</sub>; **e**: Swern-Ox.; **f**: Br<sub>2</sub>/MeOH/NaHCO<sub>3</sub>; **g**: HCl/MeOH; **h**: 6 M HCl/Δ

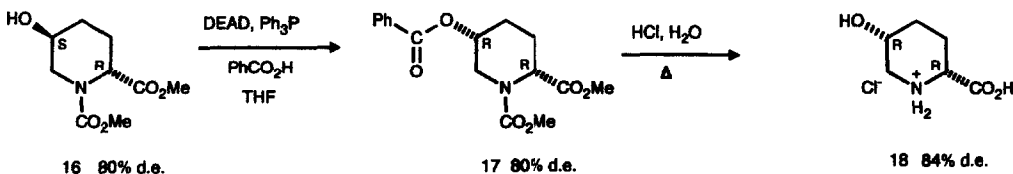
With the Oshima-Lombardo reagent (Zn-CH<sub>2</sub>Br<sub>2</sub>-TiCl<sub>4</sub>)<sup>9</sup> decomposition of the starting material **8** occurred. It turned out subsequently that the inexpensive and easy to handle dimethyltitanocene **9**<sup>10</sup> reacted with **8** to give the enecarbamate **10** in 80-85% yield. Petasis and Bzowej<sup>11</sup> showed that **9** is an excellent methylenation reagent for aldehydes, ketones, lactones and esters. Methylenation of amides or imides have not been described until now with this reagent<sup>12</sup>. This olefination works also well with other hydroxy protecting groups and

with the *t*-butoxycarbonyl (Boc) group on the amide nitrogen of 2-piperidone derivatives<sup>13</sup>. Of importance is that a carbamate group is used for protection and activation of the amide moiety. We were not successful in isolating exocyclic *N*-benzylamines. In the presence of Lewis acids, **10** is quantitatively transformed to the endocyclic enecarbamate **10a**.<sup>15</sup>



Hydroboration of **10** with  $\text{BH}_3 \cdot \text{S}(\text{CH}_3)_2$  and oxidation with  $\text{H}_2\text{O}_2/\text{NaOH}$  furnished **11a,b** in a *cis/trans* ratio of  $\sim 1:1$ . With the sterically more demanding 9-BBN the *cis/trans* ratio was 7:3. The separation of the main portion of the *cis* diastereomer by flash chromatography was accomplished on this stage.

Direct oxidation of the alcohols **11a,b** to the carboxylic acids with  $\text{RuCl}_3/\text{NaIO}_4$ <sup>16</sup> proved to be unsuccessful. However a two step procedure provided **14a** in about 55% yield. In the first step Swern oxidation of **11a** furnished the carboxaldehyde **12a** which was oxidized with bromine in methanol<sup>17</sup> to the methyl carboxylate **13a**. Deprotection of the TBDMS ether was accomplished nearly quantitatively with methanolic hydrogen chloride solution at  $0^\circ\text{C}$ . The resulting  $\text{TBDMSOCH}_3$  ether was evaporated in vacuo. The subsequent hydrolysis of **14a** with 6*M* hydrochloric acid provided 2*S*,5*S*-hydroxypipelic acid hydrochloride **15a**, identical in all spectroscopic data with material, isolated previously from *morus alba*<sup>19</sup>. On the other hand a complete separation of the diastereomers was possible with **14a,b**, though more tedious than with **11a,b**. Compound **14b** was hydrolysed to **15b**, which was identical in every respect with material prepared via the acyl iminium ion pathway<sup>19</sup>. In order to compare the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data of **15a**, we prepared (2*R*,5*R*)-5-hydroxypipelic acid hydrochloride **18** (*ent*-**15a**) in an independent way, though only in a *cis/trans* ratio of 92:8. Starting with **16**<sup>19</sup>, previously prepared by us from (*S*)-5-hydroxy-2-piperidone, Mitsunobu reaction yielded **17** with complete inversion of configuration in position 5. Hydrolysis and recrystallisation furnished **18** in 84% diastereomeric excess.



In summary, the olefination of an activated amide carbonyl group by dimethyl titanocene to exocyclic enecarbamates provides after hydroboration, oxidation and functional group transformations facile access to (2S,5S)-5-hydroxy-pipecolic acid, a compound, which was isolated recently from *morus alba*. Methylenation reactions with more complex starting materials are currently underway.<sup>13</sup>

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## Experimental:

### General:

**Diethylether** was dried with anhydrous calcium chloride over night, filtered and then distilled over sodium wire under nitrogen. **Toluene** was distilled over calcium hydride. **THF** was dried with potassium hydroxide over night, filtrated and distilled over sodium-potassium alloy under nitrogen. Reactions with organometallic and borane compounds were run in flame-dried glassware under dry and oxygen free nitrogen. **Thin layer chromatography:** Merck precoated silica gel 60 F<sub>254</sub> plates. Reaction compounds were visualized by ultraviolet light or by iodine vapour. **Melting points:** Büchi 510 apparatus, values uncorrected.  $[\alpha]_D^{20}$ : Perkin-Elmer 241 polarimeter. **IR-spectra:** Perkin-Elmer 681 infrared spectrometer. **<sup>1</sup>H-NMR** and **<sup>13</sup>C-NMR:** Bruker AC 200 and Bruker AC 400. **Mass spectra:** CH7 Varian-MAT (70 eV).

### (5S)-5-Hydroxy-2-piperidinone

This compound was prepared in five steps, starting from L-glutamic acid as described in ref.18.

### (5S)-5-t-Butyldimethylsiloxy-2-piperidinone

This compound was prepared from **1** as described in ref.1g.

### (5S)-5-t-Butyldimethylsilyloxy-N-methoxycarbonyl-2-piperidinone (**8**)

**(5S)-5-t-Butyldimethylsilyloxy-2-piperidinone** (1.15 g, 5.0 mmol) was dissolved in THF (25 ml) and cooled to -70°C. Then a 2.0 M solution n-BuLi in cyclohexane (2.6 ml, 5.2 mmol) was added. After cooling again to -70°C methyl cyanofomate (0.44 ml, 5.5 mmol) in THF (15 ml) was added. After stirring for 10 min at this temperature the solution was allowed to warm to -30°C. After addition of water (10 ml) and sat. NaHCO<sub>3</sub>/Na<sub>2</sub>CO<sub>3</sub> solution 1:1 (10 ml) the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 25 ml). The combined organic layers were dried with anhydrous sodium sulphate. After filtration and evaporation of the solvent the residue was recrystallized from n-pentane. Yield: 1.20 g

(83%) colourless powder.-  $R_f$ : 0.46 ( $\text{CHCl}_3/\text{EtOAc}$  9:1).- mp.:  $68^\circ\text{C}$ .-  $[\alpha]_D^{20} = +10.9$  ( $c = 1.0$ ,  $\text{MeOH}$ ).- IR (KBr): 2960, 2930, 2900, 2850 (CH), 1715, 1705 (C=O), 1285, (C-O)  $\text{cm}^{-1}$ .-  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta(\text{ppm}) = 0.07$  (6 H, s,  $\text{Me}_2\text{Si}$ ), 0.88 (9 H, s,  $\text{tBuSi}$ ), 1.78 - 2.05 (2 H, m, 4-H), 2.38 - 2.56 (1 H, m, 3- $\text{H}_a$ ), 2.69 - 2.88 (1 H, m, 3- $\text{H}_b$ ), 3.68 - 3.84 (2 H, m, 6-H), 3.87 (3 H, s,  $\text{OCH}_3$ ), 4.26 (1 H, q,  $J = 6.0$  Hz, 5-H).-  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ):  $\delta(\text{ppm}) = -4.9$  ( $\text{SiCH}_3$ ), 17.9 ( $\text{Me}_3\text{CSi}$ ), 25.6 ( $(\text{H}_3\text{C})_3\text{CSi}$ ), 28.8 (C-4), 30.8 (C-3), 52.8 ( $\text{OCH}_3$ ), 53.8 (C-6), 64.1 (C-5), 154.9 (C=O, urethane), 170.7 (C-2).-  $\text{C}_{13}\text{H}_{25}\text{NO}_4\text{Si}$  (287.43).- Calcd.: C 54.32 H 8.77 N 4.87 found: C 54.55 H 9.02 N 4.78.

**(5*S*)-5-*t*-Butyldimethylsilyloxy-*N*-methoxycarbonyl-2-methylene-piperidine (10)**

**8** (2.5 g, 8.7 mmol) was dissolved in a mixture of toluene (75 ml) and dry pyridine (0.75 ml). Dimethyltitanocene<sup>3</sup> (**9**) (1.94 g, 9.3 mmol) was added and the mixture was heated for 18 h to  $60^\circ\text{C}$ . After this time the TLC test (petroleum ether/EtOAc 2:1) showed almost complete absence of starting material. After evaporation of the solvent the dark brown oil was diluted with pentane (75 ml) and the solution was filtered. The solvent was evaporated and the light brown oil was purified by flash chromatography on silica gel (petroleum ether/EtOAc 2:1, 0.5 %  $\text{Et}_3\text{N}$ ). Yield: 2.0 g (82 %) yellow oil.-  $R_f$ : 0.72 (petroleum ether/EtOAc 2:1).- bp.:  $99-101^\circ\text{C}/10^{-2}$  mbar.- IR (neat): 3105, 2960, 2930, 2860 (CH), 1715 (C=O), 1660 (C=C)  $\text{cm}^{-1}$   $^1\text{H-NMR}$  ( $\text{C}_6\text{D}_6$ ):  $\delta(\text{ppm}) = 0.02$ , 0.04 (6 H, 2s,  $\text{SiMe}_2$ ), 0.94 (9 H, s,  $\text{t-BuSi}$ ), 1.40 - 1.55 (2 H, m, 4-H), 1.81 - 1.90 (1 H, m, 3- $\text{H}_a$ ), 2.20 - 2.30 (1 H, m, 3- $\text{H}_b$ ), 3.33 - 3.46 (1 H, m, 6- $\text{H}_a$ ), 3.49 (3 H, s,  $\text{OCH}_3$ ), 3.51 - 3.61 (1 H, m, 5-H), 3.68 - 3.76 (1 H, m, 6- $\text{H}_b$ ), 4.78 (1 H, s,  $=\text{CH}_2$ ), 4.96 (1 H, s,  $=\text{CH}_2$ ).-  $^{13}\text{C-NMR}$  ( $\text{C}_6\text{D}_6$ ):  $\delta(\text{ppm}) = -4.8$  ( $\text{SiCH}_3$ ), 20.5 ( $\text{Me}_3\text{CSi}$ ), 25.9 ( $(\text{H}_3\text{C})_3\text{CSi}$ ), 30.0 (C-3), 34.4 (C-4), 52.4 (C-6), 52.5 ( $\text{OCH}_3$ ), 66.4 (C-5), 107.2 ( $=\text{CH}_2$ ), 143.8 (C-2), 155.3 (C=O).- MS:  $m/z$  (%) = 285 (1.1%) [ $\text{M}^+$ ], 228 (35.1) [ $\text{M}^+ - \text{C}_3\text{H}_7\text{N}$ ], 196 (11) [ $\text{M}^+ - 89$ ], 96 (18.5), 94 (35.4), 89 (100).-  $\text{C}_{14}\text{H}_{27}\text{NO}_3\text{Si}$  (285.43) Calcd.: C 58.91 H 9.54 N 4.91 found: C 59.23 H 9.76 N 4.87.

**(2*R*,5-5*S*)-5-*t*-Butyldimethylsilyloxy-*N*-methoxycarbonyl-2-hydroxymethyl-piperidine (11*a*,*b*)**

To the enecarbamate **10** (1.4 g, 4.9 mmol) in THF (60 ml) a solution of 0.5 M 9-BBN (10.4 mmol, 5.2 ml) at  $0^\circ\text{C}$  was added. The solution was stirred at  $25^\circ\text{C}$  for 18 h then 3.0 M sodium hydroxide solution (50 ml) and 30 % hydrogen peroxide (50 ml) were added and stirred for another 2 h. The layers were separated, the aqueous layer was saturated with solid potassium carbonate and extracted with ethyl acetate (3 x 70 ml). The combined organic layers were dried over anhydrous potassium carbonate, filtered and the solvent was evaporated. The remaining faint yellow oil was diluted with pentane, stored for 2 h at  $4^\circ\text{C}$ , filtered and the solvent was removed *in vacuo*. The oily residue was purified by flash chromatography, to give a nearly colourless oil. Yield: 1.31 g (88%) as a mixture of diastereomers in a ratio of 7:3 (cis/trans).-  $R_f = 0.61$  (EtOAc).- IR (neat): 3440 (OH), 2920, 2910, 2850 (CH), 1700 (C=O), 1250 (C-O)  $\text{cm}^{-1}$ .-  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta(\text{ppm}) = 0.03 - 0.04$  (6 H, 2s,  $\text{SiMe}_2$ ), 0.83 and 0.84 (9 H, s,  $\text{tBuSi}$ ), 1.38 - 1.77 (4 H, m, 3-H, 4-H), 2.45 - 2.75 (1 H, broad, OH), 2.98 (1 H, dd, 6- $\text{H}_a$ ,  $J = 12.4$  Hz, 3.2 Hz), 3.53 - 3.81 (3 H, m,  $\text{CH}_2\text{OH}$ ,

6- $H_b$ ), 3.67 and 3.69 (3 H, s,  $OCH_3$ ), 4.10 - 4.35 (1 H, m, 5-H).-  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$ (ppm) = -5.1 and - 4.8 ( $SiCH_3$ ), 17.9 ( $Me_3CSi$ ), 25.7 ( $Me_3CSi$ ), 19.0 and 19.4 (C-3), 27.4 and 29.7 (C-4), 46.4 (C-2), 51.7 (C-6), 52.5 and 52.7 ( $OCH_3$ ), 60.3, 60.6, and 61.1 ( $CH_2OH$ ) (rotamers), 64.1, 67.6 (C-5), 157.7 and 157.9 (C=O).

**(2S,5S)-5-t-Butyldimethylsilyloxy-N-methoxycarbonyl-2-hydroxymethyl-piperidine (11a)**

A diastereomeric mixture of **11a,b** (2.8 g, 9.25 mmol) was chromatographed on silica gel (500 g, column diameter 5 cm) using ethyl acetat. Eight 50 ml fractions were collected, the solvents evaporated and the diastereomeric purity of the oily residues were checked by  $^{13}C$ -NMR spectroscopy. The first 5 fractions contained 1.54 g **11a** (cis), 1.14 g was unseparated cis/trans mixture.-  $^1H$ -NMR ( $CDCl_3$ ): 0.03 (6 H, s,  $SiMe_2$ ), 0.83 (9 H, s,  $tBuSi$ ), 1.43 - 1.78 (4 H, m, 3-H, 4-H), 2.56 - 2.81 (1 H, broad, OH), 3.51 - 3.67 (3 H, m, 2-H, 6-H), 3.69 (3H, s,  $OCH_3$ ) 3.79 (2H, dd,  $J$  = 11.1Hz, 8.8 Hz), 4.10 - 4.35 (1H, m, 5-H).-  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$  (ppm) = -4.8 ( $SiCH_3$ ), 18.0 ( $Me_3CSi$ ), 22.7 (C-3), 25.7 ( $Me_3CSi$ ), 29.7 (C-4), 46.5 (C-2), 51.7 (C-6), 52.7 ( $OCH_3$ ), 60.6, 61.1 ( $CH_2OH$ ) (rotamers), 67.6 (C-5), 157.0 (C=O).

**(2R,S-5S)-t-Butyldimethylsilyloxy-N-methoxycarbonyl-piperidine-2-carboxaldehyde (12a,b)**

To a cooled (-60°C.) solution of oxalyl chloride (0.36 ml, 4.05 mmol) in dry dichloromethane (10 ml) dimethylsulfoxide (0.58 ml, 8.1 mmol) in dry  $CH_2Cl_2$  (10 ml) was added dropwise so that the temperature did not rise above -50 °C. **11a,b** (1.12 g, 3.67 mmol) was dissolved in dry  $CH_2Cl_2$  (10 ml) and was added within 5 min. The solution was stirred for another 15 min., then triethylamine (2.55 ml, 18.4 mmol) was added, and the mixture was stirred for 5 min. After the mixture was allowed to warm to ambient temp. water (50 ml) was added and the layers were separated. The aqueous layer was extracted with  $CH_2Cl_2$  (2 x 80 ml). The combined organic layers were washed with saturated sodium chloride solution (120 ml) and then dried with sodium sulphate. After filtration and evaporation of the solvent, the oil was purified by flash chromatography. Yield: 0.78 g (72 %) colorless oil as a mixture of diastereomers in a ratio of 7:3.  $I$ ):diastereomer 30 %;  $II$ ):diastereomer 70 %.-  $R_f$  = 0.72 g (petroleum ether/ EtOAc 2:1).- IR (neat): 2985 , 2940, 2860 (CH), 1745 (HC=O), 1715 (NC=O), 1255 (C-O)  $cm^{-1}$ .-  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$ (ppm) = 0.05 (6 H, d,  $SiMe_2$ ), 0.86 (9 H, s,  $tBuSi$ ), 1.21 - 2.70 (5 H, m, 3-H, 4-H, 6- $H_a$ ), 3.00 (1 H, d, 6- $H_b^I$ ),  $J$  = 14.6 Hz), 3.55 - 3.98 (2 H, m, 2-H, 6- $H_b^{II}$ ), 3.71 $^{II}$ ) and 3.75 $^I$ ) (3 H, s,  $OCH_3$ ), 4.58 - 4.67 (1 H, m, 5-H), 9.59 $^{II}$ ) (1 H, s, HC=O), 9.60 $^I$ ) (1 H, d,  $J$  = 0.7 Hz, HC=O).-  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$ (ppm) = -5.0 $^I$ ) and - 4.7 $^{II}$ ) ( $SiCH_3$ ), 17.4 $^{II}$ ) and 18.0 $^I$ ) (C-3), 21.4 $^{II}$ ) and 22.1 $^I$ ) ( $Me_3CSi$ ), 25.7 ( $H_3C)_3CSi$ ), 27.2 $^{II}$ ) and 28.4 $^I$ ) (C-4), 48.6 $^{II}$ ) and 49.1 $^I$ ) (C-6), 52.9 $^{II}$ ) and 53.1 $^I$ ) ( $OCH_3$ ), 59.9 $^{II}$ ) and 60.7 $^I$ ) (C-2), 64.2 $^{II}$ ) and 66.9 $^I$ ) (C-5), 156.1 $^I$ ) and 156.8 $^{II}$ ) (C=O, urethane), 200.6 $^{II}$ ) and 200.9 $^I$ ) (HC=O).-  $C_{14}H_{27}NO_4Si$  (301.41).- Calcd.: C 55.77 H 9.02 N 4.60 found: C 55.82 H 9.29 N 4.61.

**Methyl (2*S*,5*S*)-5-*t*-Butyldimethylsilyloxy-*N*-methoxycarbonyl-piperidine-2-carboxylate (13a)**

11a (1.64 g, 5.4 mmol) was oxidized to the aldehyd under Swern conditions as described for 12a,b. The resulting brown oil was dissolved in methanol/water 9:1 (30 ml) then solid NaHCO<sub>3</sub> (9.1 g, 108 mmol) and bromine (0.55 ml, 16.9 mmol) was added. The mixture was stirred for 1.5 h at 25 °C. The excess of bromine was reduced with sodium thiosulphate and the solution was filtered. The solvent was evaporated and the residue was stirred in 80 ml of ether. Filtration over a short column of silicagel (petroleum ether/EtOAc 2:1) and evaporation of the solvent provided a nearly colourless oil. Yield: 1.42 g (79 %). *R*<sub>f</sub>: 0.86 (petroleum ether/EtOAc 2:1).-  $[\alpha]_D^{20} = -15.4$  (*c* = 1, MeOH).- IR (neat): 2960, 2925, 2895, 2860 (CH), 1750 (C=O ester), 1710 (C=O, urethane), 1255 (C-O) cm<sup>-1</sup>.- <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ(ppm) = 0.06 - 0.05 (6 H, m, SiMe<sub>2</sub> rotamers), 0.86 (9 H, s, *t*BuSi), 1.32 - 2.31 (5 H, m, 3-H, 4-H<sub>ab</sub>, OH), 2.65 - 2.75 (1 H, m, 6-H<sub>a</sub>) 3.49 - 3.66 (1 H, m, 6-H<sub>b</sub>), 3.69 (3 H, s, OCH<sub>3</sub>), 3.72 (3 H, s, OCH<sub>3</sub>), 3.87 - 4.18 (1 H, m, 5-H), 4.71 - 4.86 (1 H, m, 2-H, rotamers). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ(ppm) = - 4.8 (SiCH<sub>3</sub>), 18.0 (Me<sub>3</sub>CSi), 24.7(9), 25.3 (C-3) 26.0 ((CH<sub>3</sub>)<sub>3</sub>CSi) 31.0 (C-4), 48.2, 48.4 (rotamers) (C-6), 52.2, (OCH<sub>3</sub>) 53.3, 53.6 (rotamers) (C-2), 67.2, 67.9 (rotamers) (C-5), 156.6 (C=O, urethane), 171.5 (C=O, ester).

**Methyl (2*S*,5*S*)-Hydroxy-*N*-methoxycarbonyl-piperidine-2-carboxylate (14a)**

13a (0.72 g, 2.17 mmol) was dissolved in ether (40 ml) and cooled to 0 °C. Then dry methanolic hydrogen chloride (10 ml) was added and stored 2 d at 4 °C. The solvent and TBDMSOCH<sub>3</sub> was evaporated and the resulting oil was purified by flash chromatography over silica gel (EtOAc). Yield: 0.33 g (70 %).- *R*<sub>f</sub> = 0.42 (EtOAc).-  $[\alpha]_D^{20} = -24.1$  (*c* = 1, MeOH).- IR (neat): 3460 (OH), 3010, 2960, 2880 (CH), 1745 (C=O), 1710, 1690 (C=O) cm<sup>-1</sup>.- <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ(ppm) = 1.20 - 1.31 (1H, m, 3-H), 1.70 - 1.93 (3H, m, 4-H, 3-H OH), 2.25 - 2.33 (1H, m, 4-H), 2.74 - 2.82 (1H, m, 6-H<sub>a</sub>), 3.57 - 3.65 (1H, m, 6-H<sub>b</sub>), 3.72 (3H, s, OCH<sub>3</sub>), 3.74 (3H, s, COOCH<sub>3</sub>), 4.05 - 4.25 (1H, m, 5-H), 4.71 - 4.93 (1H, m, 2-H), signals are broadened by rotamers.- <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ(ppm) = 24.9 (C-3), 30.3 (C-4), 48.0 (C-6), 52.3 (OCH<sub>3</sub>), 53.0 (OCH<sub>3</sub>), 53.3 (C-2), 66.5 (C-5), 157.3 (C=O, urethane), 171.5 (C=O, ester). C<sub>9</sub>H<sub>15</sub>NO<sub>5</sub> (217.22).- Calcd.: C 49.76 H 6.96 N 6.44 found: C 48.93 H 7.58 N 5.72.

**Methyl (2*R*,5*S*)-5-Hydroxy-*N*-methoxycarbonyl-piperidine-2-carboxylate (14b)**

From 660 mg (2.08 mmol) 13b, as described for 14a. Yield: 390 mg.- (86%).- *R*<sub>f</sub> = 0.40 (EtOAc).- IR(neat): 3460 (OH), 3020-2880, 1740 (C=O ester), 1710-1685 (C=O urethane), 1450, 1405, 1370, cm<sup>-1</sup>.- <sup>1</sup>H-NMR (CDCl<sub>3</sub>) (60°C): δ(ppm) = 1.30-2.30 (5H, m, 3-H, 4-H, OH), 3.22 (1H, d, *J*<sub>6ab</sub> = 14.1Hz, 6-H<sub>a</sub>), 3.56-4.25 (8H, m, 6-H<sub>b</sub>, H-5, OCH<sub>3</sub> ester + OCH<sub>3</sub> urethane), 4.88 (1H-m, 2-H).- <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ(ppm) = 19.5

(C-3), 26.5 (C-4), 46.6 (C-6), 51.9, (OCH<sub>3</sub>) 52.6 (OCH<sub>3</sub>) 52.9 (C-2), 62.8 (C-5), 156.4 (C=O, urethane), 170.1 (C=O, ester).

**(2S,5S)-5-Hydroxy-piperidine-2-carboxylic acid hydrochloride (15a)**

**14a** (0.49 g, 2.26 mmol) was refluxed 4h in 6M HCl (10 ml). After concentration *in vacuo* EtOH/Et<sub>2</sub>O was added to the oily residue. The solvent was evaporated and the residue was dissolved in EtOH/THF (20 ml) and refluxed after addition of a small amount of charcoal. After filtration and evaporation of the solvent, the crystalline solid was triturated with acetone/EtOH (1:1) and isolated by suction. Yield: 0.31 g (76%).- m.p.: 195-196°C (dec.), (ref. **19** 183-187°C).-  $[\alpha]_D^{20} = -21.9$  (c=1, H<sub>2</sub>O), (ref. **19** -18.5 (c=1.0, H<sub>2</sub>O)).- IR (KBr): 3480, 3390 (OH), 3150 - 2400 (CH, NH<sub>2</sub><sup>+</sup>), 1735 (C=O), 1555 cm<sup>-1</sup>.- <sup>1</sup>H-NMR (D<sub>4</sub>-MeOD):  $\delta$ (ppm) = 1.83 - 2.19 (4H, m, 3-H, 4-H), 3.22 - 3.26 (2H, m, 6-H), 3.99 (1H, t, J = 7.4Hz, 2-H), 4.07-4.1 (1H, m, 5-H).- <sup>13</sup>C-NMR (D<sub>4</sub>-MeOD):  $\delta$ (ppm) = 21.9 (C-3), 29.8 (C-4), 50.4 (C-6), 57.6 (C-2), 62.1 (C-5), 170.6 (COOD). C<sub>6</sub>H<sub>12</sub>ClNO<sub>3</sub> (181.62) Calcd.: C 39.68 H 6.66 N 7.71 found: C 39.88 H 7.09 N 7.57.

**(2R,5S)-5-Hydroxy-piperidine-2-carboxylic acid hydrochloride (15b)**

**14b** (217 mg, 1.00 mmol) was refluxed for 4 h with 6 M HCl (2 ml). After evaporation of the volatiles the residue was triturated with EtOH/acetone. The crystalline solid was isolated by vacuum filtration. Yield: 130 mg (72%).- m.p.: 225 (dec.).-  $[\alpha]_D^{20} = +8.6$  (c=1, H<sub>2</sub>O) (ref. **19** for 2S,5R: - 9.7 (c=0.9, H<sub>2</sub>O)).- IR (KBr): 3360, 3220 (OH), 3020 - 2420 (CH, NH<sub>2</sub><sup>+</sup>), 1745 (C=O), 1590 cm<sup>-1</sup>.- <sup>1</sup>H-NMR (D<sub>4</sub>-MeOD):  $\delta$ (ppm) = 1.65 (1H, m, 4-H<sub>a</sub>), 1.86 (1H, m, 3-H<sub>a</sub>), 2.02 (1H, m, 4-H<sub>b</sub>), 2.39 (1H, m, 3-H<sub>b</sub>), 2.85 (1H, dd, J<sub>ab</sub> = 12.2, 9.2Hz, 6-H<sub>a</sub>), 3.42 (1H, ddd, J = 12.2, 3.9, 1.3Hz, 6-H<sub>b</sub>), 3.90 (1H, m, 5-H), 4.01 (1H, dd, J = 10.1, 3.9Hz, 2-H).- <sup>13</sup>C-NMR (D<sub>4</sub>-MeOD):  $\delta$ (ppm) = 24.4 (C-3), 31.1 (C-4), 49.1 (C-6), 56.9 (C-2), 63.9 (C-5), 170.7 (C=O).- C<sub>6</sub>H<sub>12</sub>ClNO<sub>3</sub> (181.62) Calcd.: C 39.68 H 6.66 N 7.71 found: C 39.46 H 6.64 N 7.62.

**Methyl (2R,5R)-5-benzoyloxy-N-methoxycarbonyl-piperidine-2-carboxylate (17) 80% d.e.**  
300 mg (1.38 mmol) **16** (prepared in 80% d.e. as described in ref. **19**), triphenylphosphine (472 mg, 1.80 mmol) and benzoic acid (220 mg, 1.80 mmol) were dissolved in THF (20 ml) under N<sub>2</sub>. To this mixture was added with stirring diethyl azodicarboxylate (313 mg, 1.80 mmol) in THF (2 ml). After 1h the solvent was evaporated *in vacuo* and CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added. The mixture was washed with 5 % NaHCO<sub>3</sub> solution (2x) and water (1x). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was chromatographed on silica gel (CHCl<sub>3</sub>/EtOAc 9+1). Yield: 189 mg (43%) colorless oil 80 % d.e. by <sup>1</sup>H-NMR.- R<sub>f</sub> = 0.40 (CHCl<sub>3</sub>/EtOAc 9+1).- IR



(neat): 3070-2880, 1750-1690 (C=O), 1605, 1585  $\text{cm}^{-1}$ .-  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) at  $60^\circ\text{C}$ ; only signals for 2*R*,5*R* **17** are shown:  $\delta(\text{ppm}) = 1.52$  (1H, dq,  $J_{3a,4a} \approx J_{4a,4e} \approx J_{4a,5a} \approx 11\text{-}14\text{Hz}$ ,  $J_{3e,4a} = 3.8\text{Hz}$ , 4- $\text{H}_a$ ), 1.89 (1H, ddt,  $J_{3a,4a} \approx J_{3a,3e} = 13.9\text{Hz}$ ,  $J_{3a,2e} = 6.1\text{Hz}$ ,  $J_{3a,4e} = 3.5\text{Hz}$ , 3- $\text{H}_a$ ), 2.17 (1H, m, 4- $\text{H}_e$ ), 2.36 (1H, ddd,  $J_{3a,3e} = 13.9\text{Hz}$ ,  $J_{2e,3e} = 6.2\text{Hz}$ ,  $J_{3e,4a} = 3.8\text{Hz}$ , 3- $\text{H}_e$ ), 3.08 (1H, dd,  $J_{6a,6e} = 12.4\text{Hz}$ ,  $J_{5a,6a} = 10.9\text{Hz}$ , 6- $\text{H}_a$ ), 3.74 (3H, s,  $\text{OCH}_3$ ), 3.77 (3H, s,  $\text{OCH}_3$ ), 4.38 (1H, dd,  $J_{6a,6e} = 12.4\text{Hz}$ ,  $J_{5a,6e} = 5.0\text{Hz}$ , 6- $\text{H}_e$ ), 4.89-5.04 (2H, m, 2- $\text{H}_e$ , 5- $\text{H}_a$ ), 7.37-7.59 (3H, m,  $\text{H}_{\text{arom}}$ ), 7.98-8.04 (2H, m,  $\text{H}_{\text{arom}}$ ).-  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 24.60/24.93 (C-4), 26.34/26.84 (C-3), 44.60/44.79 (C-6), 52.34/53.07 (2x  $\text{OCH}_3$ ), 53.27/53.58 (C-2), 68.65 (C-5), 128.28, 129.52, 129.79, 133.09 ( $\text{C}_{\text{arom}}$ ), 156.02/156.49 ( $\text{CO}_2\text{CH}_3$  urethane), 165.52 ( $\text{PhCO}_2$ -), 171.30 ( $\text{CO}_2\text{CH}_3$  ester)-rotamers.-  $\text{C}_{16}\text{H}_{19}\text{NO}_6$  (321.33) Calcd.: C 59.81 H 5.96 N 4.36 found.: C 59.78 H 5.91 N 4.20.

**(2*R*,5*R*)-5-Hydroxy-piperidine-2-carboxylic acid hydrochloride (**18**) 84% d.e.**

**17** (80% d.e.) (175 mg, 545  $\mu\text{mol}$ ) was refluxed with 4 M HCl (3 ml) for 6 h. After cooling, benzoic acid was extracted from the aqueous phase with  $\text{CH}_2\text{Cl}_2$  (3x). After evaporation of the aqueous layer the oily residue crystallized. The colorless crystals were triturated with acetone, isolated by vacuum filtration and dried. Yield: 58 mg (59%).- m.p.:  $187^\circ\text{C}$ - $195^\circ\text{C}$  (dec.).-  $[\alpha]_D^{20} = +18.1$  ( $c=1.3$  MeOH) (84% d.e. by  $^1\text{H-NMR}$ ).- IR (KBr): 3520, 3490 (OH), 3000-2500 ( $\text{CH}, \text{NH}_2^+$ ), 1730 (C=O), 1560, 1440, 1400, 1225,  $^1\text{H-NMR}$  ( $\text{D}_4\text{-MeOD}$ ):  $\delta(\text{ppm}) = 1.83\text{-}2.24$  (4H, m, 3-H, 4-H), 3.23 (2H, m, H-6), 4.02 (1H, t,  $J=7.5\text{Hz}$ , 2-H), 4.08-4.13 (1H, m, 5-H).-  $^{13}\text{C-NMR}$  ( $\text{D}_4\text{-MeOD}$ ):  $\delta(\text{ppm}) = 21.8$  (C-3), 29.8 (C-4), 50.3 (C-6), 57.6 (C-2), 62.1 (C-5), 170.7 (COOD).  $\text{C}_6\text{H}_{12}\text{ClNO}_3$  (181.62) Calcd.: C 39.68 H 6.66 N 7.71 found: C 39.79 H 6.54 N 7.66.

## References and Notes

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