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Synthesis of (2*S*,4*S*,5*S*)-5-hydroxy-4-methylpipecolic acid via amide methylenation of 5-hydroxy-4-methyl-2-piperidinone with dimethyltitanocene †

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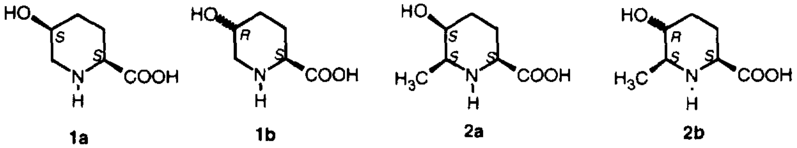
Abstract: (4*S*,5*S*)-5-hydroxy-4-methylpiperidine-2-one **4**, readily available from *S*-glutamic acid, serves as a starting material for the synthesis of (2*S*,4*S*,5*S*)-5-hydroxy-4-methylpipecolic acid **12**. The key step of this reaction sequence is the chemoselective methylenation of the amide carbonyl group of **6** with dimethyltitanocene to the exocyclic enecarbamate **7**. Hydroboration/oxidation of the double bond resulted in the formation of all-*cis* alcohol **8** which was transformed via aldehyde to **12**. © 1997 Elsevier Science Ltd

Substituted pipecolic acids have attracted attention as components and starting materials for a variety of synthetic peptides,[1] immunosuppressant products,[2] enzyme inhibitors,[4b] and NMDA antagonists,[4d] therefore new synthetic methods were developed for the preparation of racemic and especially nonracemic pipecolic acids and derivatives.[3–6]

(2*S*,5*S*)-5-hydroxypipecolic acid **1a** and (2*S*,5*R*)-5-hydroxypipecolic acid **1b** were first isolated from dates,[7] were later found in several other plants,[8] and were synthesised by us from *S*-glutamic acid.[5d,g] Methyl pipecolic acids and derivatives are much rarer. The only pair of diastereomers of a methyl hydroxypipecolic acid in nature is (2*S*,5*S*,6*S*)-5-hydroxy-6-methylpipecolic acid **2a** and (2*S*,5*R*,6*S*)-5-hydroxy-6-methylpipecolic acid **2b** isolated from beech nuts, the fruits of *fagus silvatica* (Scheme 1).[9]



Scheme 1.

In continuing our studies in the synthesis of chiral nonracemic pipecolic acids and their derivatives we now wish to report a synthesis of the all-*cis* configurated (2*S*,4*S*,5*S*)-5-hydroxy-4-methyl pipecolic acid **12**. The starting material of this synthesis was (4*S*,5*S*)-5-azidomethyl-4-methyl-4,5-dihydro-2(3H)-furanon **3** which can be prepared[10a,b] in 9 steps from *S*-glutamic acid. **3** was hydrogenated in methanol/water at 80°C with Pd/C. Under these conditions the ring expansion reaction proceeded smoothly to yield the piperidone derivative **4** in 89%. The addition of water had a significant effect on the yield of **4**. In the absence of water only 15% of the lactam was isolated.[9b] The OH-function was protected with *tert*-butyldimethylsilyl chloride to get **5** and the amide moiety was protected and activated with methyl cyanoformate[11] to provide compound **6** (Scheme 2).

The transformation of the amide carbonyl group to the carboxyl function can be achieved in two ways. First by reduction of carbonyl function to a α-hydroxycarbamate, trapping of the acyliminium-

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† Dedicated to Prof. Dr. W. Wiegrebe on the occasion of his 65th birthday.

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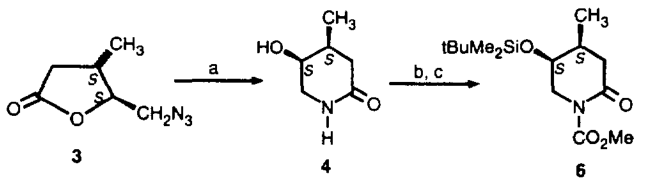
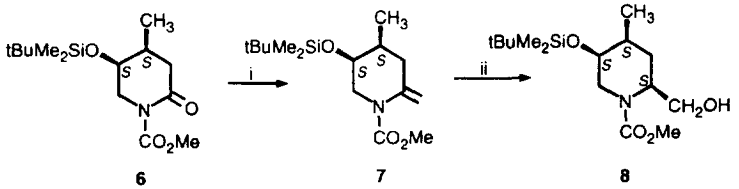


a: MeOH/H_2O 4:1, H_2, Pd/C; b: *t*-$BuMe_2SiCl$, DMF, imidazole; c: *n*-BuLi, THF, $NCCO_2Me$, -78 °C.

Scheme 2.

ion[12] with trimethylsilyl cyanide and hydrolysis to the carboxyl group. The formation of a α-cyanocarbamate was observed with high *trans* selectivity.[5g] Second, methylenation of the carbonyl group and hydroboration/oxidation of the enecarbamate furnished a *cis* configurated hydroxymethyl piperidine derivative which was transformed to pipecolic acid derivatives[5d]. The latter method seemed to be best suited for the synthesis of all-*cis* configurated pipecolic acid derivatives. Methylenation of aldehydes, ketones and lactones with dimethyltitanocene was first introduced by Petasis and Bzowej.[13] We used this reaction for the amide methylenation as a key step in the natural product synthesis[5d] of (2*S*,5*S*)-5-hydroxypipecolic acid **1a**.

The conversion of the N-methoxycarbonyl lactame **6** into the exocyclic enecarbamate group of **7** was accomplished at 105°C with dimethyltitanocene in toluene. **7** was isolated in 92% yield after column chromatography (Scheme 3).



i: Cp_2TiMe_2, toluene, pyridine, 105 °C, 1.5 h; ii: THF, 9-BBN; NaOH, H_2O_2.

Scheme 3.

After hydroboration of **7** with the sterically demanding 9-borabicyclononane and oxidation of the product with hydrogen peroxide only one diastereomer namely the all-*cis* alcohol **8** was isolated. Therefore **7** was hydroborated exclusively from the less shielded α-side. This can be rationalized by the fact that the ß-side of both conformers of **7** namely A and B is shielded by the *tert*-butyldimethylsilyloxy and the methyl group respectively. The methyl group plays a decisive part in the stereoselectivity of the hydroboration reaction. We have observed that the 4-dimethyl compound was hydroborated to a mixture of diastereomers in a *cis:trans* ratio of 7:3.[5d] In both conformers of **7** 1,3 diaxial interactions are operating so a roughly 1:1 equilibrium mixture of A and B is present and both conformers a hydroborated from the less hindered α-face (Figure 1)

The oxidation of the alcohol **8** to the carboxylic acid turned out to be troublesome, but a two step procedure as previously described[5d] for the synthesis of **1a** provided the methylester **9** in 75% yield.

On this stage chemical proof for the all-*cis* configuration of compound **9** was confirmed in the following way. When **9** was treated with methanolic HCl to deprotect the alcohol function, a mixture of **10** and bicyclic lactone **11** was formed. To complete the lactonisation the mixture was heated with p-toluene sulfonic acid to furnish **11** in 79% yield. Hydrolysis of lactone **11** with 4 M hydrochloric acid provided (2*S*,4*S*,5*S*)-5-hydroxy-4-methylpipecolic acid hydrochloride **12** (Scheme 4).

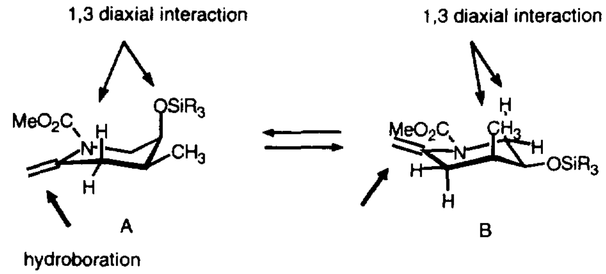
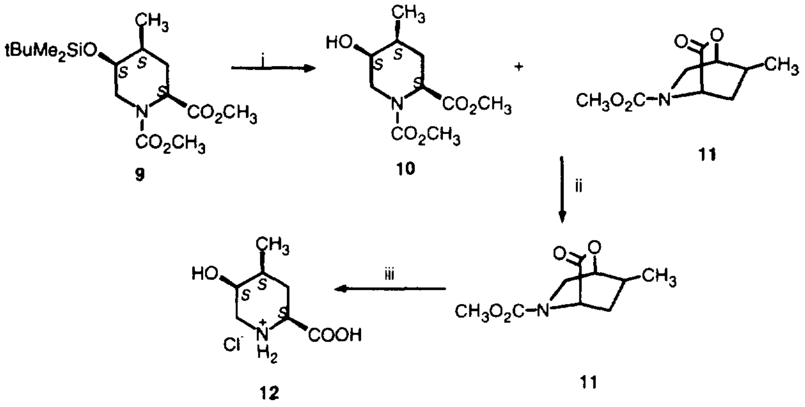


Figure 1.



i: MeOH, HCl, 20 °C; ii: *p*-TosOH, toluene, reflux; iii: 4 M HCl, reflux.

Scheme 4.

Experimental

General

Reactions with organometallic and borane compounds where carried out in flame dried glassware and under dry and oxygen free nitrogen atmosphere. Solvents were dried according common methods and distilled before use. TLC: Merck precoated silica gel 60 F-254 plates; detection with iodine vapor or UV light (254 nm). Flash chromatography: Glass columns (50×5) cm, silica gel Merck (0.063–0.2 mm), pressure 1.8 bar, detection UV-detector 87.00 (Knauer), γ=254 nm. Optical rotations: Perkin Elmer 241 spectrometer. IR spectra (KBr (solids) or neat (liquids)): Perkin Elmer 681 infrared spectrometer. FT-IR (KBr): Bruker FTIR IFS 85. ^{1}H-NMR (200 and 400 MHz) and ^{13}C-NMR (50 and 100 MHz) spectra: Bruker AC 200 and AC 400; chemical shifts in ppm relative to the solvent as internal standard, coupling constants in Hz. Mass spectra CH7 Varian-MAT (70 eV).

(4S,5S) 5-Azidomethyl-4-methyl-4,5-dihydro-2(3H)-furanone 3

To a solution of (4*S*,5*S*) 4-Methyl-5-mesyloxymethyl-4,5-dihydro-2(3H)-furanone[10b] (3.20 g, 15.4 mmol) in DMF (50 ml) was added lithium azide (1.22 g, 25.0 mmol) and the mixture was heated for 18.5 h at 70°C. After evaporation of the solvent, water was added (100 ml) and the solution was extracted wtih diethyl ether (3×100 ml). The combined organic layers were washed with sat. sodium hydrogencarbonate solution (100 ml), dried with sodium sulfate, filtered and evaporated. Yield: 2.10 g (88%) colourless oil.—R$_f$: 0.80 (PE/EtOAc 2:1).—$[\alpha]_D^{20}$=+102.3 (c=1.0, CHCl$_3$), (ref.[10b] $[\alpha]_D^{20}$=+99.5 (c=1.0, CHCl$_3$)).—IR: γ=2980, 2930, 2870 (C–H), 2100 (–N$_3$), 1780 (C=O), cm^{-1}—^{1}H-NMR (CDCl$_3$): γ (ppm)=1.13 (3 H, d, $J_{Me\text{-}4}$=6.6 Hz, CH$_3$), 2.12–2.25 (1 H, m, 3-H), 2.22 (1 H, dd, J_{gem}=17.0 Hz, $J_{3\text{-}4}$=8.7 Hz, 3-H$_a$), 2.33–2.49 (1 H, m, 4-H), 2.66–2.84 (1 H, m, 3-H), 3.42 (1 H, dd, J_{gem}=13.4 Hz, $J_{5\text{-}6}$=5.1 Hz, 6-H_a), 3.58 (1 H, dd, J_{gem}=13.4 Hz, $J_{5\text{-}6}$=3.5 Hz, 6-H_b), 4.10–4.18 (1 H, m, 5-H). — ^{13}C-NMR ($CDCl_3$): γ (ppm)=17.5 (CH_3), 32.6 (C-4), 36.5 (C-3), 52.5 (C-6), 84.5 (C-5), 175.3 (C-2).

(4S,5S) 5-Hydroxy-4-methylpiperidine-2-one 4

To a solution of **3** (1.30 g, 8.3 mmol) in methanol (40 ml), water (10 ml) and conc. aqueous ammonia solution (0.5 ml), 10% palladium/charcoal (200 mg) was added and the mixture was hydrogenated at 80 bar and 60°C for 24 h. The catalyst was filtered off and the solvent was evaporated. The pale yellow residue was recrystallized from ethyl acetate. Yield: 0.96 g (89%), (ref.[10b] 16%). — mp: 147–148°C (ref.[10b] 141°C). — R_f: 0.20 ($CHCl_3$/MeOH 9:1). — $[\alpha]_D^{20}$=+19.8 (c=1.0, MeOH), (ref.[10b] $[\alpha]_D^{20}$=+19 (c=0.2, MeOH)). — IR: 3600–3100 (OH, NH), 2980, 2920, 2900 (CH), 1630 (C=O), 1490 cm^{-1}. — ^{1}H-NMR (CD_3OD): γ (ppm)=0.96 (3 H, d, $J_{Me\text{-}4}$=6.4 Hz, CH_3), 1.91–2.17 (3 H, m, 3-H, 4-H), 3.16–3.37 (2 H, m, H-6), 3.78–3.81 (1 H, m, 5-H). — ^{13}C-NMR (CD_3OD): γ (ppm)=17.2 (CH_3), 32.8 (C-4), 35.3 (C-3), 49.4 (C-6), 67.0 (C-5), 174.6 (C-2). — MS: m/z (%)=129 (86%) [M^+], 112 (22), 100 (21), 69 (24), 59 (41), 58 (100), 57 (73), 43 (63), 42 (27), 41 (58), 39 (38). — $C_6H_{11}NO_2$ (129.16). — calcd.: C 55.81, H 8.58, N 10.8; found: C 55.55, H 8.25, N 10.71.

*(4S,5S) 5-(*tert*-Butyldimethyl)silyloxy-4-methylpiperidine-2-one 5*

To a solution of **4** (1.13 g, 8.8 mmol) in DMF (25 ml) *tert*-butyldimethylsilyl chloride (1.47 g, 9.8 mmol) and imidazole (1.33 g, 19.5 mmol) were added and the mixture was heated for 18 h at 50°C. Then abs. methanol (10 ml) was added and the mixture was stirred for another 1.5 h at 50°C. The volatiles were distilled *in vacuo*, water (80 ml) was added and the solution was extracted with diethyl ether (4×100 ml). The combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated. The residue was recrystallized with petroleum ether (40–60°C). Yield: 2.01 g (85%) colourless crystals. — mp: 79–80°C. — R_f: 0.70 ($CHCl_3$/MeOH 9:1). — $[\alpha]_D^{20}$=−20.8 (c=1.0, EtOAc). — IR: 3400, 3220 (NH), 2950, 2920, 2890, 2850 (CH), 1640 (C=O), 1530, 1490 cm^{-1}. — ^{1}H-NMR ($CDCl_3$): γ (ppm)=0.06 (3 H, s, SiMe), 0.07 (3 H, s, SiMe), 0.88 (9 H, s, Si*t*Bu), 0.99 (3 H, d, $J_{Me\text{-}4}$=6.7 Hz, CH_3), 1.96–2.02 (1 H, m, 4-H), 2.25–2.32 (2 H, m, 3-H), 3.23 (1 H, dt, $J_{6\text{-}5}$=3.3 Hz, $J_{6a,e}$=12.5 Hz, 6-H_a), 3.37 (1 H, dd, $J_{6\text{-}5}$=2.2 Hz, $J_{6a,e}$=12.4 Hz, 6-H_b), 3.85–3.91 (1 H, m, 5-H), 6.15 (1 H, broad NH). — ^{13}C-NMR ($CDCl_3$): γ (ppm)=−5.0 and −4.7 ($Si(CH_3)_2$), 16.8 (CH_3), 17.9 (Me_3CSi), 25.8 ($(H_3C)_3CSi$), 32.3 (C-4), 34.6 (C-3), 48.5 (C-6), 67.1 (C-5), 172.5 (C-2). — MS: CI-measurement (isobutane) m/z (%)=244 (100) $[M+1]^+$, 300 (0.3) $[M+C_4H_9]^+$.

*(4S,5S) 5-(*tert*-Butyldimethyl)silyloxy-N-methoxycarbonyl-4-methylpiperidine-2-one 6*

To a cooled (−70°C) solution of **5** (1.77 g, 7.3 mmol) in THF (40 ml) 1.6 M *n*-BuLi (5.6 ml, 9.0 mmol) was added and the mixture was stirred for 15 min at −70°C. Methyl cyanoformate (0.8 ml, 10 mmol) was added dropwise and the solution was stirred for 1 h at −70°C. The reaction was quenched with sat. sodium hydrogencarbonate (25 ml) and sat. sodium carbonate (25 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 ml). The combined organic layers were dried with anhydrous sodium sulfate, filtrated and the solvent was evaporated. The residue was recrystallized from petroleum ether. Yield: 1.90 g (91%) colourless crystals. — mp: 56–57°C. — R_f: 0.45 (diethyl ether). — $[\alpha]_D^{20}$=+6.0 (c=1.0, MeOH). — IR: 2950, 2930, 2900, 2855 (CH), 1770, 1710 (C=O), 1460 cm^{-1}. — ^{1}H-NMR ($CDCl_3$): γ (ppm)=0.05 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.85 (9 H, s, Si*t*Bu), 0.97 (3 H, d, $J_{Me\text{-}4}$=6.6 Hz, CH_3), 2.0–2.10 (1 H, m, 4-H), 2.37–2.49 (2 H, m, 3-H), 3.51 (1 H, dd, $J_{6\text{-}5}$=2.2 Hz, $J_{6a,e}$=12.6 Hz, 6-H_a), 3.83 (1 H, s, OCH_3), 3.82–3.96 (2 H, m, 6-H_b, 5-H). — ^{13}C-NMR ($CDCl_3$): γ (ppm)=−5.0 and −4.7 ($Si(CH_3)_2$), 16.9 (CH_3), 17.9 (Me_3CSi), 25.6 ($(H_3C)_3CSi$), 32.8 (C-4), 37.7 (C-3), 53.1 (C-6), 53.8 (OCH_3), 67.4 (C-5), 155.1 (C=O urethane), 172.5 (C-2). — MS: CI-measurement (isobutane) m/z (%)=302 (100) $[M+1]^+$.

(4S,5S) 5-(tert-Butyldimethyl)silyloxy-N-methoxycarbonyl-4-methyl-2-methylen-piperidine 7

A solution of **6** (0.90 g, 3.0 mmol) and dimethyltitanocene (0.90 g, 4.3 mmol) in toluene (50 ml) and pyridine (0.4 ml) was heated for 1.5 h to 105°C. The reaction was monitored by tlc (petroleum ether/ethyl acetate). After absence of the starting material, the solvent was evaporated and the brown oil was diluted with *n*-pentane (20 ml). After 30 min the solution was filtered and the filtrate was concentrated. The orange coloured oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 2:1, containing 0.5% triethylamine). Yield: 0.83 g (92%) pale yellow oil.—R_f: 0.70 (petroleum ether/ethyl acetate 2:1).—$[\alpha]_D^{20}$=−19.7 (c=1.0, EtOAc).—IR: 3020 (C=H), 2950, 2920, 2850 (CH), 1705 1650, (C=O), 1600 (C=C), 1440, 1385, 1255 cm^{-1}.—^{1}H-NMR (C_6D_6): γ (ppm)=−0.04 (3 H, s, SiMe), 0.10 (3 H, s, SiMe), 0.77 (3 H, d, J_{Me-4}=6.7 Hz, CH_3), 0.92 (9 H, s, Si*t*Bu), 1.76–1.85 (1 H, m, 4-H), 2.07–2.22 (2 H, m, 3-H), 2.86 (1 H, dd, J_{6-5}=2.0 Hz, $J_{6a,e}$=13.2 Hz, 6-H_{eq}), 3.25–3.30 (1 H, m, 5-H) 3.48 (1 H, s, OCH_3), 4.12 (1 H, dd, J_{6-5}=4.2 Hz, $J_{6a,e}$=13.2 Hz, 6-H_{ax}), 4.80 (1 H, d, J=1.6 Hz, =CH_E), 4.93 (1 H, d, J=1.1 Hz, =CH_Z).—^{13}C-NMR (C_6D_6): γ (ppm)=−5.0 and −4.6 ($Si(CH_3)_2$), 17.1 (CH_3), 18.3 (Me_3CSi), 26.0 ($(H_3C)_3CSi$), 35.4 (C-3), 37.0 (C-4), 51.4 (C-6), 52.3 (OCH_3), 68.9 (C-5), 107.4 (=CH), 143.5 (C-2), 155.6 (C=O urethane).—MS: m/z (%)=299 (2%) [M^+], 242 (88), 110 (26), 108 (28), 75 (100), 73 (25), 59 (27).

(2S,4S,5S) 5-(tert-Butyldimethyl)silyloxy-2-hydroxymethyl-N-methoxycarbonyl-4-methyl-piperidine 8

To a solution of **7** (1.05 g, 3.5 mmol) in THF (100 ml) was added a 0.5 M solution of 9-BBN (12.0 ml, 6.0 mmol) and the mixture was stirred for 18 h at 25°C. After addition of 35% hydrogen peroxide (30 ml) and 6.0 M NaOH (30 ml) the mixture was stirred for 2 h. Potassium carbonate was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×80 ml) and the combined organic layers were dried with anhydrous potassium carbonate. After filtration and evaporation of the solvent the yellow oil was purified by flash chromatography on silica gel (ethyl acetate). Yield: 0.99 g (89%) colourless oil.—R_f: 0.46 (EtOAc).—$[\alpha]_D^{20}$=−3.4 (c=1.0, EtOH).—IR: 3400 (OH), 2950, 2920, 2850 (CH), 1680 (C=O), 1460, 1050 cm^{-1}.—^{1}H-NMR ($CHCl_3$): γ (ppm): −0.01 (3 H, s, SiMe), and 0.01 (3 H, s, SiMe), 0.83 (9 H, s, Si*t*Bu), 0.87 (3 H, d, J_{Me-4}=6.5 Hz, CH_3), 1.38–1.82 (7 H, m, 2-H, 3-H, 4-H, 6-H, OH), 3.34–3.76 (3 H, m, 5-H, $HOCH_2$), 3.61 (1 H, s, OCH_3).—^{13}C-NMR ($CDCl_3$): γ (ppm)=−5.1 and −4.8 ($Si(CH_3)_2$), 16.7 (CH_3), 17.9 (Me_3CSi), 25.6 ($(H_3C)_3CSi$), 29.5 (C-4), 34.5 (C-3), 41.7, 41.8 (C-6, rotamers), 52.4 (OCH_3), 64.0 ($HOCH_2$), 68.4 (C-5), 156.7 (C=O).—MS: CI-measurement (NH_3) m/z (%)=335 (85) $[M+NH_4]^+$.

(2S,4S,5S) Dimethyl 5-(tert-butyldimethyl)silyloxy-4-methylpiperidine-1,2-carboxylate 9

To a cold (−60°C) solution of oxalyl chloride (0.51 g, 4.0 mmol) in dichloromethane (30 ml), DMSO (0.6 ml, 8.0 mmol) in dichloromethane (30 ml) was added dropwise so that the temperature did not rise higher than −50°C. A solution of **8** (0.98 g, 3.1 mmol) in dichloromethane (30 ml) was added within 5 min and the mixture was stirred for 15 min at −70°C. After addition of trimethylamine (1.7 ml, 12.0 mmol), water (60 ml) and 5% hydrochloric acid (30 ml) the layers were separated and the aqueous layer was extracted with dichloromethane (3×80 ml). The combined organic layers were dried with sodium sulfate, filtered and evaporated. To a solution of the oily residue in methanol (90 ml) and water (10 ml) was added sodium hydrogencarbonate (7.00 g) and bromine (0.16 ml, 6.2 mmol) and the mixture was stirred for 1 h at 25°C. After the excess of bromine was reduced with sodium thiosulfate, the solution was filtered and the solvent removed *in vacuo*. The residue was extracted with diethyl ether. After evaporation of the solvent the yellow oil was purified by 'filtration' over silica gel to yield a colourless oil. Yield: 0.80 g (75%). —R_f: 0.62 (diethyl ether).—$[\alpha]_D^{20}$=−3.1 (c=1.0, MeOH).—IR: 2950, 2890, 2860 (CH), 1750, 1705 (C=O), 1445, 1100 cm^{-1}.—^{1}H-NMR ($CHCl_3$): γ (ppm): 0.03 (3 H, s, SiMe), and 0.06 (3 H, s, SiMe), 0.81 (3 H, d, J_{Me-4}=6.1 Hz, CH_3), 0.87 (9 H, s, Si*t*Bu), 1.49–2.14 (4 H, m, 3-H, 4-H, 6-H_a), 2.85–3.18 (1 H, m, 6-H_b), 3.65–3.98 (7 H, m, 2-H, 2 OCH_3), 4.48–4.54 (1 H, m, 5-H).—^{13}C-NMR ($CDCl_3$, 50°C): γ (ppm)=−4.9 and −4.7 ($Si(CH_3)_2$), 11.5, 11.7 (CH_3, rotamers), 15.3 (Me_3CSi), 25.7 ($(H_3C)_3CSi$), 30.7, 31.2 (C-4, rotamers) 32.7 (C-3), 43.2, 43.8 (C-6), 51.8 (C-5), 52.3 (C-2), 53.0 (NCO_2CH_3), 68.0, 68.3 (CO_2CH_3, rotamers), 156.6 (C=O–urethane), 172.6 (C=O–ester). —MS: CI-measurement (NH_3) m/z (%)=363 (100) $[M+NH_4]^+$.

(1S,4S,7S) Methyl 7-methyl-3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate 11

9 (0.37 g, 1.1 mmol) was dissolved in methanol and conc. hydrochloric acid (0.5 ml) and stirred for 18 h at 25°C. The solvent was removed *in vacuo*, the brown oil was 'filtered' over silica gel (diethyl ether). After evaporation of the solvent the remaining oil was dissolved in toluene (60 ml), 4-toluene sulfonic acid (10 mg) was added and the mixture was refluxed for 18 h. The solution was allowed to cool to room temperature and a solution of sat. sodium hydrogencarbonate (50 ml) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×50 ml). The combined organic layers were dried with sodium sulfate, filtered and evaporated. The yellow oil was purified by chromatography on silica gel (diethyl ether). Yield: 0.17 g (79%) colourless oil. — R_f: 0.27 (diethyl ether). — $[\alpha]_D^{20}=-25.1$ (c=1.0, EtOAc). — IR: 2950, 2870 (CH), 1765, 1710, 1670 (C=O), 1445 cm^{-1}. — ^{1}H-NMR ($CHCl_3$): γ (ppm): 1.11 (3 H, dd, $J_{1(Me\text{-}3)}=7.1$ Hz, $J_2=1.0$ Hz, CH_3), 1.38–1.50 (1 H, m, 8-H_a), 1.95–2.13 (1 H, m, 7-H), 2.43 (1 H, dt, $J_1=10.0$ Hz, $J_2=3.3$ Hz, 8-H_b), 3.44 (1 H, d, $J_{vic}=12.0$ Hz, 6-H_a), 3.61 (1 H, dd, $J_1=12.0$ Hz, $J_2=3.3$ Hz, 6-H_b), 3.69 (3 H, s, OMe), 4.45–4.69 (2 H, m, 1-H, 4-H). — ^{13}C-NMR ($CDCl_3$): γ (ppm)=19.3 (CH_3), 29.7 (C-7), 33.3 (C-8), 47.6 (C-6), 49.9, 50.5 (C-4, rotamers), 52.9 (OCH_3), 154.9 (C=O–urethane), 169.5 (C=O–lactone). — MS: m/z (%)=199 (38%) $[M^+]$, 168 (78) $[M^+-CH_3O]$, 155 (84) $[M^+-CO_2]$, 140 (80) $[M^+-CO_2CH_3]$, 128 (41), 127 (18), 126 (100), 101 (21), 55 (66).

(2S,4S,5S) 4-Methyl-5-hydroxy-pipecolic acid hydrochloride 12

11 (0.16 g, 0.80 mmol) was refluxed in 4.0 M hydrochloric acid (50 ml) for 4 h (tlc-control showed the absence of educt). The solvent was evaporated completely, and the residue was dissolved in MeOH (20 ml), charcoal was addded and the solution was refluxed. The charcoal was removed by filtration and the solvent was distilled *in vacuo*. The residue was triturated with acetone and isolated by suction. Yield: 0.15 g (96%) colourless crystals. — mp: 106–107°C (decomposition). — $[\alpha]_D^{20}=-38.7$ (c=1.0, H_2O). — IR (KBr): 3434 (OH), 3200–2400 (NH_2^+), 2962, 2926 (CH), 1740 (C=O), 1629, 1439, 1262, 1190, 1155, 1014 cm^{-1}. — ^{1}H-NMR (CD_3OD): γ (ppm): 0.96 (3 H, d, $J_{Me\text{-}4}=6.0$ Hz, CH_3), 1.65–1.96 (3 H, m, 3-H, 4-H), 3.10 (1 H, d, $J_{gem}=12.8$ Hz, 6-H_a), 3.24 (1 H, dd, $J_{gem}=12.8$ Hz, $J_{vic}=2.5$ Hz, 6-H_b), 3.77–3.95 (2 H, m, 5-H, 2-H). — ^{13}C-NMR (CD_3OD): γ (ppm): 17.8 (CH_3), 29.0 (C-3), 34.6 (C-4), 51.4 (C-6), 55.8 (C-2), 65.6 (C-5), 170.8 (COOH). — MS: DCI-measurement (NH_3) m/z (%)=177 (6) $\{[M+NH_4]-HCl\}^+$, 159 $[M-HCl]^+$. — $C_7H_{14}NO_3Cl$ (195.65): calcd.: C 42.97, H 7.16, N 7.16; found: C 41.92, H 7.42, N 5.58.

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