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# Chiral Pool Synthesis of trans-(2S,3S)-3-Hydroxyproline and Castanodiol from S-Pyroglutamic Acid.

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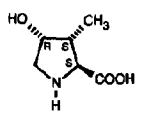
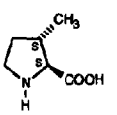
**Abstract:** The Pyroglutamic acid derivative **1** was converted through several steps into Castanodiol **9** and 2S,3S-3-Hydroxyproline **11**. Key steps of the reaction sequence were the stereoselective epoxidation of **1** to **2** and the regioselective ring opening of **2** to **3**. $BH_3$·$S(CH_3)_2$ reduction of the amide group of **3** and **4** resulted in a concomitant transformation of the acetal moiety into the N-benzyl protecting group. The air sensitive **5** and **6**, were transformed to the stable N-Boc prolinol derivatives **7** and **8**. Deprotection of **8** provided **9**, while oxidation of **8** gave the protected proline derivative **10**. Deprotection of **10** furnished enantiopure 2S,3S-3-Hydroxyproline **11**.

Nonproteinogenic proline derivatives e. g. **A** and **B** have recently been detected in a novel cyclic peptide, scytonemin A, a metabolite of the cultured cyanophyte Scytonema sp., which possesses potent calcium antagonistic properties[1]. 2S,3S-3-Hydroxyproline **11** was also found in naturally occuring peptides, namely Mucrorin-D[2a], Telomycin[2b] and in bovine Achilles tendon collagen[2c]. The reduced form of **11**, Castanodiol **9** (L-trans-3-Hydroxyprolinol), was isolated from Castanospermum australe[3].




A

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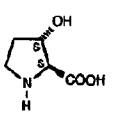
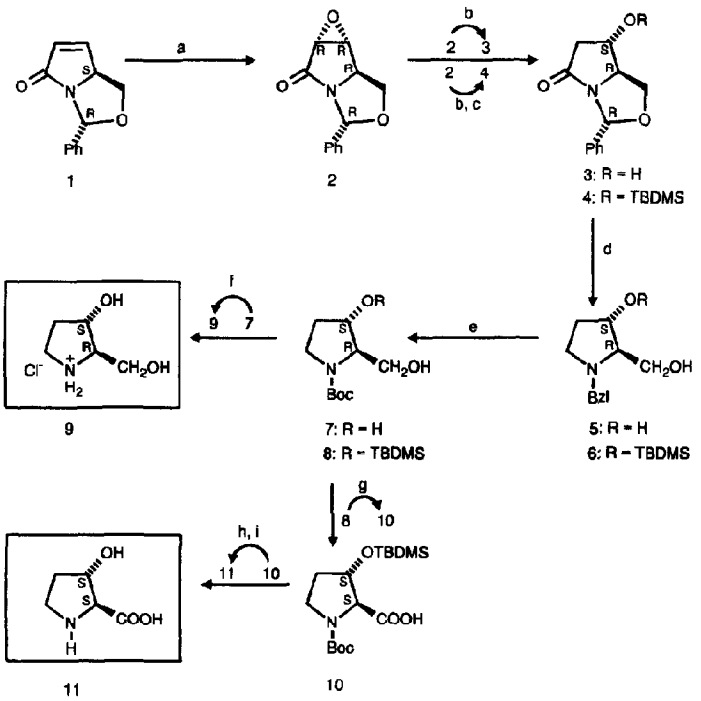


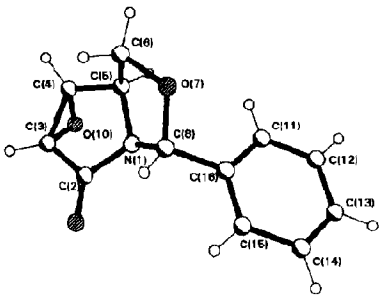

11

Here we present an expeditious route to **9** and **11**[4], starting with the readily available enantiopure bicyclic amide **1**[5], which we prepared in a slightly modified and more convenient procedure from the saturated bicyclic acetal of S-pyroglutaminol[6].

Treatment of **1** with t-butyl hydroperoxide/tetrabutylammonium fluoride[7], resulted in a rapid conversion (30-40%) into a single diastereomer **2**. X-ray crystallography revealed, that the epoxidation took place from the less hindered convex side of **1**. The x-ray structure shows that the oxirane ring holds nearly an antiperiplanar position to the acetal moiety.




**a**: t-BuOOH, n-$Bu_4NF$, $K_2CO_3$, DMF; **b**: Al/Hg, EtOH/acetone 2:1; **c**: TBDMSCl, imidazole, DMF; **d**: $BH_3{\cdot}S(CH_3)_2$, THF, 70° C; **e**: Pd/C/$H_2$, $Boc_2O$, MeOH; **f**: 5M HCl; **g**: $RuCl_3$, $NaIO_4$, $CH_3CN/H_2O$; **h**: 6M HCl; **i**: Dowex 50Wx2, $NH_4OH$.




**X-ray-structure of 2.**

An improvement in the yield of **2** (65%) was readily made by changing the solvent (DMF instead of DMSO) and by adding one equivalent of $K_2CO_3$ to the reaction mixture. There are a number of methods for the regioselective reductive ring-opening of α,ß-epoxy ketones[9a-d]. In view of the instability of **2** under the acidic conditions with chromous salt reductions[9a-b], we decided to explore the NaI/NaOAc/AcOH system[10]. However all attempts to provide **3** failed with surprisingly the α-iodo-derivative being isolated[10]. Eventually aluminum amalgam[11] proved to be the reagent of choice for this reduction and **3** was provided as the sole product in 79% yield.

The TBDMS protecting group for the secondary OH function had to be introduced as the next step, because reduction of the amide group with $BH_3{\cdot}S(CH_3)_2$ proceeded with simultaneous reductive cleavage of the acetal moiety to give rise to the primary OH function. **5** and **6** were isolated as air sensitive oils. All attempts to provide **9** by catalytic hydrogenation of **5** resulted in the isolation of intractable brown oils. Therefore **3** was hydrogenated over Pd/C in the presence of $Boc_2O$ to give the Boc-derivative **7**, as a stable crystalline compound in 71% yield. Treatment of **7** with 6M HCl provided **9** as an oil. Azeotropic removal of crystal water with boiling benzene/EtOH gave crystalline **9** with the melting point of the natural material[3]. When **4** was treated with $BH_3{\cdot}S(CH_3)_2$, the stable amine-borane adduct was isolated, which was converted to **6** by treatment with TMEDA[12]. Crude **6** was transformed to **8** as described for **5** and subsequently oxidized with $RuCl_3/NaIO_4$[13] to **10**. All attempts to oxidize **7** with $PtO_2/O_2$[14] directly to the N-Boc derivative of **11** were unsuccessful. To prevent overoxidation of **8** to the lactam of **10**, excess of $NaIO_4$ must be avoided. It turned out that 2 equivalents of $NaIO_4$ gave optimum yields of **10**. Finally **10** was deprotected with hydrochloric acid and **11** was isolated after ion exchange chromatography on Dowex 50Wx2.

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**Experimental**

General: Reactions with organometallic compounds and borane complexes were run in flame dried glassware under oxygen-free $N_2$. TLC: Merck precoated silica gel 60 F-254 plates. Reaction compounds were visualized by iodine vapor. Column chromatography was performed on silica gel 60. M.p.: Büchi 510 apparatus, values uncorrected. $[a]_D^{20}$: Perkin Elmer 241 polarimeter. IR-spectra: Perkin Elmer 681. $^1$H-NMR and $^{13}$C-NMR: Bruker AC 200. **(2R,5S)-2-Phenyl-3-oxa-1-aza-bicyclo[3.3.0]octane-8-one:** prepared according to ref.[6] from S-Pyroglutamic acid, $[\alpha]_D^{20} = +256$ (c = 0.225, $CHCl_3$) [ref.[6]: ent:- 252.2 (c = 1, $CHCl_3$)].

**(2R,5S)-2-Phenyl-3-oxa-1-aza-bicyclo[3.3.0]oct-6-ene-8-one (1):** Hexamethyldisilazane (2.9 g, 14 mmol) was dissolved in THF and 2 M BuLi (7 ml, 14 mmol) was added at -78°C. The mixture was stirred for 30 minutes at 0°C, cooled again to -78°C, and (2R,5S)-2-Phenyl-3-oxa-1-aza-bicyclo[3.3.0]octane-8-one (1.2 g, 6 mmol) in THF (10 ml) was added over a period of two minutes. After 30 min, PhSeCl (1.5 g, 7.5 mmol) in THF (15 ml) was added and the mixture was stirred. After 2 h. sat. ammonium chloride solution, water and ether (40 ml) were added. The organic layer was washed with $NH_4Cl$ solution (4x), brine (1x) and dried ($Na_2SO_4$). After filtration and evaporation of the solvent *in vacuo*, EtOAc (50 ml) and $H_2O_2$ (7 ml, 30%) were added while stirring at 0°C. The temperature was raised to 22°C after 5 min and after stirring for 40 min, the faint yellow solution was diluted with EtOAc and extracted with sat. $NaHCO_3$ solution until the water phase no longer showed a pale red colour (about 3 or 4 times). The organic layer was washed with brine (1x), dried ($Na_2SO_4$), filtered and evaporated. After standing overnight, the resulting yellow oil was chromatographed on silica gel with petroleum ether/EtOAc 1:2. Yield: 860 mg (72 %) pale yellow crystals. - $R_f$ = 0.38 (petroleum ether/EtOAc 1:2).- m.p.: 83°C (ligroin) [ref.[5]: 85°C].- IR (KBr): 3100, 3000, 2890, 1690 (C=O), 1500, 1450, 1330, 1230, 1210, 1160, 1050, 960, 950, 840, 820, 730, 700 $cm^{-1}$.- $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 3.42 (1 H, t, J = 8.3 Hz, 4-H), 4.23 (1 H, dd, $J_{4b-5} = 6.9$ Hz, $J_{gem} = 8.1$ Hz, 4-H), 4.58 (1 H, dddd, $J_{4a-5} = 8.4$ Hz, $J_{4b-5} = 6.9$ Hz, $J_{5-6} = 2$ Hz, $J_{5-7} = 1.5$ Hz, 5-H), 6.13 (1 H, dd, $J_{5-7} = 1.5$ Hz, $J_{6-7} = 5.8$ Hz, 7-H), 6.17 (1 H, s, 2-H), 7.24 (1 H, dd, $J_{5-6} = 2$ Hz, $J_{6-7} = 5.8$ Hz, 6-H), 7.38 (3 H, m, $H_{arom}$), 7.53 (2 H, m, $H_{arom}$).- $^{13}$C-NMR ($CDCl_3$): $\delta$ (ppm) = 65.1 (C-5), 68.1 (C-4), 87.4 (C-2), 126.2 ($C_{arom}$), 128.5 ($C_{arom}$), 128.7 ($C_{arom}$), 129.1 (C-7), 138.6 ($C_{arom}$), 147.9 (C-6), 177.0 (C-8).- $[\alpha]_D^{20} = +214$ (c = 0.275, $CHCl_3$). [ref.[5] **ent 1**: -215.6 (c = 1.05, $CHCl_3$). $C_{12}H_{11}NO_2$ (201.22) Calcd.: C 71.63 H 5.51 N 6.96 found: C 72.02 H 5.55 N 6.82.

**(2R,5R,6R,7R)-6,7-Epoxy-2-phenyl-3-oxa-1-aza-bicyclo[3.3.0]octane-8-one (2):** To a solution of 1 (3.01 g, 15 mmol) in DMF (15 ml) under $N_2$ was added tBuOOH (11 ml, 3M solution in isooctane, 33 mmol) and $K_2CO_3$ (2.2 g, 15.5 mmol). The mixture was stirred for 2 h, then $Bu_4NF$ (1 M solution in THF) was added in small portions, until tlc showed complete absence of starting material. The reaction was quenched with sat. ammonium chloride solution, diluted with $Et_2O$ and water (200 ml). The layers were separated and the water layer extracted with $Et_2O$ (4x). The combined organic extracts were washed with brine (1x), dried ($Na_2SO_4$),

filtered and evaporated. The pale yellow residue was chromatographed on silica gel with petroleum ether/EtOAc (1:2) to yield a colorless oil, which solidified on standing. A small sample was recrystallized from EtOAc/n-hexane to yield some single crystals for X-ray crystal analysis. Yield: 2.06 g (63%).- $R_f$ = 0.45, (petroleum ether/EtOAc 1:2).- m.p.: 93°C (EtOAc/petroleum ether 2+1).- IR (KBr): 3050, 2900, 1710 (C=O), 1490, 1450, 1400, 1360, 1250, 1220, 1160, 1080, 1040, 930, 850, 830, 770, 700 $cm^{-1}$.- $^1$H-NMR ($CDCl_3$): δ(ppm) = 3.52 (1 H, m, 4-H), 3.77 (1 H, d, J=2.46 Hz, 6-H), 4.02 (1 H, d, J=2.46 Hz, 7-H), 4.18 (2 H, m, 4-H und 5-H), 6.31 (1 H, s, 2-H), 7.34 (5 H, m, $H_{arom}$). - $^{13}$C-NMR ($CDCl_3$): δ (ppm) = 53.1 (C-6), 56.8 (C-7), 59.5 (C-5), 65.5 (C-4), 87.8 (C-2), 125.7 ($C_{arom}$), 128.3 ($C_{arom}$), 128.6 ($C_{arom}$), 138.0 ($C_{arom}$), 174.3 (C-8).- $[\alpha]_D^{20} = +240$ (c=0.185, $CHCl_3$). $C_{12}H_{11}NO_3$ (217.22). Calcd.: C 66.35 H 5.10 N 6.45 found: C 66.76 H 5.18 N 6.40.

**X-ray Crystal Structure Analysis of 2:** Data collection was carried out on a Siemens-diffractometer R3m/V, radiation CuKα (λ=1.54178Å) at 300 K. 815 reflections were collected, observed reflections: 748 (F>4.0σ (F)). The data were corrected for absorption. The structure was solved by the program SHELXTL PLUS[15] (PC-version) using direct methods. The H-atoms were calculated from the carbon positions and the structure refined to R=0.0485 (Full-Matrix Least-Squares)[16]. Crystal dimensions: 0.80 x 0.10 x 0.40 mm. Crystal system: monocline b; Space group $P2_1$; Unit Cell dimensions: a=6.3700(10) Å, b=8.965(2) Å, c=9.385(2) Å, β=81.84(3)°; Volume=530.5(2) Å$^3$; Z=2, density (calc): 1.360 Mg·m$^{-3}$, Absorption Coefficient 0.777 $mm^{-1}$, F(000): 228.

**(2R,5R,6S)-6-Hydroxy-2-phenyl-3-oxa-1-aza-bicyclo[3.3.0]octane-8-one (3):** Preparation of aluminum amalgam: 2 g aluminum foil were cut into small pieces and washed with pentane (2x), acetone (2x) and EtOH (2x). NaOH-solution (2%, 50 ml) was added until evolution of $H_2$ commenced. The NaOH solution was decanted and the aluminum was washed quickly with water (3x). $HgCl_2$-solution (0.5%, 40 ml) was added and after standing for 2-3 min, the solution was decanted and the amalgam was washed with water (4x) and EtOH (2x). The reagent has to be used immediately!, Reductive opening of epoxide 2: To a solution of 2 (217 mg, 1 mmol) in EtOH/ acetone 2:1 (50 ml) was added 1.5 g aluminum amalgam and half sat. $NaHCO_3$-solution (0.2 ml). The mixture was stirred for 2 h (TLC-control), diluted with $CHCl_3$ (100 ml) and the solids were filtered off. The solids were washed carefully with $CHCl_3$/EtOH, and the volatiles were evaporated. The residue was recrystallized from $CHCl_3$/petroleum ether.- Yield: 173 mg (79%) colorless plates.- $R_f$ = 0.25, EtOAc/petroleum ether (2:1).- m.p.: 128°C ($CHCl_3$/ petroleum ether).- IR (KBr): 3390 (O-H), 2960, 2900, 1670 (C=O), 1500, 1450, 1420, 1400, 1340, 1260, 1210, 1100, 1080, 1040, 930, 880, 840, 740, 690 $cm^{-1}$.- $^1$H-NMR ($CDCl_3$): δ (ppm) = 2.81 (2 H, d, $J_{6-7}$=7.8 Hz, 7-H), 3.02 (1 H, d, $J_{6-OH}$=4.5 Hz, OH), 3.64 (1 H, dd, $J_{4a-5}$=7.0 Hz, $J_{gem}$=8.4 Hz, 4-H), 3.99 (1 H, dt, $J_{4a-5} \approx J_{4b-5}$ =6.8 Hz, $J_{5-6}$=4.55 Hz, 5-H), 4.21 (1 H, dd, $J_{4b-5}$=6.7 Hz, $J_{gem}$=8.4 Hz, 4-H), 4.40 (1 H, m, 6-H), 6.33 (1 H, s, 2-H), 7.37 (5 H, m, $H_{arom.}$).- $^{13}$C-NMR ($CDCl_3$): δ (ppm) = 43.4 (C-7), 67.0 (C-5), 69.3 (C-4), 70.9 (C-6), 87.4 (C-2), 126.0 ($C_{arom}$), 128.5 ($C_{arom}$), 128.7

($C_{arom}$), 138.0 ($C_{arom}$), 176.0 (C-8).- $[\alpha]_D^{20}$ = +228 (c = 0.204, $CHCl_3$). $C_{12}H_{13}NO_3$ (219.24) Calcd.: C 65.74 H 5.98 N 6.39 found: C 66.06 H 6.20 N 6.36

**(2R,3S)-1-Benzyl-2-hydroxymethylpyrrolidine-3-ol (5):** To a solution of 3 (440 mg, 2 mmol) in dry THF (40 ml) $BH_3 \cdot SMe_2$ (1 M in THF, 8 ml, 8 mmol) was added. After stirring for 2 h at 70°C water was added and the mixture was acidified with 2 M HCl. After evaporation of THF *in vacuo* 5 M HCl (5 ml) was added to the solution and the mixture was refluxed for 5 min to destroy the borane-amine complex. After cooling, the solution was washed with $Et_2O$ (3x 10 ml), then the pH was adjusted with 40% NaOH-solution. The alkaline solution was extracted with $CH_2Cl_2$ (4x25 ml), the collected extracts were dried ($Na_2SO_4$), filtered and the solvents were evaporated.- Yield: 385 mg (92%), colorless oil. - $R_f$ = 0.2, EtOAc/MeOH (9:1). - IR (neat): 3400 (O-H), 3020, 2930, 1600, 1500, 1450, 1370, 1210, 1080, 1030, 750, 700 $cm^{-1}$. - $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 1.67 (1 H, ddt, $J_{3\text{-}4a} \approx J_{4a\text{-}5a} = 2.1$ Hz, $J_{4a\text{-}5b} = 6.9$ Hz, $J_{gem} = 13.3$ Hz, 4a-H), 1.93 (1 H, dddd, $J_{3\text{-}4b} = 6.8$ Hz, $J_{4b\text{-}5a} = 7.3$ Hz, $J_{4b\text{-}5b} = 10.7$ Hz, $J_{gem} = 13.3$ Hz, 4b-H), 2.60 (2 H, m, 2_H und 5b-H), 2.83 (1 H, s broad, OH), 2.93 (1 H, ddd, $J_{4a\text{-}5a} = 2.0$ Hz, $J_{4b\text{-}5a} = 7.4$ Hz, $J_{gem} = 9.2$ Hz, 5a-H), 3.48 (1 H, d, $J_{AB} = 12.9$ Hz, H-Bzl), 3.57 (1 H, dd, $J_{2\text{-}6a} = 3.8$ Hz, $J_{gem} = 11.2$ Hz, 6-H), 3.63 (1 H, dd, $J_{2\text{-}6b} = 2.8$ Hz, $J_{gem} = 11.2$ Hz, 6-H), 3.94 (1 H, d, $J_{AB} = 12.9$ Hz, H-Bzl), 4.28 (1 H, dt, $J_{3\text{-}4a} \approx J_{2\text{-}3} = 2.6$ Hz, $J_{3\text{-}4b} = 6$ Hz, 3-H), 7.29 (5 H, m, $H_{arom}$). - legend for hydrogen: 4a = proS ; 4b = proR ; 5a = proS ; 5b = proR. - $^{13}$C-NMR ($CDCl_3$): $\delta$ (ppm) = 33.7 (C-4), 51.9 (C-5), 58.8 (C-2), 60.7 (C-6), 73.4 ($\underline{C}H_2$-Bzl), 74.9 (C-3), 127.2 ($C_{arom}$), 128.4 ($C_{arom}$), 128.7 ($C_{arom}$), 138.8 ($C_{arom}$).- $[\alpha]_D^{20} = -43$ (c = 0.116, $CHCl_3$). $C_{12}H_{17}NO_2$ (207.27).

**(2R,3S)-1-tert.Butoxycarbonyl-2-hydroxymethylpyrrolidine-3-ol (7):** To a solution of 5 (830 mg, 4 mmol) in MeOH (20 ml), $Boc_2O$ (910 mg, 4.2 mmol) and Pd-C 10% (80 mg) were added and the mixture was hydrogenated at room temperature at 20 bar for 2-3 h. The catalyst was filtered off and the solvent was evaporated to yield a green-brown oil, which was chromatographed on silica gel with EtOAc/MeOH (4:1). The resulting colorless oil was triturated with EtOAc and diisopropylether and crystallized. After standing 2 h at 0°C the crystals were collected. Yield: 616 mg (71%).- $R_f$ = 0.7, EtOAc/MeOH (4:1).- m.p.: 121°C.- IR (KBr): 3430 (O-H), 3300 (O-H), 2980, 2950, 1660 1470, 1420, 1370, 1320, 1250, 1180, 1130, 1110, 1070, 1050, 1000, 980, 920, 900, 870, 770 $cm^{-1}$. - $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 1.46 (9 H, s, tBu), 1.9 (2 H, m, 4-H), 3.33-3.78 (6 H, m, 2-H, 3-H, 5-H and 6-H), 4.21 (1 H, s broad, OH), 4.62 (1 H, s broad, OH).- $^{13}$C-NMR ($CDCl_3$): $\delta$(ppm) = 28.5 ($C(\underline{C}H_3)_3$), 31.9 (C-4), 45.0 (C-5), 64.1 (C-2), 68.0 (C-6), 72.9 (C-3), 80.3 ($\underline{C}(CH_3)_3$), 156.4 (urethane). - $[\alpha]_D^{20} = -34.3$ (c = 0.21, $CHCl_3$). $C_{10}H_{19}NO_4$ (217.26) Calcd.: C 55.28 H 8.81 N 6.45 found: C 54.96 H 8.97 N 6.21

**(2R,3S)-2-Hydroxymethyl-pyrrolidine-3-ol-hydrochloride (9):** A solution of 7 (72 mg, 0.33 mmol) in acetone (3 ml) and 5 M HCl (10 ml) was stirred for 2 h at 60°C. The solvents were evaporated, the residue was dissolved in water (5 ml) and lyophilized to yield a colorless oil.

This was dissolved in EtOH (3 ml) and benzene (2 ml) and the solvents were distilled off to remove the water. The residue was treated with EtOH (1.5 ml) and EtOAc was added dropwise until the mixture became slightly cloudy. After standing for some days at -30°C colorless crystals separated. Yield: 32 mg (63%).- m.p.: 120°C (EtOH/EtOAc) [ref.[3]: 108°-112°C].- IR (KBr): 3300 (O-H), 3100 (O-H), 2940, 2800-2450 ($NH_2^+$), 1550 ($NH_2^+$), 1450, 1400 (O-H), 1330, 1120, 1070, 1030, 990, 940, 860, 700 $cm^{-1}$.- $^1$H-NMR ($D_2O/d_4$-methanol): $\delta$ (ppm) = 2.02 (1 H, dddd, $J_{3\text{-}4a}$ = 4 Hz, $J_{4a\text{-}5a}$ = 5.7 Hz, $J_{4a\text{-}5b}$ = 7.3 Hz, $J_{gem}$ = 14 Hz, 4-H), 2.26 (1 H, dddd, $J_{3\text{-}4b}$ = 5.9 Hz, $J_{4b\text{-}5a}$ = 8.5 Hz, $J_{4b\text{-}5b}$ = 8.2 Hz, $J_{gem}$ = 14 Hz, 4-H), 3.48 (2 H, m, 5-H), 3.58 (1 H, m, 2-H), 3.71 (1 H, dd, $J_{2\text{-}6a}$ = 7.1 Hz, $J_{gem}$ = 12 Hz, 6-H), 3.88 (1 H, dd, $J_{2\text{-}6b}$ = 4.3 Hz, $J_{gem}$ = 12 Hz, 6-H), 4.36 (1H, dt, $J_{3\text{-}4b}$ = 5.9 Hz, $J_{2\text{-}3} \approx J_{3\text{-}4a}$ = 3.9 Hz, 3-H). - $^{13}$C-NMR ($D_2O/d_4$-methanol): $\delta$ (ppm) = 33.1 (C-4), 45.0 (C-5), 59.6 (C-2), 68.4 (C-6), 72.0 (C-3). - $[\alpha]_D^{20} = +45.7$ (c = 0.21, $H_2O$) [ref.[3]: +46.5 ($H_2O$)]. $C_5H_{12}NO_2Cl$ (153.61) Calcd.: C 39.10 H 7.87 N 9.12 found: C 38.78 H 7.85 N 8.92

**(2R,5R,6S)-6-tert.Butyldimethylsilyloxy-3-oxa-2-phenyl-1-azabicyclo[3.3.0]octane-8-one (4):** To 3 (440 mg, 2 mmol) in dry DMF (10 ml), imidazole (340 mg, 5 mmol) and tert.butyldimethylchlorsilane (380 mg, 2.5 mmol) were added. After stirring for 6 h at 40°C dry MeOH (5 ml) was added and the mixture was stirred for 1 h. $Et_2O$ (100 ml) and sat. ammonium chloride solution were added. The organic layer was washed with water (1x), 0.1 M HCl (1x), water (1x) and brine, dried ($Na_2SO_4$), filtered and evaporated. The residue was chromatographed on silica gel with EtOAc/petroleum ether (1:4) to yield a colorless oil, which solidified on standing. Yield: 490 mg (74%).- $R_f$ = 0.55, EtOAc/petroleum ether (1:4).- m.p.: 68°C.- IR (KBr): 3080, 2960, 2940, 2860, 1720 (C=O), 1500, 1470, 1460, 1360, 1250, 1160, 1050, 1030, 905, 840, 780, 700 $cm^{-1}$.- $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 0.07 (6 H, s, $SiCH_3$), 0.88 (9 H, s, tBu), 2.75 (1 H, dd, $J_{6\text{-}7a}$ = 8.0 Hz, $J_{gem}$ = 15.9 Hz, 7-H), 2.85 (1 H, dd, $J_{6\text{-}7b}$ = 8.3 Hz, $J_{gem}$ = 15.9 Hz, 7-H), 3.69 (1 H, dd, $J_{4a\text{-}5} \approx 6.3$ Hz, $J_{gem}$ = 8.4 Hz, 4-H), 3.98 (1 H, dt, $J_{4a\text{-}5} \approx J_{4b\text{-}5}$ = 6.4 Hz, $J_{5\text{-}6}$ = 5.1 Hz, 5-H), 4.20 (1 H, dd, $J_{4b\text{-}5}$ = 6.7 Hz, $J_{gem}$ = 8.4 Hz, 4-H), 4.36 (1 H, dt, $J_{5\text{-}6}$ = 5.1 Hz, $J_{6\text{-}7a} \approx J_{6\text{-}7b}$ = 8.2 Hz, 6-H), 6.37 (1 H, s, 2-H), 7.37 (5 H, m, $H_{arom}$).- $^{13}$C-NMR ($CDCl_3$): $\delta$ (ppm) = -4.9 ($SiCH_3$), -4.8 ($SiCH_3$), 17.9 ($SiC(CH_3)_3$), 25.6 ($SiC(\underline{C}H_3)_3$), 44.0 (C-7), 67.2 (C-5), 69.6 (C-4), 72.7 (C-6), 87.2 (C-2), 126.0 ($C_{arom}$), 128.4 ($C_{arom}$), 128.6 ($C_{arom}$), 138.0 ($C_{arom}$), 175.3 (C=O).- $[\alpha]_D^{20} = +157$ (c = 0.274, $CHCl_3$). $C_{18}H_{27}NO_3Si$ (333.50) Calcd.: C 64.83 H 8.16 N 4.20 found: C 65.07 H 8.48 N 4.15

**(2R,3S)-1-Benzyl-3-tert.butyldimethylsilyloxy-2-hydroxymethylpyrrolidine (6):** To a solution of 4 (330 mg, 1 mmol) in dry THF (20 ml) was added. $BH_3{\cdot}SMe_2$ (1M in THF), (3 ml, 3 mmol). After stirring for 2 h at 70°C the mixture was cooled and $Et_2O$ (100 ml) and sat. ammonium chloride solution were added. The organic layer was washed with 1 M HCl (2x), $H_2O$ (2x), sat. $NaHCO_3$-solution (2x) and brine (1x). After drying ($Na_2SO_4$), filtration and evaporation of the solvent, the residue was dissolved in $Et_2O$ (10 ml) and TMEDA (59 mg, 0.5 mmol). The mixture was stirred for 6 h at ambient temperature. Then the suspension was centrifugated

and the precipitate was washed with $Et_2O$ (2 x 10 ml). The combined ethereal solutions were evaporated, The semisolid residue was treated with $Et_2O$/pentane (1:5). After standing for 20 min the solid was filtered off and washed carefully. The filtrates were evaporated, and if solid remained, it was treated again with $Et_2O$/pentane to remove the TMEDA-borane complex completely. After evaporation of the solvents the resulting colorless oil was chromatographed on silica gel with EtOAc/petroleum ether (4:1).- Yield: 228 mg (71%).- $R_f$=0.5, EtOAc/petroleum ether (4:1).- IR (neat): 3450 (O-H), 3080, 3040, 2930, 2860, 1600, 1500, 1470, 1450, 1370, 1250, 1220, 1100, 1050, 930, 870, 840, 770, 700 $cm^{-1}$.- $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 1.64 (1 H, ddt, $J_{3\text{-}4a} \approx J_{4a\text{-}5a}$=2.5 Hz, $J_{4a\text{-}5b}$= 7.0 Hz, $J_{gem}$=12.9 Hz, 4a-H), 1.86 (1 H, dddd, $J_{3\text{-}4b}$=6.4 Hz, $J_{4b\text{-}5a}$=7.2 Hz, $J_{4b\text{-}5b}$=10.2 Hz, $J_{gem}$=12.9 Hz, 4b-H), 2.61 (3 H, m, 2 H und 5b-H, OH), 2.92 (1 H, ddd, $J_{4a\text{-}5a}$=2.2 Hz, $J_{4b\text{-}5a}$= 7.5 Hz, $J_{gem}$=8.7 Hz, 5a-H), 3.47 (1 H, d, $J_{AB}$=13.0 Hz, H-Bzl), 3.54 (1 H, dd, $J_{2\text{-}6a}$ =2.1 Hz, $J_{gem}$=11.1 Hz, 6-H), 3.62 (1 H, dd, $J_{2\text{-}6b}$=3.5 Hz, $J_{gem}$= 11.1 Hz, 6-H), 3.94 (1 H, d, $J_{AB}$= 13.0 Hz, H-Bzl), 4.25 (1 H, quin, $J_{2\text{-}3} \approx J_{3\text{-}4a}$=3.2 Hz, $J_{3\text{-}4b}$=6.3 Hz, 3-H), 7.29 (5 H, m, $H_{arom}$) legend for hydrogen: 4a = proS ; 4b = proR ; 5a = proS ; 5b = proR.- $^{13}$C-NMR ($CDCl_3$): $\delta$ (ppm) = -4.7 ($SiCH_3$), -4.6 ($SiCH_3$), 18.0 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 34.2 (C-4), 52.1 (C-5), 58.9 (C-2), 59.9 (C-6), 73.9 ($CH_2$-Bzl), 75.1 (C-3), 127.1 ($C_{arom}$), 128.4 ($C_{arom}$), 128.7 ($C_{arom}$), 139.1 ($C_{arom}$).- $[\alpha]_D^{20}$=-12.5 (c=0.266, $CHCl_3$). $C_{18}H_{31}NO_2Si$ (321.53) Calcd.: C 67.24 H 9.72 N 4.36 found: C 67.40 H: 9.78 N 4.28

**(2R,3S)-1-tert.Butoxycarbonyl-3-tert.butyldimethylsilyloxy-2-hydroxymethyl-pyrrolidine (8):** To a solution of **6** (350 mg, 1.09 mmol) in MeOH (20 ml) were added $Boc_2O$ (265 mg, 1.2 mmol) and Pd/C 10% (40 mg) and the mixture was hydrogenated at ambient temperature and 20 bar pressure for 2-3 h. The catalyst was filtered off and the solvents were evaporated. The residue was chromatographed on silica gel with EtOAc/petroleum ether (4:1). The resulting colorless oil was dissolved in $Et_2O$ (20 ml) and unreacted $Boc_2O$ was destroyed by stirring with conc. $NH_4OH$ solution (5 ml), The organic layer was washed with sat. ammonium chloride solution, brine, dried ($Na_2SO_4$), filtered and evaporated.- Yield: 290 mg (80%).- $R_f$=0.7, EtOAc/petroleum ether (4:1).- IR (neat): 3450 (O-H), 2960, 2940, 2860, 1700, 1670, 1470, 1410, 1370, 1250, 1180, 1110, 1040, 910, 840, 770 $cm^{-1}$.- $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 0.07 ($SiCH_3$), 0.08 ($SiCH_3$), 0.88 (9 H, s, tBuSi), 1.47 (9 H, s, tBuO), 1.77 (1 H, m, 4-H), 1.93 (1 H, dddd, $J_{4b\text{-}5a}$=4.8 Hz, $J_{4b\text{-}5b}$=8.0 Hz, $J_{3\text{-}4b}$=8.2 Hz, $J_{gem}$=12.7 Hz, 4-H), 3.20 (1 H, s breit, OH), 3.35 (1 H, ddd, $J_{4b\text{-}5a}$=4.6 Hz, $J_{4a\text{-}5a}$=7.8 Hz, $J_{gem}$=10.6 Hz, 5-H), 3.55 (2 H, m, 5-H und 6-H), 3.68 (2 H, m, 2-H und 6-H), 4.08 (1 H, m, 3-H).- $^{13}$C-NMR ($CDCl_3$): $\delta$ (ppm) = -4.8 ($SiCH_3$), -4.7 ($SiCH_3$), 17.9 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 28.4 ($OC(CH_3)_3$), 33.0 (C-4), 45.1 (C-5), 64.7 (C-2), 68.3 (C-6), 73.8 (C-3), 80.1 ($OC(CH_3)_3$), 157.8 (urethane).- $[\alpha]_D^{20}$=-8.5 (c=0.2, $CHCl_3$). $C_{16}H_{33}NO_4Si$ (331.53) Calcd.: C 57.97 H 10.03 N 4.22 found: C 57.96 H 10.38 N 4.17

**(2S,3S)-1-tert.Butoxycarbonyl-3-tert.butyldimethylsilyloxypyrrolidine-2-carboxylic acid (10):** To **8** (170 mg, 0.51 mmol) in MeCN (4 ml) and $CCl_4$ (2 ml) were added $H_2O$ (3 ml) and $NaIO_4$

(216 mg, 1.01 mmol). To this solution $RuCl_3 \cdot H_2O$ (2 mg, 0.01 mmol) was added and the mixture was stirred for 1.5 h at ambient temperature. EtOAc (10 ml) and half saturated ammonium chloride solution were added and the water layer was extracted with EtOAc (3 x 10 ml). The combined extracts were washed with sat. ammonium chloride solution, dried ($Na_2SO_4$) and evaporated. The residue was dissolved in $Et_2O$ (10 ml) and extracted with half sat. $NaHCO_3$ solution. The combined solutions were acidified with 1 M HCl (pH ~ 2) and extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered and evaporated to yield a colorless oil.- Yield: 90 mg (51%).- $R_f = 0.2$, petroleum ether/EtOAc (1:2).- IR (neat): 3300-3000 (COOH), 2960, 2940, 2860, 2600, 1750, 1710, 1670, 1480, 1410, 1370, 1250, 1170, 1100, 1060, 1025, 920, 840, 780 $cm^{-1}$.- $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 0.10 ($SiCH_3$), 0.11 ($SiCH_3$), 0.89 (9 H, s, tBuSi), 1.43/ 1.49 (9 H, "s", tBuO), 1.83 (1 H, m, 4-H), 2.03 (1 H, m, 4-H), 3.57 (2 H, m, 5-H), 4.07/4.19 (1 H, "s", 2-H), 4.45/4.61 (1 H, "m", 3-H), 7.6 (1 H, s broad, COOH)-conformers-.- $^{13}$C-NMR ($CDCl_3$): $\delta$ (ppm) = -5.0 ($SiCH_3$), 17.9 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 33.1/33.6 (C-4), 44.4/45.1 (C-5), 68.2 (C-2), 74.3/76.0 (C-3), 80.4/81.0 ($OC(CH_3)_3$), 154.1/156.0 (urethane), 174.0/176.3 (COOH) -conformers.- $[\alpha]_D^{20} = +18$ (c = 0.23, EtOAc). - $C_{16}H_{31}NO_5Si$ (345.51)

**(2S,3S)-3-Hydroxyproline (11):** A solution of **10** (86 mg, 0.25 mmol) in 6 M HCl (10 ml) was refluxed for 3 h. After cooling, water (10 ml) was added and the solution was extracted with $Et_2O$ (2 x 5 ml). The water was removed *in vacuo* and the residue was dissolved in water (2 ml) and purified by ion-exchange chromatography [Dowex 50Wx2, 200 ml $H_2O$, then 2 M $NH_3$ (150 ml)]. After evaporation of the solvent, the pale yellow powder was triturated with EtOAc and the colorless crystals were collected.- Yield: 23 mg (70%).- m.p.: 232°C (decomp.) [ref.[4a]: 220°-230°C].- IR(KBr): 3250, 3080, 2900-2400, 1630, 1580, 1470, 1410, 1380, 1340, 1290, 1230, 1110, 1015, 970, 870 $cm^{-1}$.- $^1$H-NMR ($D_2O/d_6$-Aceton): $\delta$ (ppm) = 1.92 (2 H, m, 4-H), 3.41 (2 H, m, 5-H), 3.94 (1 H, s, 2-H), 4.55 (1 H, m, 3-H). - $^{13}$C-NMR ($D_2O/d_6$-Aceton): $\delta$(ppm) = 31.8 (C-4), 44.8 (C-5), 69.2 (C-2), 74.1 (C-3), 171.7 (COOH).- $[\alpha]_D^{20} = -18.8$ (c = 0.14, $H_2O$) [ref.[4c] (ent-**11**): $[\alpha]_D^{25} = +18.1$ (c = 1, $H_2O$)]. $C_5H_9NO_3$ (131.13) Calcd.: C 45.80 H 6.92 N 10.68 found: C 41.57 H 6.47 N 9.23.

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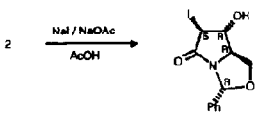


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