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Synthesis of Homochiral R-Baclofen from S-Glutamic Acid.[1]

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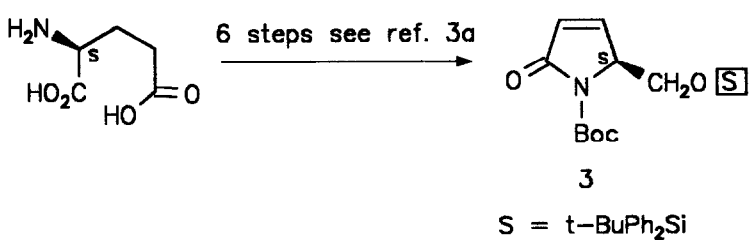
Abstract: A stereoselective synthesis of **R-Baclofen** is presented, starting from S-pyroglutamic acid derivative **3.** The key steps are the 1,4-conjugate addition of Grignard cuprate $(p\text{-ClPh})_2CuMgCl$ to **3** and Barton-Decarboxylation of **6e** to **7e.**

R-Baclofen, a derivative of the inhibitory neurotransmitter GABA (γ-aminobutyric acid) is the most lipophilic substance in this class of compounds with high affinity to the $GABA_B$-receptor (IC_{50} = 0.13μ M)[2]. The racemic form, RS-Baclofen (Lioresal®), is used in the treatment of spasticity caused by disease of the spinal cord, particularly traumatic lesions. Since S-Baclofen shows low affinity to $GABA_B$-receptor site it is highly desirable to synthesize R-Baclofen in enantiopure form. Recently, a chemoenzymatic synthesis of R- and S-Baclofen has been reported[2d].

In the course of our work on the synthesis of nonproteinogenic amino acids[1], we explored the reactivity and stereoselectivity of the 1,4-conjugate addition reaction to the highly electrophilic double bond of the known pyroglutamic acid derivative **3.** The electron-withdrawing Boc group, attached to the amide nitrogen, activates the α, ß-unsaturated system toward the conjugate addition of Gilman cuprates[3]. We turned our attention to the addition of other organo-cuprates e. g. Grignard-cuprates, to broaden the synthetic utility of the pyroglutamic acid derivative **3,** with the view to synthesizing R-Baclofen and ß-alkylated or arylated glutamic acid derivatives via ring opening of **6a-f.**

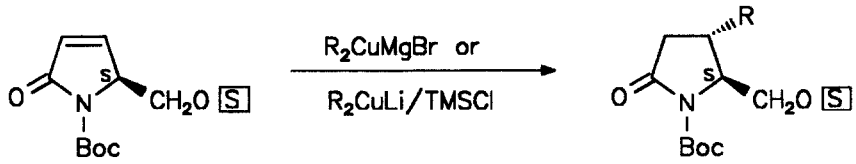


3

S = t–$BuPh_2Si$

It turned out that treatment of **3** with 5 equivalents of Gilman cuprates (R = CH_3, n-Bu, Ph) in the presence of trimethylsilyl chloride[4] furnished **4a, b, c** in excellent yield. **4d, e, f** were obtained via addition of Grignard cuprates (R = vinyl, p-Cl-Ph, allyl) in somewhat lower but satisfactory yields (60-70%). The cis isomers were not detected in the crude products by ^1H- and ^{13}C-NMR spectroscopy. Our initial efforts to add Grignard cuprates to an unsaturated bicyclic lactam, which was used by Hanessian

and Ratovelomanana in a similar reaction sequence[5] gave only traces of the desired compounds. Most of the starting material was recovered unchanged.

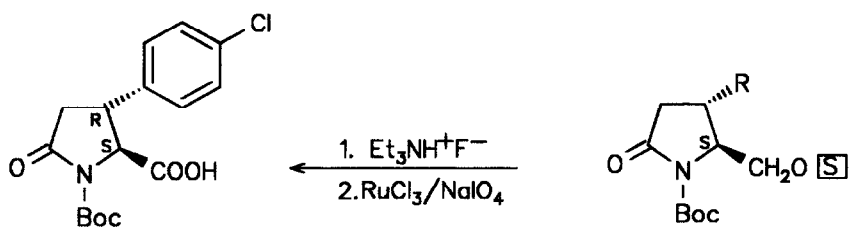


3

4a,b,c: R = CH_3, n–Bu, Ph
4d,e,f: R = vinyl, p–Cl–Ph
allyl

It is noteworthy that only a large excess of Gilman-or Grignard cuprates (5 equivalents) gave satisfactory yields of Michael addition products. This is in agreement with results of Hanessian and Tamm[6a,b] and with our findings with vinyl sulfones as substrates.[6c] Despite of the fact, that a large excess of reagent should open the γ-lactam[3b] no product of ring-opening could be detected. This can be rationalized that the amide enolate intermediate is quenched by trimethylsilyl chloride.

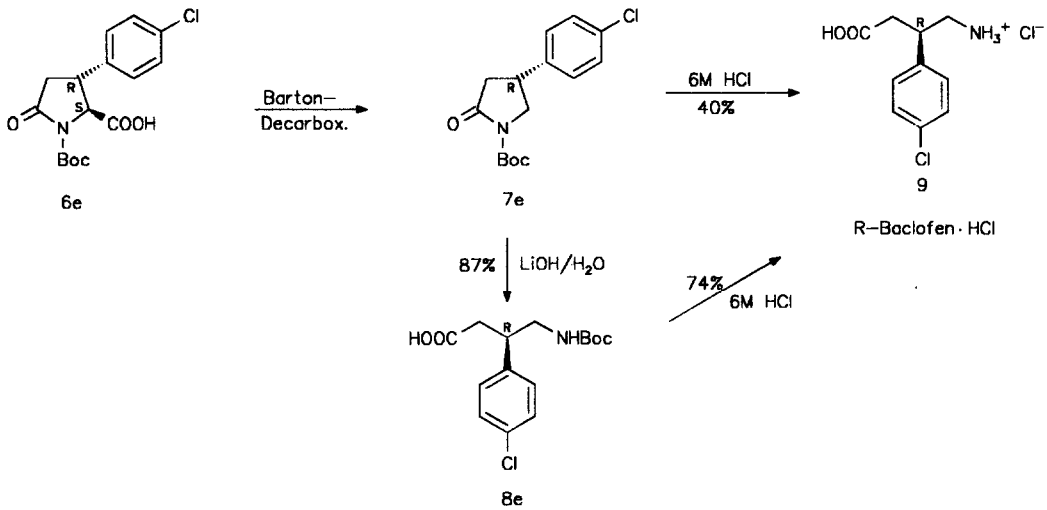
Selective deprotection of the OH-function without loss of the Boc-group was accomplished with triethylammonium fluoride[7] in THF. Despite the long reaction time (4 days), this reagent is highly selective. The usual deprotection with tetrabutyl-ammonium fluoride in THF gave only products of ring-opening, due to the high nucleophilicity of the fluoride ion. Oxidation of the primary alcohol back to the glutamic acid derivative in one step to **6e**, proved to be very successfull with the Sharpless procedure[8]. Thus oxidations of **5e** on larger scales with Cr^{VI} (e.g. PDC/DMF) could be avoided. **6e** was isolated by extractive workup without column chromatography as crystalline material.



6e

4e: R = p–Cl–Ph

Barton and coworkers described a decarboxylation procedure of N-protected α-amino acids and peptides, the stereochemical integrity of the rest of the molecule is preserved completely[9]. When this procedure was applied to **6e**, decarboxylation occurrred and the γ-aminobutyric acid derivative **7e** was isolated in 60-65% yield.



The cyclic Boc-derivative of R-Baclofen, namely **7e**, was transformed via two pathways to R-Baclofen hydrochloride. Ringopening of **7e** by Grieco's method with 1N LiOH/THF[10] furnished **8e** in 87% yield, which was treated with 6N hydrochloric acid to yield R-Baclofen·HCl in 74% yield. Alternatively, hydrolysis of the lactam **7e** yielded R-Baclofen hydrochloride in 40% yield only. The optical rotation of R-Baclofen·HCl, provided on both ways, is in accordance with material prepared from racemic compound via optical resolution[2e] and chemoenzymatic synthesis[2d].

In conclusion, this reaction sequence provides a facile access to **R-Baclofen** on a practical scale in 5 steps starting from **3** in an overall yield of 16 %. Furthermore L-glutamic- or L-pyroglutamic acid is an inexpensive starting material from the chiral pool of the amino acids.

Acknowledgement: We thank the Fonds der Chemischen Industrie for financial support and Degussa AG (Hanau-Wolfgang) for D- and L-glutamic acid.

Experimental

General: THF was distilled first from $LiAlH_4$ and then over sodium wire under N_2. Reactions with organometallic compounds were run in flame-dried glassware under dry and **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. $[\alpha]_D^{20}$: Perkin-Elmer 241 polarimeter. IR-spectra: Perkin-Elmer 681. ^{1}H-NMR and ^{13}C-NMR: Bruker AC 200.

5S-1-t-Butoxycarbonyl-5-t-butyldiphenylsiloxymethyl-1,5-dihydro-2H-pyrrol-2-one (3).

Hexamethyldisilazane (7.3 ml, 35mmol) was dissolved in THF (50ml), cooled to -78°C and treated with 2 M BuLi (17.5 ml, 35 mmol). After 5 min. the temp. was raised to 0°C for 30 min.. The mixture was then cooled to -78°C and 5S-1-Boc-5-t-butyldiphenylsiloxymethyl-pyrrolidine-2-one was added. After 30 min. phenylsenenyl chloride (3.54 g, 28.5 mmol) in THF (20 ml) was added and the mixture was stirred

for 2h. To the solution was added at -78°C sat. ammonium chloride solution and ether. The organic layer was washed with NH_4Cl solution (2x), brine (1x) and dried (Na_2SO_4). After filtration and evaporation of the solvent in vacuo , the orange colored oil was chromatographed on silica gel with petroleum ether/EtOAc 2:1. After concentration in vacuo, EtOAc (50 ml) and H_2O_2 (15 ml, 30%) were added with stirring over 45 min. The pale yellow solution was diluted with EtOAc and extracted with $NaHCO_3$ solution until the aqueous phase was colorless. The organic phase was dried (Na_2SO_4), filtered and evaporated. To the resultant oil diisopropyl ether was added and warmed. After the same volume of petroleum ether was added, 4.4 g colorless crystals separated with cooling. Another 0.45 g of material was collected from the mother liquor by the same procedure. Yield: 4.85 g (71%).- R_f = 0.56 (petroleum ether/EtOAc 2:1).- m.p. 96°C (diisopropyl ether/petroleum ether).- IR (KBr): 2900, 1725 (C=O urethane), 1690 (C=O lactam), 1450, 1420, 1360, 1340, 1310, 1145, 1110, 910, 795, 730, 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) =1.03 (9H, s, t-Bu-Si) 1.44 (9 H, s, t-Bu-O), 3.83 (1H, dd, J_{gem} = 9,7 Hz, $J_{5\text{-}6a}$ = 6,4 Hz, H-6), 4.12 (1 H, dd, J_{gem} = 9,7 Hz, $J_{5\text{-}6b}$ = 3,5 Hz, H-6), 4.64 (1 H, m, H-5), 6.17 (1 H, dd, $J_{3\text{-}4}$ = 6,13 Hz, $J_{3\text{-}5}$ = 1,5 Hz, H-3), 7.26 (1 H, dd, $J_{3\text{-}4}$ = 6,1 Hz, $J_{4\text{-}5}$ = 2,05 Hz, H-4), 7.38 (6 H, m, H-Ar), 7.60 (4 H, m, H-Ar) -^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.2 ($SiC(CH_3)_3$), 26.67 ($SiC(CH_3)_3$), 27.97 ($OC(CH_3)_3$), 62.93 (C-5), 63.42 (C-6), 82.65 ($OC(CH_3)_3$), 127.32 (C-3), 127.79 (C-Ar), 129.69 (C-4), 132.64 (C-Ar), 132.86 (C-Ar), 135.43 (C-Ar), 149.29 (C=O urethane), 169.48 (C-2).- $[\alpha]_D^{20}$ = -124 (c=0.23, $CHCl_3$).

$C_{26}H_{33}NO_4Si$ (451.64) Calcd.: C 69.14 H 7.36 N 3.10 found: C 69.61 H 7.70 N 3.09

4S,5S-1-t-Butoxycarbonyl-5-t-butyldiphenylsiloxymethyl-4-methylpyrrolidine-2-one (4a)

To $CuBr{\cdot}SMe_2$ (0.52 g, 2.5 mmol) in dry ether was added 1.6 M MeLi (3.12 ml, 5 mmol,) at -20°C with stirring. After 15 min. **3** (225 mg, 0.5 mmol) and trimethylsilyl chloride (0.1 ml, 1mmol) in THF (3ml) was added. The mixture was stirred for 1h at -78°C, then quenched with NH_4Cl solution and diluted with ether (20 ml). The organic layer was washed with NH_4Cl solution until the blue color of the water phase disappeared. After drying and evaporation of the organic phase the pale yellow oil was chromatographed on silica gel with EtOAc/petroleum ether 2:3. Trituration of the colorless oil with n-hexane provided white crystals. Yield: 190 mg (81%).- R_f = 0.3 (Et_2O/petroleum ether 2:3).- m.p. 85°C (EtOAc/hexane).-IR (KBr): 3080, 2950, 2860, 1790, 1750, 1715, 1590, 1470, 1430, 1370, 1310, 1160, 1110, 780, 700 cm^{-1}.- ^{1}H-NMR($CDCl_3$): δ (ppm) = 1.04 (9 H, s, t-Bu-Si), 1.14 (3 H, d, J=7,1 Hz, CH_3), 1.43 (9 H, s, t-Bu-O), 2.07 (1 H, dd, $J_{3a\text{-}4}$=1,8 Hz, J_{gem}=17,5 Hz, H-3), 2.44 (1 H, quin, J=7,2 Hz, H-4), 2.98 (1 H, dd, $J_{3b\text{-}4}$=8,6 Hz, J_{gem}= 17,5 Hz, H-3), 3.72 (2 H, m, H-5 , H6), 3.86 (1 H, m, H-6), 7.39 (6 H, m, H-Ar), 7.61 (4 H, m, H-Ar).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.2 ($SiC(CH_3)_3$), 21.44 (CH_3), 28.81 ($SiC(CH_3)_3$), 28.02 ($OC(CH_3)_3$), 28.26 (C-4), 40.47 (C-3), 64.23 (C-5), 66.21 (C-6), 82.72 ($OC(CH_3)_3$), 127.85 (C-Ar), 129.89 (C-Ar), 135.11 (C-Ar), 135.56 (C-Ar), 150.03 (urethane), 174.39 (lactam).- $[\alpha]_D^{20}$ = -33 (c=0.4,$CHCl_3$).

$C_{27}H_{37}NO_4Si$ (467.68) Calcd.: C 69.34 H 7.97 N 2.99 found: C 69.27 H 7.93 N 3.00

4S,5S-1-t-Butoxycarbonyl-4-butyl-5-t-butyldiphenylsiloxymethylpyrrolidine-2-one (4b)

The same procedure was applied as described for **4a**, but on double scale with 1.6 M BuLi (6.25 ml, 10 mmol). **4b** was isolated as a colorless oil. Yield: 484 mg (85%).- R_f = 0.5 (Et_2O/petroleum ether 2:3).-

IR (neat): 3080, 2950, 2860, 1790, 1750, 1710, 1590, 1470, 1430, 1370, 1310, 1150, 1110, 790, 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.90 (3 H, t, J = 6,5 Hz, CH_3-Bu), 1.04 (9 H, s, t-Bu-Si), 1.29 (6 H, m, CH_2-Bu), 1.44 (9 H, s, t-Bu-O), 2.16 (1 H, dd, $J_{3a\text{-}4}$ = 1,8 Hz, J_{gem} = 17,5 Hz, H-3), 2.26 (1 H, m, H-4), 2.91 (1 H, dd, $J_{3b\text{-}4}$ = 8,6 Hz, J_{gem} = 17,6 Hz, H-3), 3.69 (1 H, dd, $J_{6a\text{-}5}$ = 4,4 Hz, J_{gem} = 12,1 Hz, H-6), 3.83 (2 H, m, H-5 H-6), 7.39 (6 H, m, H-Ar), 7.62 (4 H, m, H-Ar).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 13.96 (CH_3-nBu), 19.18 ($SiC(CH_3)_3$), 22.51 (CH_2-nBu), 26.76 ($SiC(CH_3)_3$), 27.99 ($OC(CH_3)_3$), 29.00 (C-4), 33.28 (CH_2-nBu), 35.04 (CH_2-nBu), 38.66 (C-3), 64.48 (C-5), 64.54 (C-6), 82.74 ($OC(CH_3)_3$), 127.80 (C-Ar), 129.85 (C-Ar), 133.07 (C-Ar), 135.50 (C-Ar), 150.04 (urethane), 174.55 (lactam).- $[\alpha]_D^{20}$ = -31 (c = 0.22, $CHCl_3$).

$C_{30}H_{43}NO_4$ (509.76) Calcd.: C 70.69 H 8.50 N 2.75 found: C 70.63 H 8.74 N 2.71

4R,5S-1-t-Butoxycarbonyl-5-t-butyldiphenylsiloxymethyl-4-phenyl-pyrrolidine-2-one (4c)

The same procedure was applied as described for **4a**. 2 M PhLi (2.5 ml, 5 mmol) was used at -35°C. **4c** was isolated as colorless oil. Yield: 160 mg (60%).- R_f = 0.44 (Et_2O/petroleum ether 2:3).- IR (neat): 3080, 2950, 2860, 1790, 1750, 1715, 1610, 1590, 1430, 1370, 1310, 1150, 1110, 790, 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.09 (9 H, s, Si-t-Bu), 1.42 (9 H, s, O-t-Bu), 2.57 (1 H, dd, $J_{3a\text{-}4}$ = 2,63 Hz, J_{gem} = 17,8 Hz, H-3), 3.21 (1 H, dd, $J_{3b\text{-}4}$ = 9,6 Hz, J_{gem} = 17,8 Hz), 3.50 (1 H, dt, $J_{3a\text{-}4} \approx J_{4\text{-}5}$ = 2,3 Hz, $J_{3b\text{-}4}$ = 9,5 Hz, H-4), 3.81 (1 H, dd, $J_{6a\text{-}5}$ = 2,3 Hz, J_{gem} = 10,5 Hz, H-6), 3.98 (1 H, dd, $J_{6b\text{-}5}$ = 4,25 Hz, J_{gem} = 10,5 Hz, H-6), 4.12 (1 H, m, H-5), 7.32 (11 H, m, H-Ph and H-Ar-Si), 7.66 (4 H, m, H-Ar-Si).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.22 ($SiC(CH_3)_3$), 26.85 ($SiC(CH_3)_3$), 27.95 ($OC(CH_3)_3$), 38.68 (C-4), 39.91 (C-3), 64.22 (C-5), 66.62 (C-6), 83.04 ($OC(CH_3)_3$), 126.39 (C-Ar), 127.13 (C-Ar), 127.88 (C-Ar), 129.06 (C-Ar), 129.95 (C-Ar), 132.57 (C-Ar), 132.93 (C-Ar), 135.55 (C-Ar), 144.03 (C-Ar), 149.62 (urethane), 174.12 (lactam).- $[\alpha]_D^{20}$ = -27 (c = 0.23, $CHCl_3$).

$C_{32}H_{39}NO_4Si$ (529,75) Calcd.: C 72.55 H 7.42 N 2.64 found: C 72.67 H 7.64 N 2.51

4S,5S-1-t-Butoxycarbonyl-5-t-butyldiphenylsiloxymethyl-4-vinyl-pyrrolidine-2-one (4d)

The same procedure was applied as for **4a**, but with 1M vinylmagnesium bromide (5.0 ml, 5 mmol). The yellow oil was column chromatographed on SiO2 with Et_2O/petroleum ether 2:3. Yield: 150 mg (62%) colorless oil.- Rf = 0,38 (Et_2O/petroleum ether 2:3).-IR (neat): 3070, 2930, 2850, 1790, 1750, 1710, 1590, 1470, 1425, 1360, 1310, 1150, 1110, 970, 920, 870, 780, 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.05 (9 H, s, tBuSi), 1.43 (9 H, s, tBuO), 2.33 (1 H, dd, $J_{3a\text{-}4}$ = 6,3 Hz, J_{gem} = 20,9 Hz, H-3), 3.00 (2 H, m, $J_{3b\text{-}4}$ = 9 Hz, J_{gem} = 21 Hz, H-3 and H-4), 3.74 (1 H, dd, $J_{5\text{-}6a}$ = 3,65 Hz, J_{gem} = 11,8 Hz, H-6), 3.93 (1 H, m, $J_{5\text{-}6b}$ = 4,1 Hz, J_{gem} = 11,85 Hz, H-5 and H-6), 5.08 (2 H, m, $=CH_2$), 5.87 (1 H, ddd, J_{trans} = 17,4 Hz, J_{cis} = 10 Hz, $J_{4\text{-}Vinyl}$ = 7,4 Hz, -CH=), 7.41 (6 H, m, H-Ar), 7.63 (4 H, m, H-Ar).-^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.18 ($SiC(CH_3)_3$), 26.79 ($SiC(CH_3)_3$), 27.97 ($OC(CH_3)_3$), 37.03 (C-4), 37.92 (C-3), 63.93 (C-5), 64.35 (C-6), 82.88 ($OC(CH_3)_3$), 115.20 ($=CH_2$), 127.85 (C-Ar), 129.91 (C-Ar), 132.58 (C-Ar), 132.95 (C-Ar), 135.52 (C-Ar), 139.15 (-CH=), 149,74 (urethane), 173.80 (lactam).-$[\alpha]_D^{20}$ = -23 (c = 0.21/$CHCl_3$).

$C_{28}H_{37}NO_4Si$ (479.69) Calcd.: C 70.11 H 7.77 N 2.92 found: C 70.12 H 7.78 N 2.92

4R,5S-1-t-Butoxycarbonyl-5-t-butyldiphenylsiloxymethyl-4-(4-chlor-phenyl)pyrrolidine-2-one (4e)

To $CuBr \cdot SMe_2$ (3.28 g, 16 mmol) in dry ether (10 ml) was added 1M p-chloro-phenylmagnesium bromide (32 ml, 32 mmol) at -35°C. After 20 min. the mixture was cooled to -78°C. **3** (1.35g, 3mmol) and trimethylsilyl chloride (0.6 ml, 6 mmol) was added with stirring. The deep brown colored reaction mixture was then brought slowly to ambient temp. After 1h ammonium chloride solution and ether (100 ml) was added to the homogeneous suspension. The organic phase was washed with NH_4Cl solution until the aqueous layer remained colorless. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. Chlorobenzene was distilled off from the oily residue and the pale yellow liquid was column chromatographed on silica gel with Et_2O/petroleum ether 3:2. After evaporation of the solvent the oily residue was dissolved in ether and extracted with 0.1N NaOH (3x) to remove p-chlorophenol. The organic layer was dried (Na_2SO_4) and evaporated to leave a colorless viscous oil. Yield: 1.12g (66%).- R_f = 0.4 (Et_2O/petroleum ether 3:2).- IR (neat): 2930, 1790, 1750, 1710, 1500, 1430, 1370, 1310, 1150, 1110, 700 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.09 (9 H, s, t-Bu-Si), 1.42 (9 H, s, t-Bu-O), 2.53 (1 H, dd, J_{gem} = 17,8 Hz, J_{3a-4} = 2,5 Hz, H-3), 3.20 (1 H, dd, J_{gem} = 17,8 Hz, J_{3b-4} = 9,5 Hz, H-3), 3.48 (1 H, dt, J_{3b-4} = 9,5 Hz, $J_{3a-4} \approx J_{4-5}$ = 2,1 Hz, H-4), 3.80 (1 H, dd, J_{5-6a} = 2,3 Hz, J_{gem} = 10,43 Hz, H-6), 3.97 (1 H, dd, J_{5-6b} = 4,31 Hz, J_{gem} = 10,43 Hz, H-6), 4.05 (1 H, m, H-5), 7.08 (2 H, dd, J_{AB} = 8,4 Hz, H-Ar-p-Cl), 7.28 (2 H, dd, J_{AB} = 8,4 Hz, H-Ar-p-Cl), 7.40 (6 H, m, H-Ar-Si), 7.64 (4 H, m, H-Ar-Si).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.22 ($SiC(CH_3)_3$), 26.87 ($SiC(CH_3)_3$), 27.96 ($OC(CH_3)_3$), 38.16 (C-4), 39.71 (C-3), 64.14 (C-5), 66.51 (C-6), 83.21 ($OC(CH_3)_3$), 127.76 (C-Ar), 127.91 (C-Ar), 129.19 (C-Ar), 130.0 (C-Ar), 132.55 (C-Ar), 133.0 (C-Ar), 135.54 (C-Ar), 142.44 (C-Ar), 149.59 (C=O urethane), 173.54 (C=O lactam).- $[\alpha]_D^{20}$ = -26,5 (c = 0.226, $CHCl_3$).

$C_{32}H_{38}ClNO_4Si$ (564.19) Calcd.: C 68.12 H 6.79 N 2.48 found: C 67.90 H 6.97 N 2.40

4S,5S-4-Allyl-1-t-butoxycarbonyl-5-t-butyldiphenylsiloxymethyl pyrrolidine-2-one (4f)

The same procedure was applied as described for **4a** with 1M allylmagnesium bromide (5 ml, 5 mmol). **4f** was isolated as a colorless oil. Yield: 150 mg (60 %).- R_f = 0.3 (Et_2O/petroleum ether 2:3). IR (neat): 3040, 2940, 2860, 1790, 1750, 1715, 1650, 1590, 1470, 1430, 1370, 1310, 1150, 1110, 790, 760, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.03 (9 H, s, Si-t-Bu), 1.42 (9 H, s, O-t-Bu), 2.17 (3 H, m, H-3 and CH_2-Allyl), 2.36 (1 H, quin, J = 7,3 Hz, H-4), 2.91 (1 H, dd, J_{3-4} = 8,6 Hz, J_{gem} = 17,7 Hz, H-3), 3.67 (1 H, dd, J_{6a-5} = 4 Hz, J_{gem} = 11,9 Hz, H-6), 3.86 (2 H, m, H-5 and H-6), 5.05 (2 H, m, $=CH_2$), 5.70 (1 H, m, -CH=), 7.37 (6 H, m, H-Ar), 7.59 (4 H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.16 ($SiC(CH_3)_3$), 26.80 ($SiC(CH_3)_3$), 27.99 ($OC(CH_3)_3$), 32.78 (C-4), 38.11 (C-3), 39.38 (CH_2-Allyl), 63.72 (C-5), 64.61 (C-6), 82.72 ($OC(CH_3)_3$), 117.88 (=CH-), 127.81 (C-Ar), 129.86 (C-Ar), 132.68 (C-Ar), 113.05 (C-Ar), 134.71 (C-Ar), 135.51 ($=CH_2$), 149.90 (urethane), 174.10 (lactam). $[\alpha]_D^{20}$ = -32,7 (c = 0,22/$CHCl_3$).

$C_{29}H_{39}NO_4Si$ (493.72) Calcd.: C 70.55 H 7.96 N 2.84 found: C 70.91 H 8.27 N 2.60

4R,5S-1-t-Butoxycarbonyl-4-(4-chlorophenyl)-5-hydroxymethyl-pyrrolidine-2-one (5e)

To **4e** (1.12 g, 2 mmol) in THF (30 ml) was added triethylammonium fluoride[7] (0.98 g, 8 mmol). The mixture was stirred for 4-5 days at ambient temperature until the reaction was complete (TLC !). The mixture was diluted with ethyl acetate (30 ml) and extracted with NH_4Cl solution (3x). The combined

NH_4Cl extracts were extracted (2x) with EtOAc (10 ml). The combined EtOAc extracts were dried (Na_2SO_4) and evaporated in vacuo. Column chromatography on silica gel (EtOAc/petroleum ether 2:1) provided after evaporation of the eluant a colorless oil which crystallized upon standing. This crude material is pure enough for the next reaction step. Yield: 0.4 g (62%) colorless crystals, m.p. 137°C (EtOAc/hexane).- R_f = 0.37 (EtOAc/petroleum ether).- IR (KBr): 3400 (O-H), 2980-2940, 1790 (C=O), 1500, 1370, 1310, 1170, 1080, 1015, 770 cm^{-1}.-^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.53 (9 H, s, t-Bu), 2.53 (1 H, dd, J_{3a-4} = 3,91 Hz, J_{gem} = 17,8 Hz, H-3), 2.93 (1 H, t, J =5,31 Hz, O-H), 3.14 (1 H, dd, J_{3b-4} = 9,33 Hz, J_{gem} = 17,8 Hz, H-3), 3.43 (1 H, dt, J_{3a-4} J_{4-5} =3,7 Hz, J_{3b-4} = 9,2 Hz, H-4), 3.80 (1 H, m, H-6), 3.96 (1 H, m, H-6), 4.08 (1 H, q, J = 3,4 Hz, H-5), 7.15 (2 H, d, J_{AB} = 8,5 Hz, H-Ar), 7.31 (2 H, d, J_{AB} = 8,5 Hz, H-Ar).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 27.99 (C($\underline{C}H_3)_3$), 38.07(C-4), 39.72 (C-3), 63.41 (C-5), 66.91 (C-6), 83.79 ($\underline{C}(CH_3)_3$), 127.95 (C-Ar), 129.21 (C-Ar), 133.08 (C-Ar), 141.54 (C-Ar), 150.35 (urethane), 173.73 (lactam).- $[\alpha]_D^{20}$ = - 43 (c=0.073, $CHCl_3$).
$C_{16}H_{20}ClNO_4$ (325.79) Calcd.: C 58.98 H 6.19 N 4.30 found: C 58.69 H 6.02 N 4.30.

2S,3R-1-t-Butoxycarbonyl-3-(4-chlorophenyl)-5-oxo-pyrrolidine-2-carboxylic acid (6e)

5e (0.60 g, 1.85 mmol) was dissolved in a mixture of acetonitrile (8 ml) and CCl_4 (4 ml). To this solution were added $NaIO_4$ (1.1 g, 5.8 mmol), H_2O (6 ml) and $RuCl_3 \cdot H_2O$ (9 mg, 2.2 mol%). The mixture was stirred for 1.5 h, then diluted with CH_2Cl_2, NH_4Cl solution and 2N HCl and extracted with CH_2Cl_2 (3x). The combined organic phases were dried (Na_2SO_4), filtered and extracted with $NaHCO_3$ solution (4x). After acidification of the combined $NaHCO_3$ solutions with 2N HCl (pH 1-2) the aqueous layer was extracted with CH_2Cl_2 (4x). The combined organic phases were dried and evaporated. 450 mg of **6e** were obtained as colorless crystals from $CHCl_3$/petroleum ether. Another 50 mg were isolated from the mother liquor. Combined yield: 500 mg (80%).- m.p. 141°C.- R_f = 0.15 (EtOAc/CH_2Cl_2/AcOH 8:2:1).- IR (KBr): 3200 (broad, O-H), 2970, 1795 (C=O), 1770 (C=O), 1730 (C=O), 1490 (Ar), 1310, 1250, 1155, 830 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.49 (9 H, s, t-Bu), 2.68 (1 H, dd, J_{4a-3} = 4,5 Hz, J_{gem} = 17,8 Hz, H-4), 3.09 (1 H, dd, J_{4b-3} = 9,2 Hz, J_{gem} = 17,8 Hz, H-4), 3.54 (1H, m, H-3), 4.56 (1 H, d, J = 3,75 Hz, H-2) 7.20 (2 H, d, J_{AB} = 8,5 Hz, H-Ar), 7.36 (2 H, d, J_{AB} = 8,5 Hz, H-Ar), 9.44 (1 H, s, COOH).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 27.84 (C($\underline{C}H_3)_3$), 38.77 (C-3), 39.05 (C-4), 65.89 (C-2), 84.59 ($\underline{C}(CH_3)_3$), 127.92 (C-Ar), 129.48 (C-Ar), 133.99 (C-Ar), 139.24 (C-Ar), 149.15 (urethane), 172.10 (COOH), 175.29 (lactam).- $[\alpha]_D^{20}$ = +33,7 (c=0.162, $CHCl_3$).
$C_{16}H_{18}NO_5Cl$ (339.78) Calcd.: C 56.39 H 5.32 N 4.11found: C 56.69 H 5.44 N 4.24

4R-1-t-Butoxycarbonyl-4-(4-chlorophenyl)pyrrolidine-2-one (7e)

To a solution of **6e** (340 mg, 1 mmol) in dry THF (flame dried glassware, N_2!) and N-methylmorpholine (102 mg, 1 mmol) was added isobutyl chloroformate (136 mg, 1 mmol) at -15°C with stirrring. After 5 min. a solution of N-hydroxy-2-thiopyridone (152 mg, 1.2 mmol) and triethylamine (122 mg, 1.2 mmol) in dry THF was added. The mixture was stirred for 1 h in the dark. The precipitate was removed under N_2 by suction and washed with THF. After addition of t-butyl thiol (0.9 ml, 10 mmol) the solution was irradiated with two 100 watt lamps for 1h at room temp. The mixture was diluted with ether, washed wth 0.5N aqueous HCl, brine and water. The organic layer was dried (Na_2SO_4) and evaporated. After

chromatography of the oily residue on silica gel with EtOAc/petroleum ether 2+1 and evaporation of the eluant, the remaining oil crystallized on standing. Yield 190 mg (64%).- R_f = 0.5 (EtOAc/petroleum ether 1:2).- m.p. 103°C (diisopropyl ether/petroleum ether).- IR (KBr): 2990, 1780 (C=O), 1500, 1370, 1290, 1150, 1090, 1015, 840, 780 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.54 (9 H, s, t-Bu), 2.66 (1 H, dd, J_{3a-4}=9,5 Hz, J_{gem}=17,3 Hz, H-3), 2.90 (1 H, dd, J_{3b-4}=8,2 Hz, J_{gem}=17,3 Hz, H-3), 3.51 (1 H, quin, $J_{3a-4} \approx J_{3b-4} \approx J_{5a-4} \approx J_{5b-4}$=8,3 Hz, H-4), 3.65 (1 H, dd, J_{5a-4}=8,2 Hz, J_{gem}=10,7 Hz, H-5), 4.15 (1 H, dd, J_{5b-4}=7,5 Hz, J_{gem}=10,5 Hz, H-5), 7.17 (2 H, dt, J=1,9 Hz, J_{AB}=8,4 Hz, H-Ar), 7.33 (2 H, dt, J=2 Hz, J_{AB}=8,5 Hz, H-Ar).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.01 ($OC(\underline{C}H_3)_3$), 35.83 (C-4), 40.19 (C-3), 52.87 (C-5), 83.17 ($O\underline{C}(CH_3)_3$), 128.08 (C-Ar), 129.13 (C-Ar), 133.27 (C-Ar), 139.14 (C-Ar), 149.82 (urethane), 172.41 (lactam).- $[\alpha]_D^{20}$ = +4.5 (c=0.2, $CHCl_3$).
$C_{15}H_{18}NO_3Cl$ (295.76) Calcd.: C 60.92 H 6.13 N 4.74 found: C 60.94 H 6.31 N 4.80

3R-4-t-Butoxycarbonylamino-3-(4-chlorophenyl)butanoic acid (8e)

To **7e** (100 mg, 0.33 mmol), dissolved in THF (3 ml), was added 1M aqueous LiOH solution (1 ml). After the mixture was stirred for 1.5 h, THF was evaporated in vacuo and the aqueous phase was brought to pH 1-2 with 0.5M HCl. The mixture was extracted with 10 ml ether (3x). The organic phase was dried (Na_2SO_4) and evaporated. The residue was triturated with ether and the crystalline material was isolated by suction. Recrystallisation from $CHCl_3$/petroleum ether, yielded 90 mg (87%) of colorless plates.- R_f = 0.65 (EtOAc/CH_2Cl_2/petroleum ether, 2:8:1).- m.p. 135°-138°C.- IR (KBr): 3390 (N-H), 3000-2900 und 2630 (COOH), 1690 (C=O), 1530, 1500, 1410, 1370, 1250, 1180, 1020, 830 cm^{-1}.- ^{1}H-NMR ($CDCl_3$/d_6-DMSO): δ (ppm) = 1.39 (9 H, s, t-Bu), 2.50 (1 H, dd, J_{2a-3}=8,4 Hz, J_{gem}=15,9 Hz, H-2), 2.69 (1 H, dd, J_{2b-3}=4,3 Hz, J_{gem} = 16,1 Hz, H-2), 3.28 (3 H, m, H-3 and H-4), 5.87 (1 H, s broad, N-H), 7.19 (2 H, d, J_{AB}=8,66 Hz, H-Ar), 7.26 (2 H, d, J_{AB}=8,67 Hz, H-Ar).- ^{13}C-NMR ($CDCl_3$/d_6-DMSO): δ (ppm) = 28.29 ($C(\underline{C}H_3)_3$), 37.93 (C-3), 41.59 (C-2), 45.44 (C-4), 78.46 ($\underline{C}(CH_3)_3$), 128.28 (C-Ar), 129.29 (C-Ar), 131.83 (C-Ar), 140.78 (C-Ar), 155.95 (urethane), 173.44 (COOH).- $[\alpha]_D^{20}$ = +14 (c=0.234/MeOH).
$C_{15}H_{20}NO_4Cl$ (313.78) Calcd.: C 57.42 H 6.42 N 4.46 found: C 57.24 H 6.43 N 4.32

3R-4-Amino-3-(4-chlorophenyl)-butanoic acid hydrochloride (9) (R-Baclofen·HCl)

8e (104 mg, 0.33 mmol) was refluxed in 6M HCl (10 ml) for 3h. The colorless solution was evaporated in vacuo and after drying of the residue, in a desiccator, the crystalline material was triturated with EtOH/acetone. The colorless crystals were isolated by suction. Yield: 62 mg (74%).- m.p.: 219°C (ref.2e 215°C).- IR (KBr): 3000 (NH_3^+, COOH), 1720 (COOH), 1580 (NH_3^+), 1490, 1410, 1400, 1200, 1180, 1125, 1010, 950, 825 cm^{-1}.- ^{1}H-NMR (D_2O/d_4-methanol): δ (ppm) = 2.63 (1 H, dd, J_{2a-3}=8,7 Hz, J_{gem}=16,4 Hz, H-2), 2.78 (1 H, dd, J_{2b-3}=5,6 Hz, J_{gem}=16,3 Hz, H-2), 3.24 (3 H, m, H-3 and H-4), 7.25 (2 H, d, J_{AB}=8,5 Hz, H-Ar), 7.34 (2 H, d, J_{AB}=8,55 Hz, H-Ar).- ^{13}C-NMR: (D_2O/d_4-methanol): δ (ppm) =39.10 (C-3), 40.41 (C-2), 44.62 (C-4), 130.19 (C-Ar), 130.37 (C-Ar), 134.38 (C-Ar), 138.16 (C-Ar), 175.67 (COOH).- $[\alpha]_D^{20}$= -2 (c=0.2/H_2O) ref.2d,e: -1,5 (c=0.2/H_2O).-
$C_{10}H_{13}NO_2Cl_2$ (250.12) Calcd.: C 48.02 H 5.24 N 5.60 found: C 47.65 H 5.19 N 5.44

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