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Synthesis of Homochiral Piperidine Derivatives from S-Glutamic Acid. Stereoselective 1,4-Addition of Organocuprates to a Δ^3-Piperidine-2-one. A Paroxetine Analogue.§

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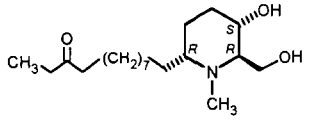
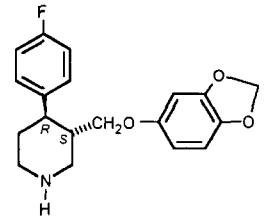
Abstract: Enantiomerically pure S-5-hydroxy-2-piperidinone **4**, readily available from S-glutamic acid, serves as a key intermediate for the synthesis of 3,4-*trans* substituted piperidine derivatives. The substituents in the 4-position are introduced via 1,4 conjugate organocuprate addition to **7** with excellent trans selectivity. This reaction is employed for the synthesis of a paroxetine analogue **21g**. All attempts to transform **16** to (+)-meroquinene **17** failed. Copyright © 1996 Elsevier Science Ltd

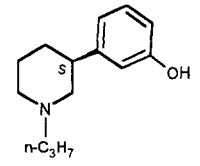
Homochiral piperidine derivatives constitute particularly attractive goals for synthetic and medicinal chemists.[1] Notable in this regard are ß-hydroxypiperidine derivatives which are present in a number of natural products, isolated from acacia, sedum and prosopis species,(e.g. (+) prosopinine[2] **1**) and are the subject of much current investigation. Futhermore pharmacologically active chiral non-racemic piperidine derivatives like (-) paroxetine[3] **2**, a serotonine uptake inhibitor, and (-) preclamol[4] **3**, a D_2-/D_3-auto-and sigma receptor agonist are acting on the central nervous system are also of interest.



(+) Prosopinine (1)



(-) paroxetine (2) · HCl



(-) preclamol (3) · HCl

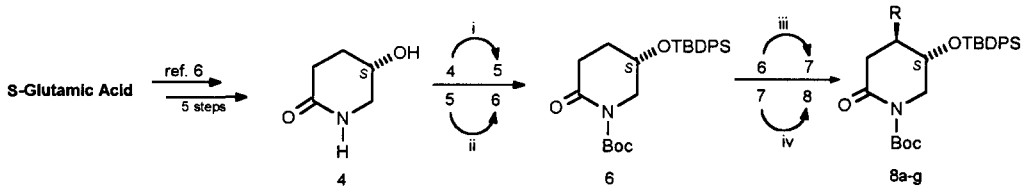
As part of our program on the synthesis of ß-substituted piperidines[5], we have extended our studies to the synthesis of the generally less accessible 3,4-*trans* substituted homochiral piperidine derivatives.

We anticipated that organocuprates would add to Δ^3-piperidinone **7** in a diastereoselective controlled conjugate 1,4-addition reaction to the trans piperidinone derivatives **8**. Starting from D-or L-glutamic acid, we prepared (R) and (S) 5-hydroxypiperidine[6] in enantiopure form and in multigram quantities as previously described. The OH function of **4** was protected with the bulky TBDPS group under standard conditions and the amide moiety with the Boc group (BuLi, DABCO, Boc_2O)[7]. This procedure afforded **6** generally in 20% higher yield than with the reported 4-DMAP/Boc_2O method[8].

The introduction of the Δ^3-double bond was accomplished via deprotonation of **6** with LiHMDS, followed by phenylselenenyl chloride, to give the phenylseleno compound which was treated with H_2O_2/EtOAc to furnish **7** in 67-70% yield. Related introductions of a double bond in 5-and 6-ring lactams have been described[9].

The 1,4-addition reaction of Grignard cuprates to **7** (entry 1-7, except entry 5 where Ph_2CuLi was used) in the presence of trimethylsilyl chloride[10] provided **8a-8g** in 56-79% yield with > 96% d.e. (Scheme 1). When $BF_3{\cdot}OEt_2$ instead of TMSCl was used, starting material was recovered. These observations are in accordance with our previous obtained results in the pyroglutamate series.[11]

Scheme 1



Entry	R	Compound	Yield (%)	de[a] (%)
1	Me	8a	68	> 96
2	Et	8b	75	> 96
3	n-Bu	8c	63	> 96
4	allyl	8d	56	> 96
5	Ph	8e[b]	68	> 96
6	p-Cl-Ph	8f	67	> 96
7	p-F-Ph	8g	79	> 96

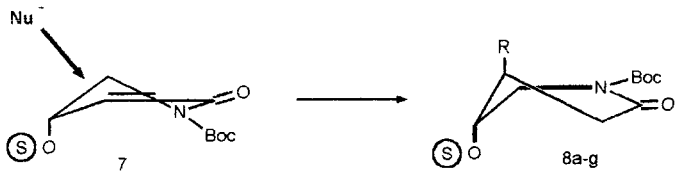
a. determined by ^1H and ^{13}C-NMR

b. Phenyllithium was used for the prep. of the cuprate

i: TBDPSCl, imidazole; **ii**: n-BuLi, DABCO, Boc_2O, -78°C; **iii**: a. HMDS, n-BuLi, PhSeCl, -78°C; b. H_2O_2/EtOAc; **iv**: RMgBr, CuBr·$S(CH_3)_2$, $(CH_3)_3SiCl$, -78°C.

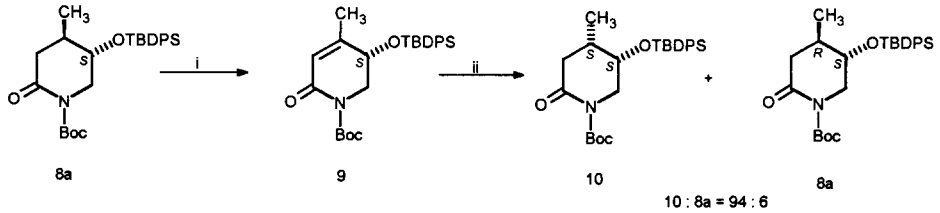
Examination of ^1H-and ^{13}C-NMR spectra of the crude addition products failed to reveal the presence of the cis-stereoisomers. The $A^{(1,2)}$ strain[12], resulting from the interaction of the protecting group and the olefinic hydrogen atom, favour the pseudoaxial orientation of the bulky TBDPSO group. So the C-nucleophile reacted from the less shielded side of **7**. This would best explain the excellent trans diastereoselectivity (see Figure 1).

Figure 1



To secure the relative configuration at the newly formed stereogenic centre, cis-**10** was synthesized for comparison of spectral data as shown in scheme 2.

Scheme 2



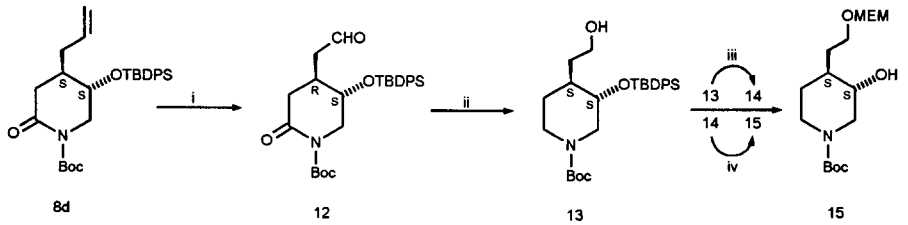
i: a. HMDS, n-BuLi, PhSeCl, -78°C; b. H_2O_2/EtOAc; ii: Pd/H_2/EtOAc, room temp.

The double bond was introduced in **8a** as shown for **6** (scheme 1) and the resulting olefin **9** was hydrogenated over Pd/C from the less shielded ß-side to afford a diastereomeric mixture of **10**:**8a** in a ratio of 94:6.

The conformation of **8a-8g** was confirmed by analysis of the coupling pattern of the $C_{6a,6e}$-H with the C_5-H, which exhibited two small (J = 3-5 Hz and J = 2-3 Hz) couplings which confirms that H-5 resides in an pseudoequatorial orientation. In no case could a large axial-axial coupling could be detected. This trans-diaxial preferred orientation of two substituents in δ-lactams was also observed by Y. Leblanc et. al.[13] and interpreted to be due to the destabilizing gauche interaction of the two large substituents in diequatorial orientation. Furthermore the attractive gauche interaction of the C-N and C-O bond (bold bonds in **8**, Fig. 1)[13,14] will contribute to the diaxial position.

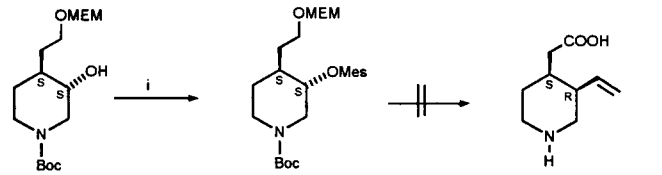
To examine its synthetic utility further, **8d** was ozonized to the aldehyde **12** in 70-90% yield. Reaction of **12** with BH_3·$S(CH_3)_2$ at 70°C resulted in the simultaneous reduction of the aldehyde and the amide function to furnish **13** in 65% yield. Protection of the OH-function with MEMCl to **14** and desilylation with TBAF provided **15**, which was treated with methanesulfonyl chloride/DMAP to obtain **16** in 86% yield. All attempts to transform **16** to meroquinene **17** via S_N2 displacement of the mesylate with vinylcuprate failed[15] (Scheme 4).

Scheme 3



i: a: O_3, MeOH/CH_2Cl_2, b: $(CH_3)_2S$; ii: BH_3.$(CH_3)_2S$, THF, 70°C; iii: MEMCl, (i-prop)$_2$EtN; iv: TBAF, THF.

Scheme 4



i: MesCl, Et_3N, 4-DMAP, CH_2Cl_2

Reduction of **8a, f, g** with borane dimethylsulfide[16] afforded **18a, f, g** in moderate yield (≈ 40%). Alternatively **8a, g** was reduced with $LiEt_3BH/Et_3SiH\text{-}Et_2O\cdot BF_3$[17] via the α-hydroxycarbamate to **18a, g** in 72-80% yield. ^{1}H-NMR of **18a, f, g** show a 3-H/4-H coupling of J = 9 Hz, which indicates a diequatorial disposition of both substituents.[18] Indeed, after desilylation of **18a, f, g** with TBAF a X-ray diffraction study of crystalline **19f** revealed that the OH and p-chlorphenyl substituents are in trans diequatorial orientation and the hydroxy group is capable of a hydrogen-bond formation to the chloro atom of an adjacent aromatic ring.[19]

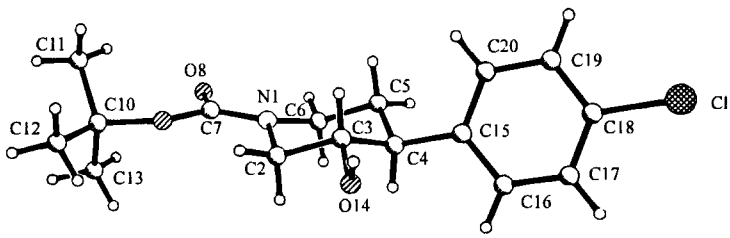


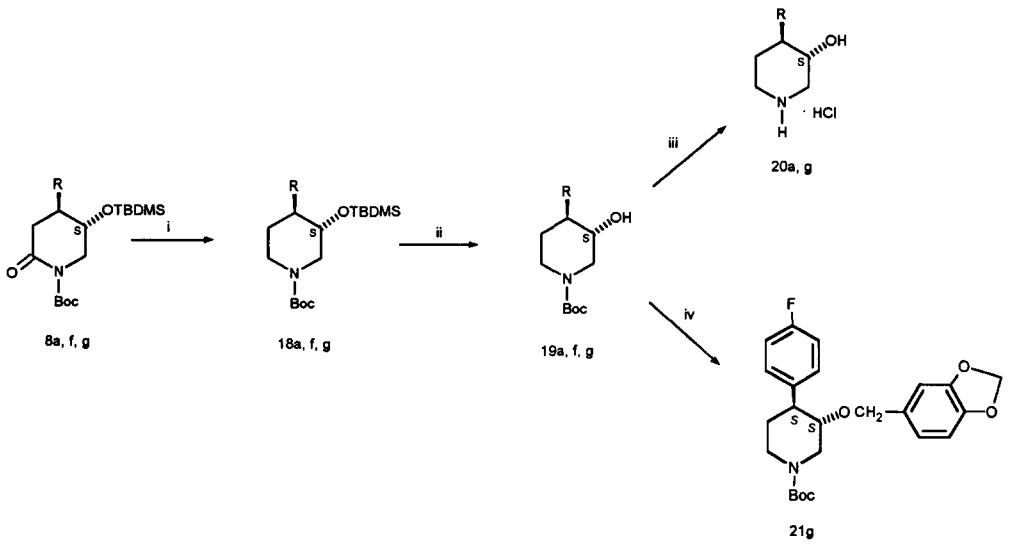
Fig. 2: X-ray structure of 19f

Treatment of **19a, g** with ethanolic hydrogen chloride provided **20a, g** in 80% yield. Compound **19g** reacted with piperonyl chloride in DMSO/KOH[20] in ≈ 80% yield to the N-Boc paroxetine analogue **21g**, which has the same absolute configuration as (-) paroxetine (Scheme 5).

Experimental

All reactions were carried out under an inert atmosphere of nitrogen. All solvents were distilled under a dry nitrogen atmosphere. The solvents were dried as follows: dichloromethane was distilled from phosphorous-(V)-oxide, diethyl ether from Na-K-alloy, N,N-dimethyl formamide, dimethyl sulphoxide and toluene from calcium hydride, THF first from calcium hydride followed by Na-K-alloy. Methanol was distilled from magnesium. ^{1}H-NMR and ^{13}C-NMR-spectra were measured on a Bruker AC 200 (200 MHz for ^{1}H-, 50 MHz for ^{13}C-NMR). IR- spectra: Perkin-Elmer 681 spectrometer. Mass spectra: Finnigan Mat 8200 (70 eV). Melting points: Büchi 510 instrument. Optical rotations: Perkin-Elmer polarimeter 241 at 589 nm (sodium D-line). Thin

Scheme 5



i: $BH_3{\cdot}(CH_3)_2S$, THF, 70°C, or: a: $LiEt_3BH$, b: $Et_3SiH{-}Et_2O{\cdot}BF_3$, ii: TBAF/THF, iii: EtOH/HCl, iv: DMSO/KOH, piperonyl chloride

layer chromatography: Merck DC-precoated silicagel plates-60 F_{245} Elemental analysis were run at the microanalytical laboratory of the Institute for Inorganic Chemistry of the University in Würzburg.

(5S)-5-tert-Butyldiphenylsilyloxy-piperidine-2-one 5

To a solution of **4** (5.4 g, 46.96 mmol) and imidazole (9.6 g, 140.67 mmol) in DMF (150 ml) was added tert butyldiphenylsilyl chloride (14.18 g, 13.2 ml, 51.6 mmol). The solution was stirred for 18 h at ambient temperature, then ice/water mixture (200 ml) and diethyl ether (200 ml) were added and the aqueous layer was extracted with of diethyl ether (3 x 50 ml). The combined organic layers were washed with water until the aqueous layer reacted neutral. The organic layer was dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. After column chromatography of the pale yellow oil (dichloromethane/methanol (9+1), R_f = 0.57, and evaporating of the solvent, the resulting colourless oil crystallises after standing at 4°C. Yield: 16.22 g (98%) of colourless crystals, m.p. 81°C.- IR (KBr): ν = 3200 (cm^{-1}) (N-H) , 3080, 2940, 2760, 1670 (C=O).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.07 (s, 9H, t-Bu), 1.77-1.92 (m, 2H, 4-H), 2.25 (ddd, J_{gem}= 17.7 Hz, $J_{3e,4e} \approx J_{3e,4a}$ = 6 Hz, 1H, 3-H_e), 2.65 (ddd, J_{gem} = 17.7 Hz, $J_{3a,4a}$ = 9.1 Hz, $J_{3a,4e}$ = 6.4 Hz, 1H, 3-H_a), 3.18-3.21 (m, 2H, 6-H), 4.06-4.11 (m, 1H, 5-H), 6.10 (s, 1H, N-H), 7.33-7.49 (m, 6H, H_{arom}), 7.62-7.68 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.1 (Si-$\underline{C}(CH_3)_3$), 26.9 (Si-C($\underline{C}H_3$)), 27.5 (C-4), 28.4 (C-3), 48.9 (C-6), 64.8 (C-5), 127.8-135.6 ($C_{arom.}$), 172.2 (C-2).- $[\alpha]_D^{20}$ = -15 (c = 0.6, EtOAc).- $C_{21}H_{27}NO_2Si$ (353.54): calcd. C 71.35, H 7.70, N 3.96; found C 71.61, H 7.99, N 3.88.

tert-Butyl (5S)-5-tert-Butyldiphenylsilyloxy-piperidine-2-one-1-carboxylate (6)

To a cooled solution (-78°C) of **5** (13.1 g, 37.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (4.21 g, 37.6 mmol) in THF (250 ml), n-butyl lithium (27.8 ml, 44.8 mmol, 1.6 M in hexane) was added. The solution was stirred for 45 minutes at this temperature. Boc_2O (9.7 g, 44.7 mmol) was dissolved in THF (100 ml) and rapidly transferred to the reaction mixture under vigorous stirring. After 2h, the reaction was quenched at -78°C with saturated $NaHCO_3$ solution. After addition of diethyl ether (200 ml) the organic layer was extracted with saturated NH_4Cl solution until the aqueous layer reacted neutral. The organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated. The remaining pale yellow liquid was purified by column chromatography (petroleum ether/EtOAc 2+1, R_f = 0.59). Yield: 14.67 g (88%) colourless oil.- IR (neat): ν = 3080 (cm^{-1}) , 2930, 2850, 1770 (urethane), 1720 (lactame).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.07 (s, 9H, $SiC(CH_3)_3$), 1.49 (s, 9H, $OC(CH_3)_3$), 1.82-1.89 (m, 2H, 4-H), 2.38 (ddd, J_{gem} = 17.2 Hz, $J_{3e,4a} \approx J_{3e,4e}$ = 6 Hz, 1H, 3-H_e), 2.73 (ddd, J_{gem} = 17.2 Hz, $J_{3a,4a}$ = 9.0 Hz, $J_{3a,4e}$ = 6.8 Hz, 1H, 3-H_a), 3.40 (dd, J_{gem} = 13.2 Hz, $J_{6,5e}$ =3.2 Hz, 1H, 6-H), 3.72 (dd, J_{gem} = 13.3 Hz, $J_{6,5e}$ = 3.9 Hz, 1H, 6-H), 4.13-4.17 (m, 1H, 5-H_e), 7.31-7.45 (m, 6H, $H_{arom.}$), 7.64-7.68 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 18.6 ($SiC(CH_3)_3$), 26.4 ($SiC(CH_3)_3$), 27.5 ($OC(CH_3)_3$), 28.2 (C-4), 30.5 (C-3), 51.6 (C-6), 64.8 (C-5), 82.0 ($OC(CH_3)_3$), 127.4, 129.5, 132.9, 135.1 ($C_{arom.}$), 151.8 (urethane), 170.1 (C-2).- $[\alpha]_D^{20}$ = -23 (c = 0.5, EtOAc).- $C_{26}H_{35}NO_4Si$ (453.65): calcd. C 68.82, H 7.78, N 3.09 found C 68.63, H 8.09, N 2.92.

tert-Butyl (5S)-5-(tert-Butyldiphenylsilyloxy)-3,4-dehydro-piperidine-2-one-1-carboxylate 8

To a solution of hexamethyldisilazane (5.84 g, 7.54 ml, 36.1 mmol) in THF (70 ml), n-butyl lithium (22.7 ml, 36.1 mmol, 1.6 M in hexane) was added at -78°C. The solution was stirred at this temperature for 30 min., then a solution of **7** (7.15 g, 15.8 mmol) in THF (70 ml) was added. After 30 min. of stirring at -78°C, phenylselenenyl chloride (3.63 g, 19.0 mmol) in THF (70 ml) was added. After 2h the yellow solution was quenched at -78°C with dil. NH_4Cl solution, ethyl acetate (150 ml) was added and the organic layer was washed with diluted NH_4Cl solution until it reacted neutral. The combined organic layers were dried with sodium sulphate, filtered and the solvent was evaporated. The remaining yellow oil was dissolved in ethyl acetate (75 ml) and hydrogen peroxide (30%) (15 ml) was added. The solution was stirred for 45 min. at ambient temperature. The organic layer was extracted with $NaHCO_3$ solution and washed with sat. NH_4Cl and sat. NaCl solution. It was dried over sodium sulphate, filtered and the solvent was evaporated. The pale yellow oil was purified by column chromatography (silica gel, petroleum ether/EtOAc (2+1), R_f =0.61). - Yield: 4.77 g (67 %) colourless oil.- IR (neat): ν = 3080 (cm^{-1}), 2980, 2860, 1770 (urethane), 1720 (lactame), 1630.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.07 (s, 9H, $SiC(CH_3)_3$), 1.50 (s, 9H, $OC(CH_3)_3$), 3.67 (dd, J_{gem} = 13.2 Hz, $J_{6,5e}$ = 4.26 Hz, 1H, 6-H), 3.90 (dd, J_{gem} = 13.2 Hz, $J_{6,5e}$ = 6.49 Hz, 1H, 6-H), 4.34-4.42 (m, 1H, 5-H_e), 5.86 (d, $J_{3,4}$ = 9.9 Hz, 1H, 3-H), 6.55 (dd, $J_{3,4}$ = 9.8 Hz, $J_{4,5e}$ = 3.7 Hz, 1H, 4-H), 7.29-7.41 (m, 6H, H_{arom}), 7.63-7.69 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 18.7 ($SiC(CH_3)_3$), 26.5 ($SiC(CH_3)_3$), 27.6 ($OC(CH_3)_3$), 50.1 (C-6), 63.6 (C-5); 82.5 ($OC(CH_3)_3$), 125.8 (C-3), 127.5, 129.8, 132.5, 135.2 (C_{arom}), 144.1

(C-4), 151.7 (urethane), 162.5 (C-2).- $[\alpha]_D^{20}$ = +42 (c = 0.5, EtOAc).- $C_{26}H_{33}NO_4Si$ (451.64): calcd. C 69.13, H 7.37, N 3.10; found C 69.35, H 7.64, N 2.91.

tert-Butyl (4R,5S)-5-(tert-Butyldiphenylsilyloxy)-4-methyl-piperidine-2-one-1-carboxylate 8a

To a suspension of $CuBr{\cdot}SMe_2$ (3.08 g, 15.0 mmol) in diethyl ether (10 ml) at -15°C was added a Grignard-solution prepared from Mg-turnings (0.8 g, 33.0 mmol) and iodomethane (4.26 g, 1.87 ml) in diethyl ether (30 ml). The yellow suspension was stirred 15 min. at -15°C, then TMSCl (1.2 ml, 9.5 mmol) and **7** (1.36 g, 3 mmol), dissolved in diethyl ether (30 ml), was added. The mixture was stirred 2 h then it was quenched at -78°C with dil. NH_4Cl solution and some drops of NH_3-solution (25%) and diethyl ether (100 ml) were added. The organic layer was washed with NH_4Cl/NH_3 solution until the aqueous layer remained colourless. The organic layer was dried over sodium sulphate, filtered and the solvent was evaporated. The remaining coulorless oil was purified by column chromatography (silica gel, petroleum ether/EtOAc (2+1), R_f = 0.39).- Yield: 0.92 g (68%) colourless oil.- IR (neat): ν = 3070 (cm^{-1}), 2980-2880, 1770 (urethane), 1720 (lactame), 1470, 1360.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.81 (d, J = 6.5 Hz, 3H, CH_3), 1.06 (s, 9H, $SiC(CH_3)_3$), 1.47 (s, 9H, $OC(CH_3)_3$), 2.02-2.17 (dd, and m $J_{gem.}$ = 18.2 Hz, $J_{3,4e}$ = 6.4 Hz, 2H, 4-H_e, 3-H), 2.84 (dd, J_{gem} = 18.2 Hz, $J_{3,4e}$ = 8.1 Hz, 1H, 3-H), 3.45 (dd, J_{gem} = 17.8 Hz, $J_{6,5e}$ = 2.8 Hz, 1H, 6-H), 3.61-3.72 (dd, and m, J_{gem}, = 17.8 Hz, $J_{6,5e}$ = 4.4 Hz, 2H, 6-H, 5-H_e), 7.37-7.46 (m, 6H, H_{arom}), 7.66 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 17.7 (CH_3), 18.6 ($SiC(CH_3)_3$), 26.4 ($SiC(CH_3)_3$), 27.4 ($OC(CH_3)_3$), 34.2 (C-4), 38.8 (C-3), 48.9 (C-6), 71.1 (C-5), 81.9 ($OC(CH_3)_3$), 127.3, 129.4, 132.7, 135.1 (C_{arom}) 151.4 (urethane), 169.8 (C-2).- $[\alpha]_D^{20}$ = -39 (c = 0.7, EtOAc).- $C_{26}H_{37}NO_4Si$ (455.67): calcd. C 68.53, H 8.18, N 3.07; found C 68.28, H 7.87, N 3.03.

tert-Butyl (4R,5S)-5-(tert-Butyldiphenylsilyloxy)-4-ethyl-piperidine-2-one-1-carboxylate 8b was prepared from 7 (340 mg, 0.75 mmol) dissolved in Et_2O (30 ml) as described for **8a**. Grignard cuprate reagent was prepared from Mg turnings (200 mg, 8.25 mmol), iodethan (1.17 g, 0.78 ml, 7.5 mmol) in Et_2O (20 ml) with $CuBr{\cdot}S(CH_3)_2$ (771 mg, 3.75 mmol) in Et_2O (5 ml) and TMSCl (0.26 g, 2.4 mmol). Yield: 274 mg colourless oil, (75%), R_f = 0.29 (petroleum/Et_2O (3+2).- IR (neat): ν = 3070 (cm^{-1}), 2960-2920, 1770, 1720, 1470.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.73 (t, J = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.06 (s, 9H, $SiC(CH_3)_3$), 1.27 (m, 2H, $C\underline{H}_2CH_3$), 1.48 (s, 9H, $OC(CH_3)_3$), 1.83 (m, 1H, 4-H_e), 2.15 (dd, J_{gem} = 16.5 Hz, $J_{3,4e}$ = 6.1 Hz, 1H, 3-H), 2.86 (dd, J_{gem} = 16.5 Hz, $J_{3,4e}$ = 6.2 Hz, 1H, 3-H), 3.40 (dd, J_{gem} = 13.2 Hz, $J_{6,5e}$ = 2.8 Hz, 1H, 6H), 3.68-3.83 (dd and m, $J_{6,5e}$ = 4.3 Hz, $J_{6,4e}$ = 1.0 Hz, 2H, 6-H, 5H_e), 7.34-7.46 (m, H_{arom}, 6H), 7.65 (m, H_{arom}, 4H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 11.1 ($CH_2\underline{C}H_3$), 19.2 ($SiC(CH_3)_3$), 25.5 ($\underline{C}H_2CH_3$), 26.9 ($SiC(\underline{C}H_3)_3$), 28.0 ($OC(\underline{C}H_3)_3$), 36.9 (C-3), 41.5 (C-4), 49.6 (C-6), 69.8 (C-5), 82.8 ($O\underline{C}(CH_3)_3$), 127.1, 129.4, 132.7, 135.1 (C_{arom}) 152.3 (C=O, urethane), 170.9 (C-2).- $[\alpha]_D^{20}$ = -28 (c = 0.2, EtOAc).- $C_{28}H_{39}NO_4Si$ (481.71): calcd. C 69.82, H 8.16, N 2.91; found C 69.97, H 8.33, N 2.78.

tert-Butyl (4R,5S)-5-(tert-Butyldiphenylsilyloxy)-4-butyl-piperidine-2-one-1-carboxylate 8c was prepared from 7 (113 mg, 0.25 mmol) dissolved in Et_2O (30 ml) as described for **8a**. Grignard cuprate reagent was prepared from Mg turnings (67 mg, 2.8 mmol), n-brombutane (343 mg,

0.27 ml, 2.5 mmol) in Et_2O (25 ml) with $CuBr{\cdot}S(CH_3)_2$ (257 mg, 1.25 mmol) in Et_2O (10 ml) and TMSCl (0.1 ml, 0.8 mmol). Yield: 80 mg (63%) colourless oil, R_f = 0.48 (petroleum/Et_2O (3+2).- IR (neat): ν = 3080-2850 (cm^{-1}), 1770, 1730, 1470.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.79 (t, J = 6.5 Hz, 3H, $(CH_2)_3C\underline{H}_3$), 1.02-1.22 (s and m, 15H, $SiC(CH_3)_3$ and $(C\underline{H}_2)_3CH_3$)), 1.48 (s, 9H, $OC(CH_3)_3$), 1.91 (m, 1H, 4-H_e), 2.15 (dd, J_{gem} = 16.2 Hz, $J_{3,4e}$ = 6.3 Hz, 1H, 3-H), 2.86 (dd, J_{gem} = 16.2 Hz, $J_{3,4e}$ = 6.3 Hz, 1H, 3-H), 3.40 (dd, J_{gem} = 12.7 Hz, $J_{6,5e}$ = 2.2 Hz, 1H, 6H), 3.69-3.80 (ddd, J_{gem} = 12.7 Hz, $J_{6,5e}$ = 4.3 Hz, $J_{6,4e}$ = 1.0 Hz, 2H, 6-H, 5H_e), 7.34-7.45 (m, H_{arom}, 6H), 7.65 (m, H_{arom}, 4H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 13.9 ($(CH_2)_3\underline{C}H_3$), 19.2 ($Si\underline{C}(CH_3)_3$), 22.5 ($(CH_2)_2\underline{C}H_2CH_3$), 26.9 ($SiC(\underline{C}H_3)_3$), 28.1 ($OC(\underline{C}H_3)_3$), 28.9 ($CH_2\underline{C}H_2CH_2CH_3$), 32.4 ($\underline{C}H_2(CH_2)_2CH_3$), 37.3 (C-3), 39.7 (C-4), 49.6 (C-6), 70.0 (C-5), 82.8 ($O\underline{C}(CH_3)_3$), 127.8-135.8 (C_{arom}), 152.1 (C=O, urethane), 170.0 (C-2).- $[\alpha]_D^{20}$ = -22 (c = 0.2, EtOAc).- $C_{30}H_{43}NO_4Si$ (509.76): calcd. C 70.69, H 8.50, N 2.75; found C 70.94, H 8.86, N 2.78.

tert-Butyl (4R,5S)-4-Allyl-5-(tert-butyldiphenylsilyloxy)-piperidine-2-one-1-carboxylate 8d was prepared from 7 (3.0 g, 6.25 mmol) dissolved in Et_2O (100 ml) and allylmagnesium bromide (66.5 ml, 66.5 mmol, 1M in Et_2O) with $CuBr{\cdot}S(CH_3)_2$ (6.8 g, 33.2 mmol) in Et_2O (50 ml) and TMSCl (2.1 g, 2.5 ml, 19.9 mmol) as described for **8a**. . Yield: 1.8 g (56%) colourless oil, R_f = 0.47 (petroleum/EtOAc (4+1).-IR (neat): ν = 3080-2850 (cm^{-1}), 1770, 1715, 1640.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.07 (s, 9H, $SiC(CH_3)_3$), 1.48 (s, 9H, $OC(CH_3)_3$), 1.75-1.86 (m, 1H, 4-H_e), 1.93-2.07 (m, 2H, $C\underline{H}_2CH=CH_2$), 2.16 (dd, J_{gem} = 16.3 Hz, $J_{3,4e}$ = 6.1 Hz, 1H, 3-H), 2.81 (dd, J_{gem} = 16.3 Hz, $J_{3,4e}$ = 5.7 Hz, 1H, 3-H), 3.41 (dd, J_{gem} = 12.9 Hz, $J_{6,5e}$ = 2.5 Hz, 1H, 6H), 3.70-3.84 (dd and m, $J_{6,5e}$ = 4.4 Hz, 2H, 6-H, 5H_e), 4.85-4.96 (m, 2H, $CH_2CH=C\underline{H}_2$), 5.45 (ddd, J_{CH,CH_2trans} = 16.9 Hz, J_{CH,CH_2cis} = 10.2 Hz, J_{CH,CH_2} = 6.7 Hz, 1H, $CH_2C\underline{H}=CH_2$), 7.35-7.50 (m, H_{arom}, 6H), 7.64 (m, H_{arom}, 4H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.2 ($Si\underline{C}(CH_3)_3$), 26.9 ($\underline{C}H_2CH=CH_2$), 28.1 ($OC(\underline{C}H_3)_3$), 36.9 (C-3), 39.4 (C-4), 49.6 (C-6), 69.5 (C-5), 82.8 ($O\underline{C}(CH_3)_3$), 117.6 ($CH_2CH=\underline{C}H_2$), 134.5 ($CH_2\underline{C}H=CH_2$), 127.6-135.8 (C_{arom}) 152.0 (C=O, urethane), 170.6 (C-2).- $[\alpha]_D^{20}$ = -21 (c = 0.2, EtOAc).- $C_{29}H_{39}NO_4Si$ (493.72): calcd. C 70.55, H 7.96, N 2.84; **found C 70.26, H 8.05, N 2.65.**

tert-Butyl (4S,5S)-5-(tert-Butyldiphenylsilyloxy)-4-phenyl-piperidine-2-one-1-carboxylate 8e was prepared from 7 (226 mg, 0.5 mmol) dissolved in Et_2O (20 ml) and phenyllithium (2.5 ml, 5 mmol, 2 M in cyclohexane/Et_2O) with $CuBr{\cdot}S(CH_3)_2$ (514 mg, 2.5 mmol) in Et_2O (5 ml) and TMSCl (0.17 g, 0.2 ml, 1.6 mmol) as described for **8a**. Yield: 160 mg (68%) colourless oil, R_f = 0.35 (petroleum/Et_2O (3+2).- IR (neat): ν = 3060-2840 (cm^{-1}), 1770, 1720, 1470.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.01 (s, 9H, $SiC(CH_3)_3$), 1.48 (s, 9H, $OC(CH_3)_3$), 2.62-2.74 (dd, J_{gem} = 16.8 Hz, $J_{3,4e}$ = 5.9 Hz, 1H, 3-H), 3.09 (dd, J_{gem} = 17.1 Hz, $J_{3,4e}$ = 6.5 Hz, 1H, 3-H), 3.22 (dd, $J_{4e,3} \approx J_{4e,5e}$ = 6.1 Hz, 1H, 4-H_e), 3.30 (dd, J_{gem} = 13.4 Hz, $J_{6,5e}$ = 3.1Hz, 1H, 6-H), 3.67 (dd, J_{gem} = 13.4 Hz, $J_{6,5e}$ = 4.3 Hz, 1H, 6-H), 4.06 (m, 1H, 5-H), 6.89-7.62 (m, 15H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.1 ($Si\underline{C}(CH_3)_3$), 26.8 ($SiC(\underline{C}H_3)_3$), 28.0 ($OC(\underline{C}H_3)_3$), 37.3 (C-3), 45.8 (C-4), 49.6 (C-6), 71.1 (C-5), 82.9 ($O\underline{C}(CH_3)_3$), 127.1-140.7 (C_{arom}) 152.2 (C=O, urethane), 170.5 (C-2).- $[\alpha]_D^{20}$ = -18.5 (c =

0.5, EtOAc).- $C_{32}H_{39}NO_4Si$ (529.75): calcd. C 72.65, H 7.42, N 2.64; found C 72.07, H 7.58, N 2.49.

tert-Butyl (4S,5S)-5-(tert-Butyldiphenylsilyloxy)-4-(4'-chlorophenyl)-piperidine-2-one-1-carboxylate 8f was prepared from 7 (3.2 g, 7.1 mmol) dissolved in Et_2O (50 ml) and 4-chlorphenyl magnesium bromide (71 ml, 71 mmol, 1 M in Et_2O) with $CuBr{\cdot}S(CH_3)_2$ (7.3 g, 35.5 mmol) in Et_2O (50 ml) and TMSCl (3.77 g, 4.5 ml, 35.5 mmol) as described for **8a**. . Yield: 2.7 g (68%) colourless oil, R_f = 0.4 (petroleum/Et_2O (3+2).- IR (neat): ν = 3080 (cm^{-1}), 2960-2860, 1775, 1720, 1500.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.92 (s, 9H, $SiC(CH_3)_3$), 1.40 (s, 9H, $OC(CH_3)_3$), 2.53 (dd, J_{gem} = 16.9 Hz, $J_{3,4e}$ = 6.7 Hz, 1H, 3-H), 2.96 (dd, J_{gem} = 16.9 Hz, $J_{3,4e}$ = 6.4 Hz, 1H, 3-H), 3.09 (ddd, $J_{4,3a} \approx J_{4,3e} = J_{4,5}$ = 6.5 Hz, 1H, 4-H_e), 3.25 (dd, J_{gem} = 13.4 Hz, $J_{6,5e}$ = 3.4 Hz, 1H, 6-H), 3.60 (dd, J_{gem} = 13.4 Hz, $J_{6,5e}$ = 5.1 Hz, 1H, 6-H), 3.88-3.96 (m, 1H, 5-H), 6.76 (m, 2H, $H_{p\text{-Cl-phenyl}}$), 7.12 (m, 2H, $H_{p\text{-Cl-phenyl}}$), 7.15-7.55 (m, 10H, $H_{Si(Ph)_2}$).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.0 ($SiC(CH_3)_3$), 26.8 ($SiC(CH_3)_3$), 27.9 ($OC(CH_3)_3$), 37.6 (C-3), 45.5 (C-4), 49.7 (C-6), 71.1 (C-5), 83.0 ($OC(CH_3)_3$), 127.7-135.7 (C_{arom}) 151.8 (C=O, urethane), 170.0 (C-2).- $[\alpha]_D^{20}$ = -9.3 (c = 0.2, EtOAc).- $C_{32}H_{38}ClNO_4Si$ (564.20): calcd. C 68.12, H 6.79, N 2.48; **found C 68.44, H 7.18, N 2.46.**

tert-Butyl (4S,5S)-5-(tert-Butyldiphenylsilyloxy)-4-(4'-fluorophenyl)-piperidine-2-one-1-carboxylate 8g

To magnesium turnings (1.96 g, 80.7 mmol) in diethyl ether (20 ml) a solution of 4-fluoro-bromo benzene (12.85 g, 8.03 ml, 73.4 mmol) in diethyl ether (10 ml) was added, so that the diethyl ether was gently boiling. After complete addition the mixture was refluxed for 1 h. The solution was then cooled to -40°C and added to a suspension of $CuBr{\cdot}SMe_2$ (7.54 g, 26.7 mmol) in diethyl ether (100 ml) at -40°C. The resulting dark brown solution was stirred at this temperature for 30 min. and cooled down to -78°C. TMSCl (2.55 g, 2.97 ml, 23.5 mmol) was added followed immediately by a solution of **7** (3.68 g, 8.15 mmol) in diethyl ether (70 ml). The solution was stirred for an additional 2 h. Then it was quenched at -78°C with dil. NH_4Cl solution and some drops of ammonia solution (25%) and diethyl ether (100 ml) were added. The organic layer was washed with NH_4Cl/ammonia solution until the aqueous layer remained colourless. The organic layer was dried over sodium sulphate, filtered and the solvent was evaporated. The remaining pale yellow oil was purified by column chromatography (silica gel, petroleum ether/diethyl ether (3+2), R_f = 0.43).- Yield: 3.5 g (79%) slightly yellow oil.- IR (neat): ν (cm^{-1}) = 3060, 2920, 1760 (urethane), 1710 (lactame), 1500.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.01 (s, 9H, $SiC(CH_3)_3$), 1.44 (s, 9H, $OC(CH_3)_3$), 2.61 (dd, $J_{gem.}$ = 16.8 Hz, $J_{3,4e}$ = 6.8 Hz, 1H, 3-H), 3.06 (dd, J_{gem} = 16.8 Hz, $J_{3,4e}$ = 6.4 Hz, 1H, 3-H), 3.21 (ddd, $J_{4e,3e} \approx J_{4e,3a} \approx J_{4e,5e}$ = 6.3 Hz, 1H, 4-H_e), 3.35 (dd, $J_{gem,}$ = 13.4 Hz, $J_{6,5e}$ = 3.34 Hz, 1H, 6-H), 3.71 (dd, J_{gem} = 13.4 Hz, $J_{6,5e}$ = 5.2 Hz, 1H, 6-H), 4.00-4.07 (m, 1H, 5-H_e), 6.68-6.91 (m, 4H, 4-F-Ph), 7.25-7.63 (m, 10H, $Si(Ph)_2$).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 18.9 ($SiC(CH_3)_3$), 26.6 ($SiC(CH_3)_3$), 27.8 ($OC(CH_3)_3$), 37.6 (C-3), 45.2 (C-4), 49.5 (C-6), 71.1 (C-5), 82.9 ($OC(CH_3)_3$), 115.4 (d, $J_{C\text{-}3',F}$ = 21.2 Hz, C-3'), 118.7 (d, $J_{C\text{-}2',F}$ = 7.7 Hz, C-2'), 127.7, 129.9, 133.1, 135.5 ($C_{arom\ Si\text{-}Ph}$), 136.3 (d, $J_{C\text{-}1',F}$ = 3 Hz, C-1'), 151.1

(urethane), 161.5 (d, $J_{C\text{-}4',F}$ = 242.7 Hz, C-4'), 171.3 (C-2).- $C_{32}H_{38}FNO_4Si$ (547.74). - MS (70 eV): m/z (%) = 434 (27) [M^+ -2 x t-Bu], 390 (100) [M^+- t-Bu -Boc], 346 (22), 312 (63), 241 (45), 199 (50), 181 (23), 135 (19), 77 (14).- $[\alpha]_D^{20}$ = -37 (c = 0.4, EtOAc).

tert-Butyl (5S)-5-(tert-Butyldiphenylsilyloxy)-4-methyl-2H-2-oxo-5,6-dihydro-pyridine-1-carboxylate 9

To HMDS (1.0 g, 1.3 ml, 6.23 mmol), dissolved in THF (20 ml), n-BuLi (3.1 ml, 6.2 mmol, 2 M in cyclohexane) was added at -78° C. The solution was stirred for 30 min. at 0° C, then cooled to -78° C and a solution of **8a** (1.3 g, 2.78 mmol) in THF (30 ml) was added. After 45 min. a solution of phenylselenenyl chloride (0.64 g, 3.34 mmol) in THF (30 ml) was added and stirring was continued for 2 h. The reaction was quenched with NH_4Cl solution (100 ml) and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and evaporated. The brown oil was dissolved in EtOAc (50 ml) and treated with 30% H_2O_2 (6 ml) with stirring for 45 min. at ambient temperature. The organic layer was washed with sat. $NaHCO_3$ solution (2x), brine (2x), dried with Na_2SO_4 and evaporated. The yellow oil was purified by column chromatography, petroleum ether/EtOAc (2+1), R_f = 0.64).- Yield: 1.0 g (80%) yellow oil.- IR (neat): ν = 3080-2860 (cm^{-1}), 1770, 1720, 1650.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.07 (s, 9H, $SiC(CH_3)_3$), 1.48 (s, 9H, $OC(CH_3)_3$), 1.84 (s, 3H, CH_3), 3.56 (dd, J_{gem} = 13.4 Hz, $J_{6,5e}$ = 4.0 Hz, 1H, 6-H), 3.87 (dd, J_{gem} = 13.4 Hz, $J_{6,5e}$ = 6.0 Hz, 1H, 6-H), 4.13 (m, 1H, 5-H_e), 5.74 (d, $J_{3,5e}$ = 1.3 Hz, 1H, 3-H), 7.38-7.51 (m, 6H, H_{arom}), 7.65-7.70 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.4 (CH_3), 19.9 ($SiC(CH_3)_3$), 26.9 ($SiC(CH_3)_3$), 28.0 ($OC(CH_3)_3$), 50.3 (C-6), 67.5 (C-5), 82.8 ($OC(CH_3)_3$), 122.6 (C-3), 127.9-135.9 (C_{arom}) 152.0 (C-4), 155.4 (C=O, urethane), 163.3 (C-2).- $[\alpha]_D^{20}$ = +14.4 (c = 0.92, EtOAc).- $C_{27}H_{35}NO_4Si$ (465.66) calcd. C 69.64, H 7.58, N 3.00; found C 70.04, H 8.61, N 2.58.

tert-Butyl (4S,5S)-5-(tert-butyldiphenylsilyloxy)-4-methyl-piperidine-2-one-1-carboxylate (10) and **tert-Butyl (4R,5S)-5-(tert-butyldiphenylsilyloxy)-4-methyl-piperidine-2-one-1-carboxylate 8a**

To a solution of **9** (0.45 g, 0.97 mmol) in EtOAc (50 ml) Pd/C (100 mg, 10% Pd) was added and the mixture was hydrogenated at room temp. for 12 h under 2 bar hydrogen pressure. Pd/C was removed by filtration and the solvent was evaporated. The remaining colourless oil was purified by column chromatography; petroleum ether/EtOAc (4+1), R_f = 0.49 for both diastereomers. Yield: 0.32 g (71%) colourless oil.- The ratio **10** : **8a** = 94 : 6 was determined by ^{13}C-NMR. ^{1}H-NMR ($CDCl_3$) for **10**: δ (ppm) = 1.02 (d, J = 7.0 Hz, 3H, CH_3), 1.06 (s, 9H, $SiC(CH_3)_3$), 1.44 (s, 9H, $OC(CH_3)_3$), 1.90-1.99 (m, 1H, 4-H_a), 2.43 (dd, J_{gem} = 17.3 Hz, $J_{3e,4a}$ = 5.6 Hz, 1H, 3-H_e), 2.66 (dd, J_{gem} = 17.3, Hz, $J_{3a,4e}$ = 11.3 Hz, 1H, 3-H_a), 3.24 (dd, $J_{gem,}$ = 13.4 Hz, $J_{6,5e}$ = 2.6 Hz, 1H, 6-H), 3.63 (dd, J_{gem} = 13.4 Hz, $J_{6,5e}$ = 3.6 Hz, 1H, 6-H), 3.92 (m, 1H, 5-H_e), 7.32-7.48 (m, 6H, H_{arom}), 7.60-7.70 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 16.6 (CH_3), 19.4 ($SiC(CH_3)_3$), 26.7 ($SiC(CH_3)_3$), 27.8 ($OC(CH_3)_3$), 34.6 (C-4), 38.0 (C-3), 52.1 (C-6), 68.6 (C-5), 82.5 ($OC(CH_3)_3$), 127.7-135.8 (C_{arom}) 152.2 (C=O, urethane), 170.3 (C-2).- $C_{26}H_{37}NO_4Si$ (455.67) calcd. C 68.53, H 8.18, N 3.07; found C 68.16, H 8.10, N 2.70.

tert-Butyl (4R,5S)-5-(tert-Butyldiphenylsilyloxy)-4-formylmethyl-piperidine-2-one-1-carboxylate 12

8d (2 g, 4.1 mmol) was dissolved in CH_2Cl_2/MeOH (150 ml, 1+1) and ozone (1 g O_3/h, rate = 25 ml/h, 0.5 A) was passed through the mixture at -78° C with stirring until the solution showed a faint blue colour. N_2 was passed through the solution for 3 min. and dimethyl sulfide (5ml, 114 mmol) was added. After stirring for 3 h at room temp. CH_2Cl_2 (100 ml) was added to the mixture and the organic layer was washed with water and brine (2x). The organic phase was dried (Na_2SO_4), evaporated and the colourless oil was purified by column chromatography (petroleum ether/EtOAc, 1+1; R_f = 0.62). Yield: 1.34-1.79 g (66-89%) colourless oil.- IR (neat): ν = 3080-2960 (cm^{-1}), 1770, 1730, 1470.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.08 (s, 9H, $SiC(CH_3)_3$), 1.47 (s, 9H, $OC(CH_3)_3$), 2.16 (ddd, J_{gem} = 17.8 Hz, $J_{CH_2,4e}$ = 8.6 Hz, $J_{CH_2,CHO}$ = 1.4 Hz, 1H, CH_2-CHO), 2.19 (dd, J_{gem} = 16.6 Hz, $J_{3,4e}$ = 7.2 Hz, 1H, 3-H), 2.37 (ddd, J_{gem} = 17.8, Hz, $J_{CH_2,4e}$ = 4.7 Hz, $J_{CH_2,CHO}$ = 1.0 Hz, 1H, CH_2-CHO), 2.47-2.58 (m, 1H, 4-H_e), 2.87 (dd, J_{gem}, = 16.6 Hz, $J_{3,4e}$ = 6.0 Hz, 1H, 3-H), 3.52 (dd, J_{gem} = 13.3 Hz, $J_{6,5e}$ = 3.5 Hz, 1H, 6-H), 3.67-3.86 (dd and m, J_{gem} = 13.3 Hz, $J_{6,5e}$ = 5.4 Hz, 2H, 6-H, 5-H_e), 7.35-7.51 (m, 6H, H_{arom}), 7.62-7.70 (m, 4H, H_{arom}), 9.51(t, J =1.1 Hz, 1H, CHO).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.2 ($SiC(CH_3)_3$, 26.9 ($SiC(CH_3)_3$), 28.2 ($OC(CH_3)_3$), 36.4 (C-4), 36.7 (CH_2-CHO), 37.1 (C-3), 50.0 (C-6), 70.5 (C-5), 83.2 ($OC(CH_3)_3$), 127.9-135.7 (C_{arom}) 151.7 (C=O, urethane), 169.9 (C-2), 175.8 (CHO).- $[\alpha]_D^{20}$ = -23 (c = 0.8, EtOAc).- $C_{28}H_{37}NO_5Si$ (495.69) calcd. C 67.85, H 7.52, N 2.83; found C 67.86, H 7.37, N 2.67.

tert-Butyl (3S,4S)-3-(tert-Butyldiphenylsilyloxy)-4-(hydroxyethyl)-piperidine-1-carboxylate 13

To a solution of **12** (1.6 g, 3.2 mmol) in THF (75 ml) was added $BH_3{\cdot}S(CH_3)_2$ (6.5 ml, 6.5 mmol, 1 M in THF). The mixture was stirred for 3 h at 70° C, cooled to room temp. and treated with 2 M HCl (20 ml). After addition of EtOAc (75 ml) the organic layer was washed with brine and $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated. The colourless oil was dissolved in ether (100 ml) and treated with TMEDA (2 ml). The precipitation was removed by filtration and the remaining TMEDA was extraxted with 2 M HCl. The organic layer was dried and evaporated. The colourless oil was purified by column chromatography; (petroleum ether/EtOAc 1+1, R_f = 0.28). Yield: 0.94-1.03 g (60-66%) colourless oil.- IR (neat): ν = 3400 (cm^{-1}), 3080-2860, 1690, 1480.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.08 (s, 9H, $SiC(CH_3)_3$), 1.14-1.34 (s, and m, 10H, $OC(CH_3)_3$, 4-H), 1.54-1.63 (m, 2H, 5-H), 1.83 (ddd, J_{gem} = 13.3 Hz, $J_{C\underline{H}_2CH_2OH}$ = $J_{CH_2C\underline{H}_2OH}$ = 4.1 Hz, 1H, $C\underline{H}_2CH_2OH$), 2.78-2.98 (m, 2H, 6-H), 3.34 (ddd, $J_{3a,2a} \approx J_{3a,4a}$ = 8.2 Hz, $J_{3a,2e}$ = 4.1 Hz, , 1H, 3-H_a), 3.50 (t, J = 6.7 Hz, 2H, $CH_2C\underline{H}_2OH$), 3.60-3.85 (dd, and m, J_{gem} = 13.4 Hz, $J_{2e,3a}$ = 4.1 Hz, 2H, 2-H), 7.32-7.45 (m, 6H, H_{arom}), 7.64-7.73 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.4 ($SiC(CH_3)_3$, 27.1 ($SiC(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 28.4 (C-5), 34.3 (CH_2CH_2OH), 39.9 (C-4), 42.2 (C-6), 49.4 (C-2), 60.6 (CH_2CH_2OH), 72.2 (C-3), 79.3 ($OC(CH_3)_3$), 127.5-135.9 (C_{arom}) 154.5 (C=O, urethane).- $[\alpha]_D^{20}$ = -24 (c = 0.4, EtOAc).- $C_{28}H_{41}NO_4Si$ (483.72) calcd. C 69.53, H 8.54, N 2.90; found C 69.95, H 9.40, N 2.72.

tert-Butyl (3S,4S)-3-(tert-Butyldiphenylsilyloxy)-4-[2-(2-methoxyethoxy)-methoxyethyl]-piperidine-1-carboxylate 14

To a solution of **13** (1.34 g, 2.77 mmol) in CH_2Cl_2 (100 ml) was added ethyldiisopropyl amine (0.83 g, 1.1 ml, 4.16 mmol) and MemCl (0.52 g, 0.47 ml, 4.16 mmol) and the mixture was stirred for 24 h at room temperature. The reaction progress was monitored by thin layer chromatography. When the starting material was consumed the reaction was quenched by the addition of water (20 ml) and the organic layer was washed with NH_4Cl solution (2x) and brine (2x). The organic phase was dried (Na_2SO_4), filtered and evaporated. The colourless oil was purified by column chromatography with petroleum ether/EtOAc, 1+1, Rf = 0.58. Yield: 1.4 g (88%) colourless oil.- IR (neat): ν = 3080-2860 (cm^{-1}), 1700, 1430.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.07 (s, 9H, $SiC(CH_3)_3$), 1.33 (s, 9H, $OC(CH_3)_3$), 1.53-1.74 (m, 2H, C-4-$C\underline{H}_2CH_2O$), 1.79-2.17 (dd, and m, J_{gem} = 13.6 Hz, $J_{5a,4e}$ = $J_{5e,4a}$ = 3.9 Hz, 3H, 5-H, 4-H), 2.77-2.88 (m, 2H, 6-H), 3.29-3.65 (m, and s, 10H, C-4-$CH_2C\underline{H}_2O$, $OC\underline{H}_2C\underline{H}_2OC\underline{H}_3$, 3-H), 3.70-3.87 (dd, and m, J_{gem} = 12.7 Hz, $J_{2,3}$ = 3.7 Hz, 2H, 2-H), 4.62 (s, 2H, OCH_2O), 7.32-7.39 (m, 6H, H_{arom}), 7.63-7.72 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.3 ($Si\underline{C}(CH_3)_3$, 27.0 ($SiC(\underline{C}H_3)_3$), 28.2 ($OC(\underline{C}H_3)_3$), 29.6 (C-4-$\underline{C}H_2CH_2O$), 31.0 (C-5), 40.3 (C-4), 42.2 (C-6), 49.7 (C-2), 58.9 ($O\underline{C}H_3$), 65.4, 66.7, (OCH_2CH_2O), 71.7 (C-4-$CH_2\underline{C}H_2O$), 72.3 (C-3), 79.2 ($O\underline{C}(CH_3)_3$), 95.2 (OCH_2O), 127.4-135.8 (C_{arom}) 154.5 (C=O, urethane).- $[\alpha]_D^{20}$ = -20 (c = 0.8, EtOAc).- $C_{32}H_{49}NO_6Si$ (571.83) calcd. C 67.22, H 8.64, N 2.45; found C 67.62, H 9.12, N 2.32.

tert-Butyl (3S,4S)-3-Hydroxy-4-[2-(2-methoxyethoxy)-methoxyethyl]-piperidine-1-carboxylate 15

To a solution of **14** (1.34 g, 2.34 mmol) in THF (50 ml) was added n-Bu_4NF (2.3 ml, 2.5 mmol, 1.1 M in THF) and the mixture was stirred for 2 h at room temperature. The reaction progress was monitored by thin layer chromatography. When the starting material was consumed the reaction was quenched by the addition of acetic acid (1 ml) and EtOAc (100 ml) was added. The organic layer was washed with NH_4Cl solution (2x) and brine (2x). The organic phase was dried (Na_2SO_4), filtered and evaporated. The colourless oil was purified by column chromatography with CH_2Cl_2/CH_3OH, 9+1, R_f = 0.54. Yield: 0.53 g (84 %).- IR (neat): ν = 3460 (cm^{-1}), 3000-2860 1690, 1430.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.12-1.92 (s, and m, $OC(CH_3)_3$ C-4-$C\underline{H}_2CH_2O$, 14H, 4-H, 5-H), 2.34 (dd, J_{gem} = 12.8 Hz, $J_{6a,5a}$ = 10.1 Hz, 1H, 6-H_a), 2.57-2.78 (m, 1H, 6-H_e), 3.20-3.30 (m, 1H, 3-H_a), 3.38 (s, 3H, OCH_3), 3.5-3.78 (m, 6H, C-4-$CH_2C\underline{H}_2O$, $OC\underline{H}_2C\underline{H}_2O$, 3-H), 4.04 ($d_{br}$, J_{gem} = 12.2 Hz, 1H, 2-H_a), 4.18 (dd, J_{gem} = 12.4 Hz, $J_{2e,3a}$ = 3.4 Hz, 1H, 2-H_e), 4.73 (s, 2H, OCH_2O).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.4 ($OC(\underline{C}H_3)_3$), 30.5 (C-4-$\underline{C}H_2CH_2O$), 33.5 (C-5), 42.2 (C-4), 43.3 (C-6), 49.9 (C-2), 58.9 ($O\underline{C}H_3$), 66.4, 67.1, (OCH_2CH_2O), 71.1 (C-3), 71.7 (C-4-$CH_2\underline{C}H_2O$), 79.6 ($O\underline{C}(CH_3)_3$), 95.5 (OCH_2O), 154.7 (C=O, urethane).- $[\alpha]_D^{20}$ = -16.3 (c = 0.17, EtOAc).- $C_{16}H_{31}NO_6$ (333.42) calcd. C 57.64, H 9.37, N 4.20; found C 58.41, H 10.09, N 4.04.

tert-Butyl (3S,4S)-3-Methanesulfonyloxy-4-[2-(2-methoxyethoxy)-methoxyethyl]-piperidine-1-carboxylate 16

To a solution of **15** (535 mg, 1.6 mmol) in CH_2Cl_2 (50 ml) was added at -20°C 4-DMAP (235 mg, 1.9 mmol), triethylamine (0.3 ml, 2.2 mmol) and methane sulfonyl chloride (0.2 ml, 8.6 mmol) and the mixture was stirred for 2 d at room temperature. The reaction progress was monitored by thin layer chromatography. When the starting material was consumed the reaction was quenched by the addition 2 M HCl (10 ml) and the organic layer was washed with 2 M HCl solution (2x) and brine (2x). The organic phase was dried (Na_2SO_4), filtered and evaporated. The brown oil was purified by column chromatography with petroleum ether/EtOAc, 1+2, R_f = 0.51. Yield: 0.57 g (86 %).- IR (neat): ν = 3000-2820 (cm^{-1}), 1690, 1430.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.24-1.54 (s, and m, 11H, $OC(CH_3)_3$ $C\underline{H}_2CH_2O$), 1.77-2.08 (m, 3H, 5-H, 4-H), 2.81-3.03 (m, 2H, 6-H), 3.05 (s, 3H, SO_2CH_3), 3.38 (s, 3H, OCH_3), 3.49-3.70 (m, 6H, C-4-$CH_2C\underline{H}_2O$, $OC\underline{H}_2C\underline{H}_2O$), 3.85 (m, 1H, 3-H),), 4.69 (s, 2H, OCH_2O).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.3 ($OC(\underline{C}H_3)_3$), 28.6 (C-5), 31.0 (C-4-$\underline{C}H_2CH_2O$), 37.9 (C-4), 38.6 ($SO_2\underline{C}H_3$), 42.3 (C-6), 47.3 (C-2), 59.0 ($O\underline{C}H_3$), 64.9, 66.9, 71.9 (C-4-$CH_2\underline{C}H_2O$, $O\underline{C}H_2CH_2O$), 79.5 (C-3), 80.2 ($O\underline{C}(CH_3)_3$), 95.5 (OCH_2O), 154.4 (C=O, urethane).- $[\alpha]_D^{20}$ = -17 (c = 0.7, EtOAc).- $C_{17}H_{33}NO_8S$ (411.51) calcd. C 49.62, H 8.03, N 3.40; found C 49.44, H 8.30, N 3.23.

tert-Butyl (3S,4R)-3-(tert-Butyldiphenylsilyloxy)-4-methyl-piperidine-1-carboxylate 18a

To a solution of **8a** (2.53 g, 5.4 mmol) in THF (50 ml) was added $BH_3{\cdot}S(CH_3)_2$ (6.5 ml, 6.5 mmol, 1M in THF), and the mixture was stirred for 3 h at 70°C with stirring. After the reaction was allowed to cool to room temperature diethyl ether (100 ml) was added and the reaction was quenched with 2 M HCl (10 ml). The organic layer was washed with 2 M HCl solution (2x) and brine (2x). The organic phase was dried (Na_2SO_4), filtered and evaporated. The colourless oil was purified by column chromatography with petroleum ether/EtOAc, 4+1, R_f = 0.62. Yield: 1.1 g (45 %).- IR (neat): ν = 3080-2860 (cm^{-1}), 1700, 1430.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.86 (d, J = 6.3 Hz, 3H, CH_3), 1.07 (s, 9H, $SiC(CH_3)_3$), 1.32 (s, 9H, $OC(CH_3)_3$), 1.43-1.67 (m, 3H, 4-H_a, 5-H), 2.63-2.74 (dd, and m, J_{gem} = 12.7 Hz, $J_{6a,5a}$ = 9.4 Hz, 2H, 6-H), 3.22 (ddd, $J_{3a,2a} \approx J_{3a,4a}$ = 8.9 Hz, $J_{3a,2e}$ = 4.3 Hz, 1H, 3-H_a), 3.88-3.96 (m, 2H, 2-H), 7.26-7.43 (m, 6H, H_{arom}), 7.64-7.73 (m, 4H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 18.2 (CH_3), 19.4 ($Si\underline{C}(CH_3)_3$, 27.1 ($SiC(\underline{C}H_3)_3$), 28.3 ($OC(\underline{C}H_3)_3$), 31.7 (C-5), 38.6 (C-4), 42.6 (C-6), 50.1 (C-2), 74.2 (C-3), 79.2 ($O\underline{C}(CH_3)_3$), 127.5-135.9 (C_{arom}) 154.5 (C=O, urethane).- $[\alpha]_D^{20}$ = -34 (c = 0.1, EtOAc).- $C_{27}H_{39}NO_3Si$ (453.70) calcd. C 71.48, H 8.66, N 3.09; found C 71.80, H 8.97, N 3.08.

tert-Butyl (3S,4S)-5-(tert-Butyldiphenylsilyloxy)-4-(4'-chlorophenyl)-piperidine-1-carboxylate 18f

To a solution of **8f** (700 mg, 1.27 mmol) in THF (70 ml) was added $BH_3{\cdot}S(CH_3)_2$ (1.4 ml, 1.4 mmol, 1 M in THF). The mixture was stirred for 3 h at 70° C, cooled to room temp. and treated with 2 M HCl (20 ml). After addition of diethylether (50 ml) the organic layer was washed with 2 M HCL (2x), brine and $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated. The colourless oil was dissolved in ether (30 ml) and treated with TMEDA (1 ml). The precipitation was removed by filtration and the remaining TMEDA was extracted with 2 M HCl. The organic

layer was dried and evaporated. The colourless oil crystallized and the crystals were recrystallized from ether/pentane. Yield: 0.29 g (42%) colourless crystals.- m.p. 99°C.- IR (neat): ν = 3080-2860 (cm^{-1}), 1700, 1430.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.82 (s, 9H, $SiC(CH_3)_3$), 1.32 (s, 9H, $OC(CH_3)_3$), 1.44-1.71 (m, 2H, 5-H), 2.56-2.71 (m, 3H, 4-H_a, 6-H), 3.61 (ddd, $J_{3a,2a} \approx J_{3a,4a}$ = 10.0 Hz, $J_{3a,2e}$ = 4.7 Hz, 1H, 3-H_a), 4.05-4.17 (m, 2H, 2-H), 6.90 (m, 2H, $H_{p\text{-}Cl\text{-}phenyl}$), 7.16 (m, 2H, $H_{p\text{-}Cl\text{-}phenyl}$), 7.2o-7.51 (m, 10H, H_{arom}).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.0 ($SiC(CH_3)_3$, 26.7 ($SiC(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 32.5 (C-5), 43.4 (C-6), 51.2 (C-2), 51.3 (C-4), 72.6 (C-3), 79.6 ($OC(CH_3)_3$), 127.5-141.5 (C_{arom}) 154.3 (C=O, urethane).- $[\alpha]_D^{20}$ = -11 (c = 0.2, EtOAc).- $C_{32}H_{40}ClNO_3Si$ (550.21) calcd. C 69.86, H 7.33, N 2.55; found C 69.97, H 7.51, N 2.47.

tert-Butyl (3S,4S)-3-(tert-Butyldiphenylsilyloxy)-4-(4´-fluorophenyl)-piperidine-1-carboxylate 18g

a: To a solution of **8g** (0.75 g, 1.37 mmol) in toluene (75 ml) BH_3 $S(CH_3)_2$ (0.75 ml, 1.5 mmol, 2M in toluene) was added. The mixture was kept at 70°C for 2h. The reaction was quenched with methanol (20 ml) and the solution was refluxed for 18 h. The mixture was cooled to room temperature and 2 M HCl (10 ml) was added. The organic layer was washed with sat. $NaHCO_3$-, NH_4Cl- solution and brine, dried with sodium sulphate and the solvent was evaporated. The pale yellow oil was subjected to column chromatography.Yield: 0.33 g (45%).

b: A solution of **8g** (3.68 g , 6.7 mmol) in of dichloromethane (100 ml) was cooled to -78°C and a solution of lithium triethylborohydride (8.1 ml, 8.1 mmol, 1 M in THF) was added with stirring. After 30 min. the reaction was quenched with dil.$NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (3 x 25 ml) and the combined organic layers were washed with brine, dried over sodium sulphate and evaporated. The crude product was used without further purification. It was dissolved in dichloromethane (100 ml) and cooled to -78°C. Triethylsilane (0.87 g, 1.1 ml, 7.4 mmol) was added, followed immediately by boron trifluoride etherate (1.06 g, 0.86 ml, 7.4 mmol). To this mixture was added again 1.1 ml of triethylsilane and 0.86 ml of boron trifluoride etherat. After additional stirring for 2h, the reaction was quenched with dil. $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (3 x 25 ml) and the combined organic layers were dried over sodium sulphate, filtered and the solvent was evaporated. The slightly yellow oil was purified by column chromatography on silica gel with petroleum ether/EtOAc 4+1, R_f = 0.57. - Yield: 2.86 g (80 %) colourless crystals. - m.p.: 83° C. - IR (KBr): ν = 3040 (cm^{-1}), 2920, 2850, 1690 (urethane), 1500. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.81 (s, 9H, $SiC(CH_3)_3$), 1.32 (s, 9H, $OC(CH_3)_3$), 1.39-1.75 (m, 2H, 5-H), 2.59-2.73 (m, 3H, 4-H_a, 6-H), 3.63 (ddd, $J_{3a,4a} \approx J_{3a,2a}$ = 10.0 Hz, $J_{3a,2e}$ = 4.7 Hz, 1H, 3-H_a), 4.04-4.19 (m, 2H, 2-H), 6.81-6.99 (m, 4H, 4'-F-Ph), 7.20-7.54 (m, 10H, $Si(Ph)_2$).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.0 ($SiC(CH_3)_3$), 26.8 ($SiC(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 32.7 (C-5), 43.6 (C-6), 51.2 (C-4), 51.3 (C-2), 72.9 (C-3), 79.4 ($OC(CH_3)_3$), 114.8 (d, $J_{C\text{-}3',F}$ = 20.9 Hz, C-3´), 129.3 (d, $J_{C\text{-}2',F}$ = 10.2 Hz, C-2´), 138.5 (d, $J_{C\text{-}1',F}$ = 2.8 Hz, C-1´), 127.3, 132.7, 134.1, 135.8 ($C_{arom.\ SiPh}$), 154.1 (urethane), 161.5 (d, $J_{C\text{-}4',F}$ = 242.7 Hz, C-4´).- $[\alpha]_D^{20}$ = -13 (c = 0.3, EtOAc).- $C_{32}H_{40}FNO_3Si$ (533.76): calcd. C 72.00, H 7.55, N 2.67; found C 71.76, H 7.50, N 2.37.

tert-Butyl (3S,4R)-3-Hydroxy-4-methyl-piperidine-1-carboxylate 19a

To a solution of **18a** (0.53 g, 1.17 mmol) in THF (20 ml) was added tetrabutyl ammonium fluoride (n-Bu_4NF) (1.2 ml, 1.32 mmol, 1M in THF), and the mixture was stirred for 2 h at room temperature. After the reaction was compete (tlc control!) acetic acid (1 ml) and EtOAc was added (50 ml) and the organic layer was washed with NH_4Cl solution (2x) and brine (2x). The organic phase was dried (Na_2SO_4), filtered and evaporated. The colourless oil was purified by column chromatography with petroleum ether/EtOAc, 1+2, R_f = 0.60. Yield: 0.19 g (76 %) colorless crystals. m. p. 97°C. - IR (KBr): ν = 3400 (cm^{-1}), 2990-2880, 1680, 1470.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.06 (d, J = 6.3 Hz, 3H, CH_3), 1.14-1.29 (m, 2H, 5-H), 1.45 (s, 9H, $OC(CH_3)_3$), 1.67 (ddd, $J_{4a,3a}$ = 10. Hz, $J_{4a,CH3}$ = 6.4 Hz, $J_{4a,5e}$ = 3.1 Hz, 1H, 4-H_a), 1.70-2.40 (s, 1H, OH), 2.55 (dd, J_{gem} = 12.5 Hz, $J_{6a,5a}$ = 9.9 Hz, 1H, 6-H_a), 2.71 (t_{br}, J_{gem} = 11.8 Hz, 1H, 6-H_e), 3.19 (ddd, $J_{3a,2a} \approx J_{3a,4a}$ = 9.5 Hz, $J_{3a,2e}$ = 4.5 Hz, 1H, 3-H_a), 3.96 (d_{br}, J_{gem} = 12.4 Hz, 1H, 2-H_a), 4.20 (dd, J_{gem} = 12.4 Hz, $J_{2e,3a}$ = 4.3 Hz, 1H, 2-H_e).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 17.7 (CH_3), 28.4 ($OC(\underline{C}H_3)_3$), 32.1 (C-5), 38.3 (C-4), 43.5 (C-6), 49.9 (C-2), 72.5 (C-3), 79.6 ($O\underline{C}(CH_3)_3$), 154.8 (C=O, urethane).- $[\alpha]_D^{20}$ = +2 (c = 0.7, EtOAc).- $C_{11}H_{21}NO_3$ (215.29) calcd. C 61.37, H 9.83, N 6.51; found C 61.33, H 10.19, N 6.54.

tert-Butyl (3S,4S)-4-(4-Chlorophenyl)-3-hydroxy-piperidine-1-carboxylate 19f

To a solution of **18f** (0.243 g, 0.44 mmol) in THF (30 ml) was added n-Bu_4NF (0.44 ml, 0.58 mmol, 1M in THF), and the mixture was stirred for 2 h at room temperature. After the reaction was compete (tlc control!) acetic acid (1 ml) and EtOAc (50 ml) was added and the organic layer was washed with NH_4Cl solution (2x) and brine (2x). The organic phase was dried (Na_2SO_4), filtered and evaporated. The colourless oil was purified by column chromatography with petroleum ether/EtOAc, 1+2, R_f = 0.26. Yield: 0.115 g (83%) colourless crystals from diethyl ether/pentane. m. p. 121°C. - IR (KBr): ν = 3450 (cm^{-1}), 2980-2860, 1680, 1500.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.48 (s, 9H, $OC(CH_3)_3$), 1.57-1.77 (m, J_{gem} = 11.7 Hz, $J_{4a,5e}$ = 4.2. Hz, 1H, 5-H), 2.44-2.81 (3dd, J_{gem} = 12.4 Hz, $J_{4a,3a}$ = 9.5 Hz, $J_{4a,5e}$ = 4.6 Hz, J_{gem} = 12.2 Hz, $J_{6a,5a}$ = 10.4 Hz, $J_{6a,5e}$ = 3.3 Hz, 3H, 4-H_a, 6-H), 3.64 (ddd, $J_{3a,4a} \approx J_{3a,2a}$ = 10.0 Hz, $J_{3a,2e}$ = 4.8 Hz, 1H, 3-H_a), 4.13-4.42 (m, J_{gem} = 13.4 Hz, $J_{2e,3a}$ = 4.9 Hz, 2H, 2-H), 7.20 (m, 2H, H_{arom}), 7.32 (m, 2H, H_{arom}), .- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.4 ($OC(\underline{C}H_3)_3$), 32.0 (C-5), 43.8 (C-6), 49.9 (C-2), 50.9 (C-4), 70.9 (C-3), 80.0 ($O\underline{C}(CH_3)_3$), 129.0-140.1 (C_{arom}), 154.6 (C=O, urethane).- $[\alpha]_D^{20}$ = -13 (c = 0.2, EtOAc).- $C_{16}H_{22}ClNO_3$ (311.81) calcd. C 61.63, H 7.11, N 4.49; found C 62.31, H 7.39, N 4.60.

tert-Butyl (3S,4S)-4-(4´-Fluorophenyl)-3-hydroxy-piperidine-1-carboxylate 19g

To a solution of **18g** (1.57 g, 2.9 mmol) in THF (90 ml) a solution of n-Bu_4NF (3.8 ml, 3.8 mmol, 1 M in THF) was added. After stirring the mixture for 18h at room temperature the reaction was quenched with a few drops of acetic acid. Ethyl acetate (75 ml) was added. and the organic layer was washed with diluted NH_4Cl- and brine, dried over sodium sulphate, filtered and evaporated. The colourless oil was purified by column chromatography on silica gel with petroleum ether/EtOAc 2+1, R_f = 0.26. - Yield: 0.64 mg (74 %) colourless crystals. - m.p. 107°C. - IR (KBr): ν = 3480 (cm^{-1}) (OH), 2960, 2910, 2840, 1670 (urethane), 1500.-

^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.47 (s, 9H, $OC(CH_3)_3$), 1.60-1.81 (m, 2H, 5-H), 2.27 (s, 1H, OH), 2.43-2.64 (m, 3H, 4-H_a, 6-H), 3.59 (ddd, $J_{3a,4a} \approx J_{3a,2a}$ = 10 Hz, $J_{3a,2e}$ = 4.9 Hz, 1H, 3-H_a), 4.15 (d, $J_{gem.}$ = 12.6 Hz, 1H, 2-H), 4.35 (dd, J_{gem} = 12.6 Hz, $J_{2,3a}$ = 3.9 Hz, 1H, 2-H), 6.95-7.07 (m, 2H, $H_{arom,}$), 7.15-7.25 (m, 2H, $H_{arom,}$).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 28.3 ($OC(\underline{C}H_3)_3$), 32.2 (C-5), 43.8 (C-6), 49.9 (C-2), 50.5 (C-4), 70.7 (C-3), 79.9 ($O\underline{C}(CH_3)_3$), 115.5 (d, $J_{C\text{-}3',F}$ = 21.1, C-3′), 129.1 (d, $J_{C\text{-}2',F}$ = 7.9 Hz, C-2′), 137.4 (C-1′), 154.5 (urethane), 161.8 (d, $J_{C\text{-}4',F}$ = 243.3, C-4′).- $[\alpha]_D^{20}$ = -7 (c = 1.5, EtOAc).- $C_{16}H_{22}FNO_3$ (295.36): calcd. C 65.06, H 7.51, N 4.74; found C 64.89, H 7.68, N 4.60.

(3S,4R)-3-Hydroxy-4-methyl-piperidine hydrochloride 20a

A solution of **19a** (0.21 g, 1.4 mmol) in ethanolic HCl (25 ml) was stirred at room temperature for 18 h. The solvent was evaporated and the remaining pale brown powder was recrystallized from isobutanol/diethyl ether. Yield: 0.17 g (80%) colourless crystals. m.p. 178°C.- IR (KBr): ν = 3350 (OH) (cm^{-1}), 2940, 2800, 1580.- ^{1}H-NMR (D_4-methanol): δ (ppm) = 1.25 (d, J = 6.3 Hz, 3H, CH_3), 1.55-1.85 (m, 2H, 5-H), 2.08-2.19 (m, 1H, 4-H), 2.91 (dd, $J_{gem.}$ = 12.1 Hz, $J_{6a,5a}$ = 9.8 Hz, 1H, 6-H_a), 3.13 (ddd, $J_{gem.}$ = 12.6 Hz, $J_{6e,5e} \approx J_{6e,5a}$ = 3.5 Hz, 1H, 6-H_e), 3.41-3.65 (m, 3H, 3-H, 2-H).- ^{13}C-NMR (D_4-methanol): δ (ppm) = 18.4 (CH_3), 30.2 (C-5), 38.2 (C-4), 45.2 (C-6), 50.1 (C-2), 70.8 (C-3).- $[\alpha]_D^{20}$ = -32 (c = 1, EtOH).- $C_6H_{14}ClNO$ (151.64) calcd. C 47.52, H 9.31, N 9.24; found C 47.37, H 9.93, N 8.97.

(3S,4S)-4-(4′-Fluorophenyl)-3-hydroxy-piperidine hydrochloride 20g

A solution of **19g** (150 mg, 0.5 mmol) in of ethanolic HCl (25 ml) was stirred at room temperature for 18 h. The solvent was evaporated and the remaining pale yellow powder was recrystallized from isobutanol/diethyl ether. Yield: 0.10 g (83 %) colourless crystals. m.p. 231°C.- IR (KBr): ν = 3300 (OH) (cm^{-1}), 2940, 2700, 2500, 1510.- ^{1}H-NMR (D_4-methanol): δ (ppm) = 2.17-2.26 (m, 2H, 5-H), 2.89-3.11 (m, 2H, 6-H), 3.20-3.35 (m, 1H, 4-H_a), 3.59-3.75 (m, 2H, 2-H), 4.20 (ddd, $J_{3a,2a} \approx J_{3a,4a}$ = 10.6 Hz, $J_{3a,2e}$ = 4.6 Hz, 1H, 3-H_a), 7.21-7.30 (m, 2H, H_{arom}), 7.49-7.56 (m, 2H, H_{arom}).- ^{13}C-NMR (D_4-methanol): δ (ppm) = 30.3 (C-5), 45.0 (C-6), 49.1 (C-4), 50.1 (C-2), 68.6 (C-3), 116.1 (d, $J_{C\text{-}3',F}$ = 21.3 Hz, C-3′), 130.5 (d, $J_{C\text{-}2',F}$ = 8.2 Hz, C-2′), 138.6 (d, $J_{C\text{-}1',F}$ = 2.9 Hz, C-1′), 162.3 (d, $J_{C\text{-}4',F}$ = 242.6 Hz, C-4′).- $[\alpha]_D^{20}$ = -73 (c = 0.4, EtOH). $C_{11}H_{15}ClFNO$ (231.70): calcd. C 57.02, H 6.53, N 6.05; found C 56.97, H: 6.34, N 5.77.

tert-Butyl (3S,4S)-4-(4′-Fluorophenyl)-3-piperonyloxy-piperidine-1-carboxylate 21g

To a solution of **19g** (0.4 g, 1.4 mmol) in of DMSO (8 ml) potassium hydroxide (0.30 g, 5.2 mmol) was added. The suspension was stirred for 5 minutes then piperonyl chloride (0.43 g, 2.7 mmol) was added and the solution was stirred overnight at room temperature. After addition of diethyl ether (100 ml) the organic layer was extracted with water (2x20 ml) and brine. The organic layer was dried with sodium sulphate, filtered and evaporated. The remaining colourless oil was purified by column chromatography on silica gel with petroleum ether/EtOAc, 3 + 1, R_f = 0.43. Yield: 0.46 g (80%) colourless oil. IR (neat): ν = 2980-2880 (cm^{-1}) 1690 (urethane), 1600.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.48 (s, 9H, $OC(CH_3)_3$), 1.62-1.81 (m, 2H, 5-H), 2.52-2.80 (m, 3H, 4-H_a, 6-H), 3.25-3.37 (ddd, $J_{3a,4a} \approx J_{3a,2a}$ = 10.0

Hz, $J_{3a,2e}$ = 4.3 Hz, 1H, 3-H_a), 4.02-4.45 (m, 4H, 2-H, OCH_2Ph), 5.89 (s, 2H, acetal), 6.32-6.78 (m, 3H, piperonylphenyl), 6.92-7.15 (m, 4H, p-F-Ph).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 23.4 ($OC(\underline{C}H_3)_3$), 32.2 (C-5), 43.8 (C-6), 47.9 (C-2), 48.9 (C-4), 71.6 ($O\underline{C}H_2Ph$), 77.5 (C-3), 79.8 ($O\underline{C}(CH_3)_3$), 100.9 (acetale), 115.5, 129.1, 138.3, 161.8 (p-F-Ph), 107.6, 108.4, 121.2, 131.7, 147.0, 147.5 (piperonylphenyl), 154.5 (urethane).- $[\alpha]_D^{20}$ = -37 (c = 3, CH_2Cl_2).- $C_{24}H_{28}FNO_5$ (429.26).- MS (70 eV): m/z (%) = 429 (1) [M^+], 372 (2) [M^+- t.Bu], 199 (24), 135 (46), 97 (20), 85 (22), 71 (32), 57 (100), 43 (32), 41 (26).

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References and Notes

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