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Synthesis of *trans*-epoxy-L-proline and *cis*-aziridino-L-proline from *S*-pyroglutamic acid. Regio- and diastereoselective ring opening of its derivatives †

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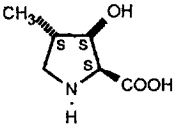
Abstract: The pyroglutamic acid derivative **4** was converted through several steps into 2*S*,3*R*,4*S*-epoxyproline **8**. Key steps of the reaction sequence were the stereoselective epoxidation of **4** to **5** and the chemoselective reduction of the amide group of **5** with concomitant transformation of the acetal moiety into the N-benzyl protecting group without oxirane ring opening. The air sensitive benzyl derivative was transformed to the stable N-Boc prolinol derivative **6**. Oxidation of **6** gave the protected epoxyproline derivative **7**. Deprotection of **7** furnished enantiopure 2*S*,3*R*,4*S*-epoxyproline **8**. Ring opening of the oxirane **6** or **16** was accomplished with C, N, Cl-nucleophiles under complete regiocontrol. Azidoprolinol **9** served as a starting material for the synthesis of epiminoproline derivative **23**. © 1997 Elsevier Science Ltd

Nonproteinogenic highly substituted proline derivatives have recently been detected in novel cyclic peptides. **1** in Echinocandin B,[1] isolated from Aspergillus nidulans and **2** in Scytonemin A, a metabolite of the cultured cyanophyte Scytonema sp., which possesses potent calcium antagonistic properties.[2] 2*S*,3*S*-3-Hydroxyproline **3a** was found in naturally occuring peptides, namely Mucrorin-D,[3a] Telomycin[3b] and in bovine Achilles tendon collagen[3c] and was synthesized recently.[4a–g] The unusual 3,4-dichloroproline was found in cyclochlorotine and is essential for its cytotoxic activity.[5]



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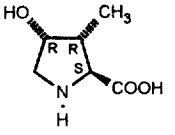

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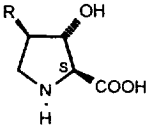

(3S) **3a**: R = H
(3S,4R) **3b**: R = CH_3
(3S,4R) **3c**: R = NH_2
(3R,4R) **3d**: R = Cl

In previous papers[6] we have demonstrated an entry to β-chloropipecolic acids in chiral nonracemic form. 2*R*,5*R*-5-chloropipecolic acid showed weak cytotoxic activity. As an extension to our studies of the synthesis of proline derivatives[7] we became interested in the synthesis of *trans*-3,4-epoxy-L-proline **8** for peptide synthesis and the regioselective ring opening of its derivatives to yield **3b–d**. Proline-4-hydroxylase catalyses epoxidation of 3,4-dehydro-L-proline to give *trans*-3,4-epoxy-L-proline[8a] and may serve as an *in vitro* reagent to produce hydroxylated proline derivatives. Herein we report the synthesis[9] of **3c** and **3d** *via* ring opening reactions of epoxyprolinol derivate **6**.

Cis- and *trans*-3,4-epoxy-L-proline were first synthesized in unprotected form from 2*S*,4*R*-hydroxyproline *via* a 7 step reaction sequence with a phenylselenenyl proline intermediate.[8a] We

† Dedicated to Prof. Dr Wolfgang Beck, Institut für Anorganische Chemie der Univ. München on the occasion of his 65th birthday.

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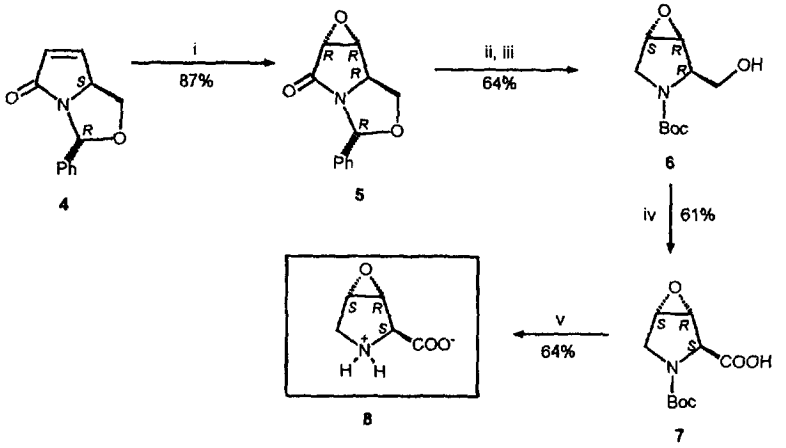
anticipated that acetal **5**, which we prepared recently as a single diastereomer[4b] from compound **4**, should be the ideal substrate for N-Boc-3,4-epoxy-L-proline **7**. Although the production of **4** works well *via* the selenium based elimination starting from the saturated pyroglutaminol derivative we decided to introduce the double bond with methyl phenylsulfinate according to Meyers method[10] to avoid the ecological problems with selenium compounds. Indeed we achieved higher yields of **4** and the unsatisfactory yield of the epoxidation reaction[4b] (63%) increased to 87% when the double bond had been introduced with the phenyl sulfinate method. When **5** was treated with borane in THF both functional groups, namely amide carbonyl and acetal group were reduced to yield N-benzyl-epoxyprolinol, an air sensitive compound, which was immediately debenzylated with H_2/Pd/C in the presence of Boc_2O to provide the prolinol derivative **6** in 64% overall yield. Under Sharpless oxidation conditions[11] **6** was smoothly oxidized to **7**, which was deprotected with trifluoroacetic acid to give *trans* epoxy-L-proline **8** in an overall yield of 20% starting from **4**. Because **4** can now be produced conveniently on a 10 g scale from L-pyroglutamic acid this reaction sequence is a facile entry to 2*S*,3*R*,4*S*-epoxyproline (Scheme 1).



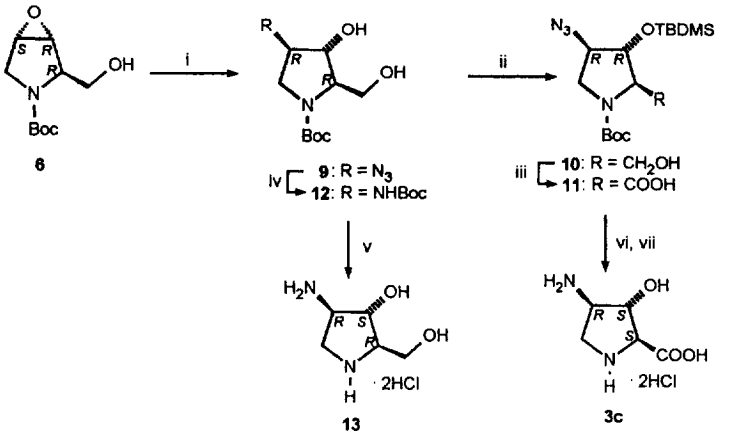
Scheme 1. i: t-BuOOH, K_2CO_3, DMF, 30 min, $(Bu)_4NF$, r.t.; ii: BH_3·THF, 0°C, 16 h; iii: Pd/C/H_2, Boc_2O, EtOAc, 18 h; iv: $NaIO_4$, $RuCl_3$, MeCN/CCl_4/H_2O, r.t. 1 h; v: TFA, 0°C, 30 min.

Ring opening of 6 and 16 with nucleophiles

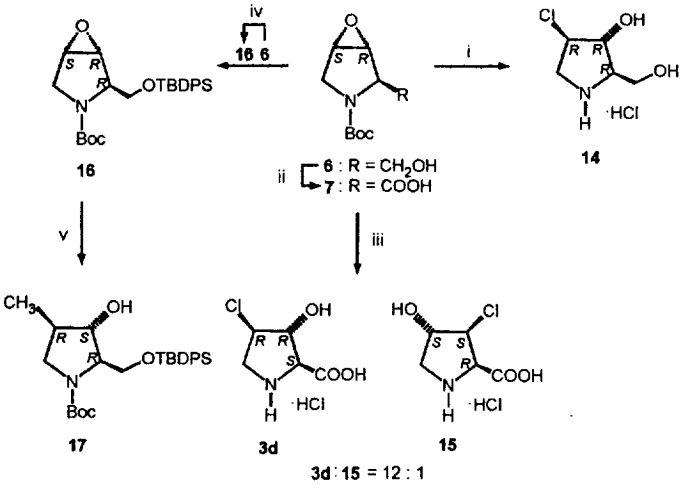
Remuzon reported the first example of a ring opening reaction of N-protected *trans*-ethyl 3,4-epoxy-D-prolinate with dimethyl lithium cuprate to yield a mixture of stereo- and regioisomeric methylated ethylprolinates.[8b] Due to the acidic proton, epimerisation took place at C-2. Starting with the epoxyprolinol derivative **6** we envisaged a highly regioselective attack of nucleophiles at the 4-position for two reasons. First, the pseudoaxial disposition of the hydroxymethyl group, due to $A^{[1,3]}$ strain exerted by the N-Boc group, makes the attack of a nucleophile at C-3 unfavourable. Second, no metal assisted chelate bidentate structures are possible with the *trans*-3,4-epoxy proline derivative which would assist an attack of the nucleophile in 3-position.[12]

When compound **6** was reacted with sodium azide/ammonium chloride without metal alkoxide assistance[13] only one regioisomer of the ring open product namely compound **9** was isolated (Scheme 2). C-4 attack was also found when **6** was reacted with hydrochloric acid in MeOH to give **14** (Scheme 3). This high regioselectivity was also observed by Blechert, when O-trityl protected **rac-6** was reduced with $LiBH_4$ to yield **rac-9** (R=H) under complete regiocontrol.[14]

When N-Boc-epoxyproline **7** was treated with HCl/THF the ring opening reaction was not completely regioselective (Scheme 3). ^1H NMR spectroscopy of the crude reaction product revealed a ratio of **3d**:**15** of 12:1. This is reasonable considering the inductive electron withdrawing effect



Scheme 2. i: NaN_3, NH_4Cl, $MeOH/H_2O$ (8+1), refl., 3 d; ii: a. TBDMSCl, imidazole, DMF, r.t., 18 h; b. $AcOH/H_2O/THF$ (3+1+1), 50°C, 3 h; iii: $NaIO_4$, $RuCl_3$, $MeCN/CCl_4/H_2O$, r.t., 80 min; iv: $Pd/C/H_2$, Boc_2O, MeOH, 18 h; v: HCl/MeOH, r.t.; vi: $Pd/C/H_2$, MeOH, 4 h; vii: HCl/acetone, r.t., 18 h.



Scheme 3. i: HCl/MeOH, r.t., 2 h; ii: $NaIO_4$, $RuCl_3$, $MeCN/CCl_4/H_2O$, r.t. 1 h; iii: HCl/THF, −78°C ⇒ r.t., 22 h; iv: TBDPSCl, imidazole, DMF, r.t., 18 h; v: $Me_2CuCNLi_2$, THF, −78°C ⇒ −10°C, 4 h.

of the carbonyl function. Recrystallization of the regioisomeric mixture furnished pure **3d** whose structure was unambigously determined by X-ray crystallographic analysis (Figure 1).[15] Unprotected epoxyprolinol **6** reacted sluggishly with C-nucleophiles so the primary hydroxyl function was protected as TBDPS ether **16**. When **16** was treated with dimethyllithium cyanocuprate smooth ring opening was observed and compound **17** was isolated as the only regioisomer (Scheme 3).

Azidoprolinol derivative **9** seemed to us an ideal substrate for the entry to aziridinoproline. To this end the 1-OH-function was selectively protected as the TBDPS ether **18** which gave compound **19** upon hydrogenation in the presence of Boc_2O. **19** was reacted with methane sulfonyl chloride to give the mesylate **20**. The cyclization to the fully protected *cis*-aziridinoprolinol derivative **21** was achieved with potassium carbonate in boiling acetonitrile[16] in 87% yield. After O-desilylation of **22** and oxidation of the primary hydroxyl function L-*cis* N-diboc-aziridinoproline **23** was isolated as a crystalline compound (Scheme 4). All attempts to deprotect **23** under standard conditions to *cis*-L-aziridinoproline were unsuccessful.

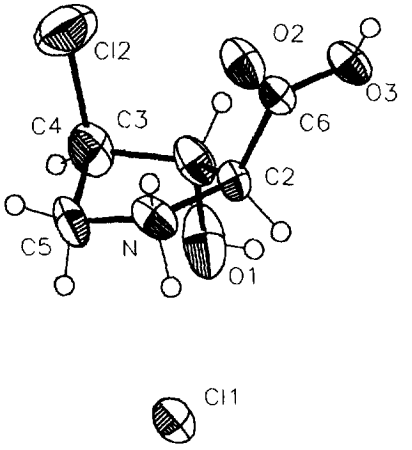
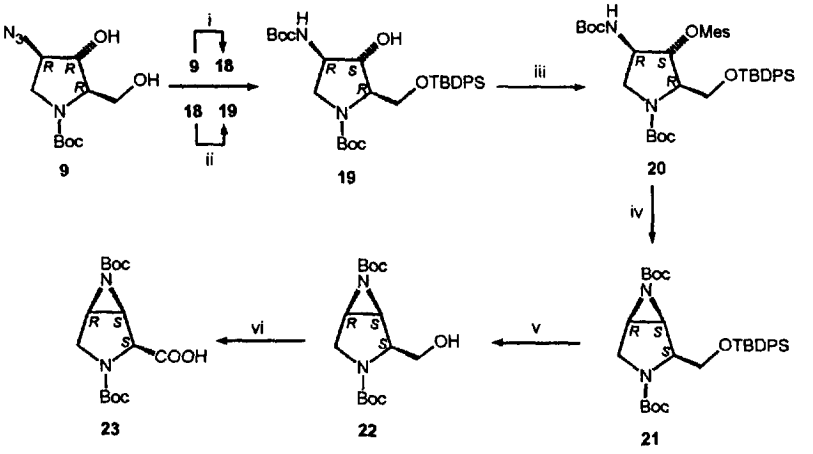


Figure 1. X-Ray structure of **3d**.



Scheme 4. **i**: TBDPSCl, imidazole, DMF, r.t., 36 h; **ii**: Pd/C/H_2, Boc_2O, MeOH, 18 h; **iii**: MesCl, Et_3N, CH_2Cl_2, r.t., 18 h; **iv**: K_2CO_3, MeCN, 20 h, rflx.; **v**: Bu_4NF, THF, 18 h; **vi**: $NaIO_4$, $RuCl_3$, MeCN/CCl_4/H_2O, r.t., 70 min.

Experimental

General

Solvents were dried according to common methods and distilled before use. TLC: Merck precoated silica gel 60 F-254 plates; detection with iodine vapour or UV light. Column chromatography: silica gel Merck 60 (0.063–0.2 mm). M.p. are uncorrected. Optical rotations: Perkin Elmer 241 spectrometer. IR spectra (KBr): Perkin Elmer 681. Mass spectra: Finnigan Mat 8200 spectrometer. ^1H, and ^{13}C NMR, spectra: Bruker AC 200 spectrometer; chemical shifts in ppm relative to the solvent as internal standard, coupling constants in Hz.

(2R,5S)-2-Phenyl-3-oxa-1-aza-bicyclo[3.3.0]oct-6-en-8-one 4

To a solution of (2*R*,5*S*)-2-phenyl-3-oxa-1-aza-bicyclo[3.3.0]octane-8-on[4b] (10.16 g, 50 mmol) and $PhSO_2Me$ (9.35 g, 60 mmol) in anhydrous THF (300 ml) under nitrogen was added oil-free KH (5.1 g, 125 mmol) in portions. After stirring at ambient temperature for two hours the reaction was quenched with dilute H_3PO_4. Additional H_3PO_4 (250 ml) and dichloromethane (250 ml) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (2×250 ml). The

combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated. Toluene (200 ml) and Na_2CO_3 (26.5 g, 250 mmol) were added to the residue. The mixture was heated to reflux for two hours, cooled to room temperature, filtered and concentrated *in vacuo*. The remaining light brown oil was purified by column chromatography (PE/EtOAc 1:2) to afford pale yellow crystals which were recrystallized from EtOAc/n-hexane. Yield: 8.95 g (89%) colourless crystals. The analytical data were identical with those in Ref.[4b]

(2R,5R,6R,7R)-6,7-Epoxy-2-phenyl-3-oxa-1-aza-bicylo[3.3.0]octan-8-one **5**

To a solution of **4** (8.04 g, 40 mmol) in anhydrous DMF (30 ml) under nitrogen was added K_2CO_3 (5.87 g, 41 mmol) and t-BuOOH (3 M solution in isooctanol, 29.3 ml, 88 mmol). After stirring at ambient temperature for 30 min, $Bu_4NF \cdot 3H_2O$ was added in small portions until the reaction was complete (tlc-control). Saturated NH_4Cl solution (30 ml) was added, then water (300 ml) and diethylether (200 ml). The layers were separated and the aqueous layer was extracted with diethylether (200 ml × 4). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. **5** was crystallized from EtOAc/n-hexane. Yield: 7.55 g (87%) colourless crystals. The analytical data were identical with those in Ref.[4b]

tert.*Butyl (2R,3R,4S)-3,4-epoxy-2-hydroxymethylpyrrolidine-1-carboxylate* **6**

To a solution of **5** (4.34 g, 20 mmol) in dry THF (80 ml), borane–THF (1 M in THF) (70 ml, 70 mmol) was added at 0°C and the mixture was stirred under nitrogen for 16 hours. The reaction was quenched by cautiously adding methanol until gas evolution stopped. Additional methanol (50 ml) was added and the solvents were evaporated. The residue was dissolved in methanol (150 ml) and heated to reflux for one hour. The solution was concentrated *in vacuo*, methanol (100 ml) was added and evaporated. This procedure was repeated twice. Diethylether (100 ml) and 0.5 M HCl (100 ml) were added and the layers were separated. The organic layer was extracted with 0.5 M HCl (100 ml × 2). The combined aqueous layers were adjusted to pH 11–12 with 10 M NaOH and extracted with dichloromethane (200 ml × 4). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford a colourless oil. To a solution of this oil in EtOAc (60 ml) Boc_2O (4.36 g, 20 mmol) was added and the mixture was hydrogenated with Pd/C (10%, 500 mg) at 5 atm overnight. Filtration of the catalyst and evaporation of the solvent afforded a colourless oil which was purified by column chromatography with EtOAc. Yield: 2.75 g (64%), R_f=0.36 (EtOAc). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.31 (s, 9H, $C(CH_3)_3$), 3.20–3.27 (m, 1H, 5-H_a), 3.52–3.72 (m, 5H, 3-H, 4-H, 5-H_b, 6-H), 3.83–3.88/3.93–3.98 (t, 1H, 2-H, rotamers). ^{13}C NMR ($CDCl_3$): δ (ppm)=29.13 ($C(CH_3)_3$), 47.25/47.50 (C-5), 54.38/54.80 (C-4), 56.96/57.67 (C-3), 59.40/59.56 (C-2), 61.30 (C-6), 80.03/80.16 ($C(CH_3)_3$, 154.60/155.18 (C=O) rotamers. IR (neat): ν (cm^{-1})=3460–3380 (OH), 2960, 2920, 2870, 1670 (C=O). MS (70 eV), *m/z* (%): 215 (1)[M^+], 184 (16) [M^+-CH_2OH], 128 (17), 84 (64), 61 (15), 59 (18), 45 (21), 43 (85), 41 (35). $[\alpha]_D^{20}$ −78 (*c*=1, $CHCl_3$). $C_{10}H_{17}NO_4$ (215.2) calcd.: C 55.80, H 7.96, N 6.51; found: C 55.00, H 8.50, N 6.13.

*(2S,3R,4S)-1-*tert.*Butoxycarbonyl-3,4-epoxypyrrolidine-2-carboxylic acid*

trans-*1-*tert.*Butoxycarbonyl-3,4-epoxy-*L-*proline* **7**

To a solution of **6** (2.15 g, 10 mmol) and $NaIO_4$ (4.27 g, 20 mmol) in MeCN (40 ml), CCl_4 (20 ml) and H_2O (30 ml) was added $RuCl_3 \cdot H_2O$ (45 mg, 0.22 mmol) and the mixture was stirred vigorously at ambient temperature for 1 hour. Dichloromethane (100 ml) and 0.5 M HCl (100 ml) were added, the layers were separated and the aqueous layer was extracted with dichloromethane (100 ml × 2). The combined organic layers were dried over Na_2SO_4, filtrated and extracted with dilute $NaHCO_3$ solution (300 ml × 3). The aqueous solution was adjusted to pH 1–2 with concentrated HCl and extracted with dichloromethane (500 ml × 3). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was crystallized from $CHCl_3$/petroleum ether. Yield: 1.4 g (61%), colourless powder, R_f=0.1 (EtOAc), m.p. 132°C. ^{1}H NMR (D_6-DMSO): δ (ppm)=1.42/1.46 (s, 9H,

$C(CH_3)_3$), 3.42/3.43 (d, $J_{5a,5b}$=11.8 Hz, 12.5 Hz, 1H, 5-H_a), 3.69/3.71 (d, $J_{5b,5a}$=12.5 Hz, 12.6 Hz, 1H, 5-H_b), 3.88/3.98 ("m", 2H, 3-H, 4-H), 4.39/4.42 (s, 1H, 2-H), rotamers. ^{13}C NMR (D_6-DMSO): δ (ppm)=28.06/28.18 ($C(CH_3)_3$), 47.03/47.34 (C-5), 54.10/54.62 (C-4), 56.17/56.89 (C-3), 60.47/60.95 (C-2), 79.46/79.61 ($C(CH_3)_3$), 153.71/154.10 (C=O, urethane), 170.44/170.60 (C=O, acid), rotamers. IR (KBr): ν (cm^{-1})=3000–2900 (broad, OH), 2600, 1735 (C=O, acid), 1630 (C=O, urethane). $[\alpha]_D^{20}$ −112 (*c*=0.4, $CHCl_3$). $C_{10}H_{15}NO_5$ (229.2) calcd.: C 52.40, H 6.60, N 6.11; found: C 52.68, H 6.48, N 6.00.

(2S,3R,4S)-3,4-Epoxypyrrolidine-2-carboxylic acid

trans *3,4-Epoxy-*L*-proline* ***8***

A solution of **7** (668 mg, 2.9 mmol) in TFA (5 ml) was stirred for 30 min at 0°C. Water was added (20 ml) and the solvents were evaporated *in vacuo*. This was repeated several times. The aqueous solution was filtered and concentrated *in vacuo*. The residue was crystallized from water/isopropanol. Yield: 239 mg (64%) colourless crystals, m.p. 188°C. ^{1}H NMR (CD_3OD/D_2O): δ (ppm)=3.71 (d, $J_{5a,5b}$=12.9 Hz, 1H, 5-H_a), 3.84 (d, $J_{5b,5a}$=12.9 Hz, 1H, 5-H_b), 4.18 (d, $J_{4,3}$=2.7 Hz, 1H, 4-H), 4.30 (d, $J_{3,4}$=2.7 Hz, 3-H), 4.53 (s, 1H, 2-H). ^{13}C NMR (CD_3OD/D_2O): δ (ppm)=46.81 (C-5), 54.52 (C-4), 56.67 (C-3), 60.98 (C-2), 168.17 (C=O). IR (KBr): ν (cm^{-1})=3000 (OH), 2900–2200, 1620 (C=O), 1570 (NH_2^+), 1370. $[\alpha]_D^{20}$ −119 (*c*=0.3, H_2O). $C_5H_7NO_3$ (129.1) calcd.: C 46.51, H 5.46, N 10.85; found: C 46.25, H 5.51, N 10.68.

tert.*Butyl (2R,3R,4R)-4-azido-3-hydroxy-2-hydroxymethylpyrrolidine-1-carboxylate* ***9***

To a solution of **6** (2.15 g, 10 mmol) in MeOH/H_2O (8+1, 135 ml), NaN_3 (3.3 g, 50 mmol) and NH_4Cl (1.15 g, 22 mmol) were added and the mixture was refluxed for three days. The solution was concentrated *in vacuo* to approximately one fifth of its original volume and water (300 ml) and EtOAc (400 ml) were added. The layers were separated, the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The remaining oil crystallized on standing and was recrystallized from EtOAc/light petroleum ether. Yield: 1.89 g (73%), colourless crystals, R_f=0.46 (EtOAc), m.p. 76–80°C. ^{1}H NMR ($CDCl_3$): δ (ppm)=1.43 (s, 9H, $C(CH_3)_3$), 3.15–3.23 (m, 1H, 5-H_a), 3.68–4.02 (m, 6H, 2-H, 3-H, 4-H, 5-H_b, 6-H). ^{13}C NMR ($CDCl_3$): δ (ppm)=28.27 ($C(CH_3)_3$), 49.28 (C-5), 61.39/63.39 (C-6), 64.02 (C-4), 65.05/66.27 (C-2), 76.13 (C-3), 81.18 ($C(CH_3)_3$), 155.90 (C=O), rotamers. IR (KBr): ν (cm^{-1})=3450, 3340 (OH), 2990, 2950, 2920, 2895, 2100 (N_3), 1650 (C=O). $[\alpha]_D^{20}$ −44 (*c*=0.4, CH_2Cl_2). $C_{10}H_{18}N_4O_4$ (258.28) calcd.: C 46.50, H 7.02, N 21.69; found: C 46.32, H 7.30, N 21.48.

tert.*Butyl (2R,3R,4R)-4-azido-3-*tert.*butyldimethylsilyloxy-2-hydroxymethylpyrrolidine-1-carboxylate* ***10***

To a solution of **9** (564 mg, 2 mmol) in anhydrous DMF (5 ml) was added imidazole (780 mg, 10 mmol) and TBDMSCl (760 mg, 5 mmol) under nitrogen and the solution was stirred overnight. Methanol (5 ml) was added and stirring was continued for 1 hour. Diethylether (100 ml) and water (100 ml) were added, the layers were separated and the aqueous layer was extracted with diethylether (2×). The combined organic layers were washed with 1 M HCl (300 ml), water (300 ml) and brine (300 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The remaining oil was dissolved in THF (5 ml), H_2O (5 ml) and AcOH (15 ml) and the mixture was stirred at 50°C for 3 hours. The solvents were evaporated under reduced pressure, diethylether (100 ml) and 2 M NaOH (100 ml) were added and the layers were separated. The organic layer was washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/EtOAc 4+1) afforded a colourless oil. Traces of TBDMSOH were removed under high vacuum, whereupon the oil crystallized. Yield: 490 mg (66%), colourless crystals, R_f=0.47 (petroleum ether/EtOAc 4+1), m.p. 59–62°C. ^{1}H NMR ($CDCl_3$): δ (ppm)=0.01 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.78 (s, 9H, $SiC(CH_3)_3$), 1.34 (s, 9H, $OC(CH_3)_3$), 3.10–3.24 (m, 1H, 5-H_a), 3.60–3.86 (m, 5H, 2-H, 4-H, 5-H_b,

6-H), 4.17/4.40 (s, 1H, 3-H, rotamers). ^{13}C NMR ($CDCl_3$): δ (ppm)=−5.04 (Si*C*H$_3$), −4.99 (Si*C*H$_3$), 17.60 (Si*C*(CH$_3$)$_3$), 25.39 (SiC(*C*H$_3$)$_3$), 28.09 (OC(*C*H$_3$)$_3$), 49.16 (C-5), 61.03/63.06 (C-6), rotamers), 65.18 (C-4), 66.98 (C-2), 76.51 (C-3), 80.33 (O*C*(CH$_3$)$_3$), 155.41 (C=O). IR (KBr): ν (cm^{-1})=3450 (OH), 2940, 2890, 2860, 2100 (N_3), 1680 (C=O). $[\alpha]_D^{20}$ −33 (*c*=0.7, CH_2Cl_2). $C_{16}H_{32}N_4O_4Si$ (372.5) calcd.: C 51.59, H 8.66, N 15.04; found: C 51.64, H 8.97, N 14.89.

*(2S,3R,4R)-4-Azido-3-*tert.*butyldimethylsilyloxy-1-*tert. *butoxycarbonyl-2-pyrrolidinecarboxylic acid* ***11***

Compound **11** was prepared following the general procedure used for the preparation of compound **7** on a one millimole scale. Reaction time was 80 min. Purification of the crude product was achieved by column chromatography, eluated with petroleum ether/EtOAc 3+1 first, then with petroleum ether/EtOAc/AcOH 30+10+1. Yield: 250 mg (65%), colourless oil, R_f=0.25 (PE/EtOAc/AcOH 30+10+1). ^{1}H NMR ($CDCl_3$): δ (ppm)=0.06/0.08 (s, 6H, SiCH$_3$), 0.83 (s, 9H, SiC(CH$_3$)$_3$), 1.35/1.40 (s, 9H, OC(CH$_3$)$_3$), 3.33–3.43 (m, 1H, 5-H$_a$), 3.68–3.85 (m, 2H, 4-H, 5-H$_b$), 4.00/4.15 (d, *J*=2.4 Hz, 3.5 Hz, 1H, 2-H), 4.22/4.29 (t, 1H, 3-H), rotamers. ^{13}C NMR ($CDCl_3$): δ (ppm)=−5.23 (Si*C*H$_3$), 17.63 (Si*C*(CH$_3$)$_3$), 25.34 (SiC(*C*H$_3$)$_3$), 27.92/28.05 (OC(*C*H$_3$)$_3$), 47.91/49.74 (C-5), 64.74/65.43 (C-4), 65.90 (C-2), 78.10/79.12 (C-3), 81.13/81.24 (O*C*(CH$_3$)$_3$), 153.84/154.59 (C=O, urethane), 173.77/174.81 (C=O, acid), rotamers. IR (neat): ν (cm^{-1})=3200–3000 (broad, OH), 2980–2840, 2100 (N_3), 1750–1630 (C=O; acid, urethane). $[\alpha]_D^{20}$ −43 (*c*=0.3, CH_2Cl_2). $C_{16}H_{30}N_4O_5Si$ (386.5) calcd.: C 49.72, H 7.82, N 14.50; found: C 49.22, H 8.46, N 13.41.

(2S,3S,4R)-4-Ammonio-2-carboxy-3-hydroxypyrrolidine dihydrochloride ***3c***

all trans*-4-Amino-3-hydroxy-*L*-proline dihydrochloride*

11 (200 mg, 0.51 mmol) was dissolved in methanol, Pd/C (10%, 20 mg), was added and the mixture was hydrogenated at 3 atm. for 4 hours. Filtration of the catalyst and evaporation of the solvent afforded a colourless powder. This was dissolved in conc. HCl/acetone (9+1) (10 ml) and the solution was stirred overnight. The solvents were removed under reduced pressure, isopropanol (40 ml) was added and the procedure was repeated three times. The residue was crystallized from methanol/isopropanol. Yield: 65 mg (62%) colourless hygroscopic powder, that dissolves upon contact with air. ^{1}H NMR (CD_3OD): δ (ppm)=3.81 (dd, $J_{5a,5b}$=14.7 Hz, $J_{5a,4}$=11.7 Hz, 1H, 5-H$_a$), 4.17 (dd, 2H, 4-H, 5-H$_b$), 4.56 (d, $J_{2,3}$=7.5 Hz, 1H, 2-H), 4.93 ("t", *J*=6.9, 6.2 Hz, 1H, 4-H). ^{13}C NMR (CD_3OD):δ (ppm)=46.19 (C-5), 56.25 (C-4), 64.13 (C-2), 75.48 (C-3), 169.17 (C=O). IR (neat): ν (cm^{-1})=3400–2700 (broad, OH), 1730 (C=O), 1620 (NH_2^+, NH_3^+).

tert.*Butyl (2R,3S,4R)-4-*tert.*butoxycarboxamido-3-hydroxy-2-hydroxymethylpyrrolidine-1-carboxylate* ***12***

Boc_2O (261 mg, 1.2 mmol) and Pd/C (10%, 30 mg) were added to a solution of **9** (258 mg, 1 mmol) in methanol (10 ml) and hydrogenated at 5 atm. overnight. The mixture was filtered, concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc) to yield a colourless oil which solidified to a glass-like substance upon drying under high vacuum. Yield: 289 mg (87%), colourless solid, R_f=0.31 (EtOAc), m.p. 66–69°C. ^{1}H NMR ($CDCl_3$): δ (ppm)=1.36 (s, 9H, C(CH$_3$)$_3$), 1.38 (s, 9H, C(CH$_3$)$_3$), 3.03–4.00 (m, 8H, 2-H, 3-H, 4-H, 5-H, 6-H, OH), 4.81 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ (ppm)=28.27 (C(*C*H$_3$)$_3$), 50.60 (C-5), 55.62 (C-4), 62.9 (C-6), 65.63 (C-2), 77.00 (C-3), 80.00 (*C*(CH$_3$)$_3$), 80.50 (*C*(CH$_3$)$_3$), 155.38 (C=O), 156.23 (C=O). IR (KBr): ν (cm^{-1})=3500–3300 (OH), 2980, 2940, 2895, 1730–1640 (C=O). $[\alpha]_D^{20}$ −5 (*c*=0.3, CH_2Cl_2). $C_{15}H_{28}N_2O_6$ (332.4) calcd.: C 54.20, H 8.49, N 8.43; found: C 53.48, H 8.83, N 8.01.

(2R,3S,4R)-3-Amino-4-hydroxy-2-hydroxymethylpyrrolidine dihydrochloride ***13***

To a solution of **12** (230 mg, 0.69 mmol) in methanol (9.5 ml) was added concentrated HCl (0.5 ml) and stirred overnight. The solution was concentrated, isopropanol was added and evaporated again

several times. The residue was washed with diethylether twice, was then dried under high vacuum and crystallized from methanol/isopropanol. Yield: 178 mg (87%), colourless, hygroscopic crystals, that dissolve upon prolonged contact with air, m.p. 146°C. ^{1}H NMR (D_2O/CD_3OD): δ (ppm)=3.72 (dd, $J_{gem.}$=15.8 Hz, $J_{5a,4}$=10.3 Hz, 1H, 5-H_a), 3.95 (m, 1H, 2-H,), 4.07–4.24 (m, 4H, 4-H, 5-H_b, 6-H), 4.65 (dd, $J_{3,4}$=7.0 Hz, $J_{2,3=}$ 5.4 Hz, 1H, 3-H). ^{13}C NMR (D_2O/CD_3OD): δ (ppm)=46.64 (C-5), 56.02 (C-4), 58.97 (C-6), 66.48 (C-2), 74.26 (C-3). IR (KBr): ν (cm^{-1})=3440, 3240, 2940 (broad), 2550, 2420, 2230, 2140, (OH, NH_2^+), 1550 (NH_2^+). $[\alpha]_D^{20}$ +13 (*c*=0.2, H_2O). $C_5H_{14}N_2O_2Cl_2$ (205.1) calcd.: C 29.28, H 6.88, N 13.66; found: C 28.56, H 10.48, N 13.14.

(2R,3R,4R)-3-Chloro-4-hydroxy-2-hydroxymethylpyrrolidine hydrochloride ***14***

6 (100 mg, 0.46 mmol) was dissolved in methanolic HCl (5 M, 10 ml) at 0°C and stirred at ambient temperature for two hours. The solution was concentrated *in vacuo*, isopropanol (30 ml) was added and evaporated. This was repeated three times. The remaining light brown solid was recrystallized from isopropanol. Yield: 60 mg (69%) pale beige crystals, m.p. 161°C. ^{1}H NMR (*) (CD_3OD): δ (ppm)=3.67–3.79 (m, 2H, 2-H, 5-H_a), 3.98–4.19 (m, 3H, 5-H_b, 6-H), 4.43 ("t", $J_{3,2}$=$J_{3,4}$=4.5 Hz, 1H, 3-H), 4.58 (dt, $J_{4,3}$=$J_{4,5a}$=4.2, $J_{4,5b}$=6.0 Hz, 1H, 4-H). ^{13}C NMR (CD_3OD): δ (ppm)=51.94 (C-5), 60.13 (C-6), 60.80 (C-4), 68.38 (C-2), 78.41 (C-3). IR (KBr): ν (cm^{-1})=3310 (OH), 2900 (NH_2^+), 2500, 2460, 1585 (NH_2^+). MS (70 eV), *m/z* (%): 152 (1) [M^+], 122 (30), 120 (100) [M^+-CH_2OH], 116 (40), 91 (11), 60 (81), 57 (16), 42 (12), 38 (13), 36 (41). $[\alpha]_D^{20}$ +17 (*c*=0.5, MeOH). $C_5H_{11}NO_2Cl_2$ (188.1) calcd.: C 31.93, H 5.90, N 7.45; found: C 32.01, H 5.84, N 7.45.

(2S,3R,4R)-2-Carboxy-4-chloro-3-hydroxypyrrolidine hydrochloride ***3d***

all-trans-*4-Chloro-3-hydroxy*-L-*proline hydrochloride*

7 (180 mg, 0.78 mmol) was dissolved in THF (5 ml) at −78°C, 2 M HCl/THF (5 ml, 4 ml THF +1 ml concentrated HCl) was added and the solution was stirred at −78°C for two hours and then warmed to room temperature within 4 hours. Stirring was continued at ambient temperature for 16 hours. The solution was concentrated *in vacuo*, isopropanol (30 ml) was added and evaporated (2×). The residue was crystallized and recrystallized from isopropanol/dichloromethane/diisopropylether. Yield: 132 mg (66%) pale rose-coloured crystals, m.p. 204°C. ^{1}H NMR (CD_3OD): δ (ppm)=3.92 (d, $J_{5a,5b}$=13.1 Hz, 1H, 5-H_a), 4.18 (dd, $J_{5b,5a}$=13.1 Hz, $J_{5b,4}$=4.6 Hz, 1H, 5-H_b), 4.56 ("s", 1H, 2-H), 4.66 ("d", $J_{4,5b}$=4.6 Hz, 1H, 4-H), 4.96 ("s", 1H, 3-H). ^{13}C NMR (CD_3OD): δ (ppm)=53.72 (C-5), 61.00 (C-4), 67.83 (C-2), 80.83 (C-3), 169.11 (C=O). IR (KBr): ν (cm^{-1})=3250, 2980 (OH), 2750, 2630, 2590, 2490, 2410, 1745 (C=O), 1565 (NH_2^+). $[\alpha]_{D20}$ +13 (*c*=0.3, MeOH). $C_5H_9NO_3Cl_2$ (201.8) calcd. C 29.75, H 4.49, N 6.94; found C 29.82, H 4.54, N 6.82.

tert.*Butyl (2R,3R,4S)-2-*tert.*butyldiphenylsilyloxymethyl-3,4-epoxypyrrolidine-1-carboxylate* ***16***

To a solution of **6** (4.35 g, 20 mmol) in anhydrous DMF (20 ml) was added imidazole (3.4 g, 50 mmol) and $tBuPh_2SiCl$ (6.1 ml, 24 mmol) under nitrogen atmosphere and the solution was stirred overnight. Methanol (5 ml) was added and stirring was continued for another hour. Diethylether (150 ml) and 0.5 M HCl (150 ml) were added, the layers were separated and the aqueous layer was extracted with diethylether (2×). The combined organic layers were washed with 0.5 M HCl, water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The remaining oil was purified by column chromatography (PE/Et_2O 3+1) to yield a colourless oil that crystallized after drying in high vacuum. Yield: 8.5 g (94%), colourless solid, R_f=0.33 (PE/Et_2O 3+1), m.p. 78°C. ^{1}H NMR ($CDCl_3$): δ (ppm)=1.06 (s, 9 H, $SiC(CH_3)_3$), 1.36/1.48 (s, 9 H, $OC(CH_3)_3$), 3.43/3.48 (dd, $J_{5a,5b}$=12.4 Hz, $J_{5a,4}$=1.2 Hz, 1 H, 5-H_a), 3.64–4.14 (m, 6 H, 2-H, 3-H, 4-H, 5-H_b, 6-H), 7.37–7.70 (m, 10 H, Ar-H), rotamers. ^{1}H NMR (D_6-DMSO, 366 K): δ (ppm)=1.14 (s, 9 H, $SiC(CH_3)_3$), 1.45 (s, 9 H, $OC(CH_3)_3$), 3.40 (dd, $J_{5a,5b}$=12.5 Hz, $J_{5a,4}$=1.1 Hz, 1 H, 5-H_a), 3.74–3.85 (m, 3 H, 3-H, 4-H, 5-H_b), 3.96 ("d", *J*=3.5 Hz, 2 H, 6-H), 4.07 ("t", *J*=3.9, 4.3 Hz, 1 H, 2-H), 7.49–7.75 (m, 10 H, Ar-H). ^{13}C NMR ($CDCl_3$): δ (ppm)=19.01 ($SiC(CH_3)_3$), 26.73 ($SiC(CH_3)_3$), 28.33/28.42 ($OC(CH_3)_3$), 47.59/48.33

(C-5), 54.59/55.19 (C-4), 57.69/58.15 (C-3), 59.11/59.36 (C-2), 62.69/63.08 (C-6), 79.61/79.76 ($OC(CH_3)_3$), 127.79, 129.70, 129.79, 132.83, 133.07, 135.37, 135.43 (C-Ar), 154.32 (C=O), rotamers. IR (neat): ν (cm^{-1})=3080, 3050, 2960, 2930, 2860, 1700 (C=O), 1590. $[\alpha]_D^{20}$ −56 (*c*=0.8, CH_2Cl_2). $C_{26}H_{35}NO_4Si$ (453.7) calcd. C 68.84, H 7.78, N 3.09; found C 68.51, H 7.75, N 3.03.

tert.*Butyl (2R,3S,4R)-2-*tert.*butyldiphenylsilyloxymethyl-3-hydroxy-4-methylpyrrolidine-1-carboxylate* ***17***

CuCN (1.344 g, 15 mmol) was dispersed in anhydrous diethylether (80 ml), cooled to −78°C and MeLi (1.6 M solution in Et_2O, 18.5 ml 29.6 mmol) was added. The mixture was warmed to −20°C until all CuCN was dissolved, then cooled to −78°C again. A cooled (−78°C) solution of **16** (908 mg, 2 mmol) in diethylether (40 ml) was added and the mixture was warmed to −10°C within four hours. The reaction was quenched with half-saturated NH_4Cl solution to which a few drops of ammonia had been added. Et_2O was added (100 ml) and the organic layer was washed with the NH_4Cl/NH_3 solution until all precipitate had dissolved and the aqueous layer did not turn blue any more. The organic layer was then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. **17** was crystallized from Et_2O/n-hexane. Yield: 874 mg (93%), colourless crystals, R_f=0.45 (PE/EtOAc 2+1), m.p. 128°C. ^1H NMR ($CDCl_3$, 332 K): δ (ppm)=1.08 (s, 3 H, CH_3), 1.11 (s, 9 H, $SiC(CH_3)_3$), 1.37 (s, 9 H, $OC(CH_3)_3$), 2.04 (m, 1 H, 4-H), 2.85 (t, $J_{5a,5b}$=$J_{5a,4}$=10.9 Hz, 1 H, 5-H_a), 3.59 (dt, $J_{2,3}$=$J_{2,6a}$=6.4 Hz, $J_{2,6b}$=3.5 Hz, 1 H, 2-H), 3.53 ("dd", *J*=7.8, 10.9 Hz, 2 H, 5-H_b, 6H_a), 3.98 (dd, $J_{3,6a}$=8.8 Hz, $J_{3,2}$=6.3 Hz, 1 H, 3-H), 4.15 (dd, $J_{gem.}$=9.8 Hz, $J_{6b,2}$=3.5 Hz, 1 H, 6-H_b), 7.33–7.71 (m, 10 H, Ar-H). ^{13}C NMR ($CDCl_3$): δ (ppm)=14.60 (CH_3), 19.16 ($SiC(CH_3)_3$), 26.85 ($SiC(CH_3)_3$), 28.28 ($OC(CH_3)_3$), 38.89/ 39.41 (C-4), 51.41/52.27 (C-5), 57.69/58.15 (C-3), 62.91/64.55 (C-6), 64.93 (C-2), 79.51 ($OC(CH_3)_3$), 81.24 (C-3), 127.75, 129.77, 129.79, 132.95, 135.45 (C-Ar), 154.25 (C=O), rotamers. IR (KBr): ν (cm^{-1})=3450 (OH), 3070, 2980, 2960, 2920, 2860, 1660 (C=O), 1590. $[\alpha]_D^{20}$ −39 (*c*=0.9, CH_2Cl_2). $C_{27}H_{39}NO_4Si$ (469.7) calcd. C 69.04, H 8.37, N 2.98; found C 68.73, H 8.28, N 3.00.

tert.*Butyl (2R,3R,4R)-4-azido-2-*tert.*butyldiphenylsilyloxymethyl-3-hydroxy-pyrrolidine-1-carboxylate* ***18***

To a solution of **9** (5.166 g, 20 mmol) in anhydrous DMF (30 ml) was added imidazole (3.403 g, 50 mmol) and *tert.*butyldiphenylsilylchloride (5.5 ml, 20 mmol) under nitrogen atmosphere. The solution was stirred for 36 hours, methanol (10 ml) was added and stirring was continued for another hour. Water (200 ml) and Et_2O (200 ml) were added and the layers were separated. The aqueous layer was extracted with Et_2O (2×200 ml) and the combined organic phases were washed with 0.5 M HCl (400 ml), water (400ml), and brine (400 ml), dried over Na_2SO_4 and concentrated in *vacuo*. The remaining oil was purified by column chromatography with petroleum ether/EtOAc (3:1) to yield a colourless oil that solidified upon drying *in vacuo*. Yield: 5.85 g (59%), colourless solid, R_f=0.32 (PE/EtOAc 3+1), m.p. 39–44°C. ^1H NMR ($CDCl_3$): δ (ppm)=1.09 (s, 9 H, $SiC(CH_3)_3$), 1.31/1.48 (s, 9 H, $OC(CH_3)_3$), rotamers, 3.14–3.25 (m, 1 H, 5-H_a), 3.73–3.81 (m, 1 H, 5-H_b) 3.91–4.00 (m, 4 H, 2-H, 4-H, 6-H), 4.40–4.50 (m, 1 H, 3-H). ^{13}C NMR ($CDCl_3$): δ (ppm)=19.13 ($SiC(CH_3)_3$), 26.76 ($SiC(CH_3)_3$), 28.27 ($OC(CH_3)_3$), 49.75/49.96 (C-5), 61.83/63.01 (C-6), 63.97, 64.57 (C-2, C-4), 76.99 (C-3), 80.24 ($OC(CH_3)_3$), 127.69, 129.72, 133.03, 135.39 (C-Ar), 154.14 (C=O), rotamers. IR (KBr): ν (cm^{-1})=3420 (OH), 3060, 3040, 2960, 2920, 2880, 2850, 2100 (N_3), 1695,1660 (C=O). $[\alpha]_D^{20}$ −19 (*c*=0.5, CH_2Cl_2). $C_{26}H_{36}N_4O_4Si$ (496.7).

tert.*Butyl (2R,3S,4R)-4-*tert.*butoxycarboxamido-2-*tert.*butyldiphenylsilyloxymethyl-3-hydroxy-pyrrolidine-1-carboxylate* ***19***

Boc_2O (3.60 g, 16.5 mmol) and Pd/C (10%, 500 mg) were added to a solution of **18** (5.46 g, 11 mmol) in methanol (50 ml) and hydrogenated at 5 atm. overnight. The mixture was filtrated, concentrated *in vacuo* and the residue was purified by column chromatography (PE/EtOAc 2+1) to

yield a colourless oil that solidified as a foam upon drying under high vacuum. Yield: 6.03 g (96%), colourless solid, R_f=0.32 (PE/EtOAc 2+1), m.p. 52–59°C. ^{1}H NMR ($CDCl_3$): δ (ppm)=1.06 (s, 9 H, $SiC(CH_3)_3$), 1.28/1.41/1.44 (s, 18 H, 2×$OC(CH_3)_3$), 3.09–3.18 (m, 1 H, 5-H_a), 3.68–4.37 (m, 6 H, 2-H, 3-H, 4-H, 5-H_b, 6-H,) 5.29–5.42 (s, 1 H, NH), rotamers. ^{13}C NMR ($CDCl_3$, 332 K): δ (ppm)=19.18 ($SiC(CH_3)_3$), 26.94 ($SiC(CH_3)_3$), 28.23 (2×$OC(CH_3)_3$), 50.62 (C-5), 56.65 (C-4), 63.40 (C-6), 65.18 (C-2), 78.75 (C-3), 79.65 ($OC(CH_3)_3$), 80.00 ($OC(CH_3)_3$), 127.61, 129.59, 133.43, 135.41 (C-Ar), 154.02 (C=O), 156.16 (C=O). IR (KBr): ν (cm^{-1})=3460–3320 (OH, NH), 3060, 3030, 2960, 2920, 2870, 2840, 1710–1650 (C=O). $[\alpha]_D^{20}$ −20 (*c*=0.2, CH_2Cl_2). $C_{31}H_{46}N_2O_6Si$ (570.8) calcd.: C 65.23, H 8.12, N 4.91; found: C 65.47, H 8.24, N 4.92.

tert.*Butyl (2R,3S,4R)-4-*tert.*butoxycarboxamido-2-*tert.*butyldiphenylsilyloxymethyl-3-mesyloxypyrrolidine-1-carboxylate* ***20***

Mesylchloride (0.97 ml, 12.5 mmol) was added to a solution of **19** (5.71 g, 10 mmol) and NEt_3 (2.77 ml, 20 mmol) in anhydrous dichloromethane (60 ml) under nitrogen atmosphere and stirred overnight. 0.5 M HCl (200 ml) and dichloromethane (300 ml) were added and the layers were separated. The organic layer was washed with 0.5 M HCl (200 ml) and brine (200 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The remaining oil was purified by column chromatography with petroleum ether/EtOAc (2:1) to yield a colourless oil that solidified as a foam upon drying in high vacuum. Yield: 6.16 g (95%), colourless solid, R_f=0.42 (PE/EtOAc 2:1), m.p. 65–72°C. ^{1}H NMR ($CDCl_3$, 332 K): δ (ppm)=1.09 (s, 9 H, $SiC(CH_3)_3$), 1.34 (s, 9 H, $OC(CH_3)_3$), 1.38 (s, 9 H, $OC(CH_3)_3$), 3.01 (s, 3 H, SO_2CH_3), 3.25 (dd, $J_{5a,5b}$=11.5 Hz, $J_{5a,4}$=5.6 Hz, 1 H, 5-H_a), 3.86–4.05 (m, 4 H, 4-H, 5-H_b, 6-H), 4.18–4.30 (m, 1 H, 2-H) 5.21–5.30 (m, 2 H, 3-H, NH). ^{13}C NMR ($CDCl_3$, 332 K): δ (ppm)=19.05 ($SiC(CH_3)_3$), 26.74 ($SiC(CH_3)_3$), 28.10 (2×$OC(CH_3)_3$), 38.16 (SO_2CH_3), 50.73 (C-5), 54.75 (C-4), 62.11 (C-6), 63.56 (C-2), 80.06 (2×$OC(CH_3)_3$), 84.32 (C-3), 127.69, 129.68, 133.16, 135.34 (C-Ar), 153.54 (C=O), 155.04 (C=O). IR (KBr): ν (cm^{-1})=3350 (NH), 3070, 3040, 2980, 2930, 2890, 2860, 1720–1670 (C=O), 1585. $[\alpha]_D^{20}$=−16 (*c*=0.6, CH_2Cl_2). $C_{32}H_{48}N_2O_8SSi$ (648.9) calcd. C 59.23, H 7.46, N 4.32, S 4.94; found C 59.29, H 7.75, N 4.16, S 5.03.

tert.*Butyl (2S,3S,4R)-3,4-*tert.*butoxycarboxepimino-2-*tert.*butyldiphenylsilyloxymethyl-pyrrolidine-1-carboxylate*

*(Di-*tert.*butyl (2S,3S,4R)-2-*tert.*butyldiphenylsilyloxymethyl-3,6-diazabicyclo[3.1.0]hexan-3,6-dicarboxylate)* ***21***

To a solution of **20** (6.0 g, 9.25 mmol) in anhydrous acetonitrile (60 ml) was added pulverized K_2CO_3 (2.55 g, 18.5 mmol) under nitrogen atmosphere. The mixture was refluxed for 20 hours, cooled to room temperature, filtrated and the solvent was evaporated. The remaining oil was purified by column chromatography with petroleum ether/EtOAc (4:1) to yield a colourless oil that solidified as a foam upon drying in high vacuum. Yield: 4.45 g (87%), colourless solid, R_f=0.40 (PE/EtOAc 4: 1), m.p. 43–47°C. ^{1}H NMR ($CDCl_3$, 332 K): δ (ppm)=1.12 (s, 9 H, $SiC(CH_3)_3$), 1.27 (s, 9 H, $OC(CH_3)_3$), 1.46 (s, 9 H, $OC(CH_3)_3$), 3.21 (dd, $J_{4,3}$=5.2 Hz, $J_{4,5a}$=3.1 Hz, 1 H, 4-H), 3.47 (dd, $J_{5a,5b}$=11.9 Hz, $J_{5a,4}$=3.1 H, 1 H, 5-H_a), 3.58–3.97 (m, 4 H, 3-H, 5-H_b, 6-H), 4.28–4.34 (m, 1 H, 2-H). ^{13}C NMR ($CDCl_3$): δ (ppm)=18.97 ($SiC(CH_3)_3$), 26.67 ($SiC(CH_3)_3$), 27.61 ($OC(CH_3)_3$), 27.90 ($OC(CH_3)_3$), 40.94 (C-4), 45.74 (C-3), 49.53 (C-5), 59.34 (C-2), 62.22 (C-6), 79.50 ($OC(CH_3)_3$), 81.18 ($OC(CH_3)_3$), 127.69, 127.39, 129.29, 133.40, 135.26, 135.34 (C-Ar), 154.45 (C=O), 161.14 (C=O, aziridine). IR (KBr): ν (cm^{-1})=3420 (NH), 3070, 3040, 2970, 2930, 2890, 2860, 1720, 1690 (C=O), 1585. $[\alpha]_D^{20}$ −9 (*c*=0.4, CH_2Cl_2). $C_{31}H_{44}N_2O_5Si$ (552.8) calcd. C 67.36, H 8.02, N 5.07; found C 67.04, H 7.79, N 5.04.

tert.*Butyl (2S,3S,4R)-3,4-*tert.*butoxycarboxepimino-2-hydroxymethylpyrrolidine-1-carboxylate (di-*tert.*butyl (2S,3S,4R)-2-hydroxymethyl-3,6-diazabicyclo[3.1.0]hexan-3,6-dicarboxylate)* ***22***

To a solution of **21** (4.35 g, 7.87 mmol) in anhydrous THF (60 ml) was added $Bu_4NF{\cdot}3H_2O$ (3.58 g, 9.44 mmol) under nitrogen atmosphere. The solution was stirred overnight, water (1 ml) and AcOH (0.3

ml) were added and the solvents were evaporated. The residue was purified by column chromatography with petroleum ether/EtOAc (1:2) to yield a colourless oil that crystallized after several days. Yield: 1.91 g (77%), colourless solid, R_f=0.40 (PE/EtOAc 1: 2), m.p. 68–72°C. ^{1}H NMR ($CDCl_3$, 332 K): δ (ppm)=1.35 (s, 9 H, $OC(CH_3)_3$), 1.36 (s, 9 H, $OC(CH_3)_3$), 3.06 (dd, $J_{4,3}$=5.2 Hz, $J_{4,5a}$=3.1 Hz, 1 H, 4-H), 3.21 (dd, $J_{3,4}$=5.2 Hz, $J_{3,2}$=2.8 Hz, 1 H, 3-H), 3.35 (dd, $J_{5a,5b}$=12.0 Hz, $J_{5a,4}$=3.1 Hz, 1 H, 5-H_a), 3.62 (d, $J_{5b,5a}$=12.0 Hz, 1 H, 5-H_b), 3.70–3.90 (m, 3 H, 2-H, 6-H), 4.28–4.34 (m, 1 H, 2-H). ^{13}C NMR ($CDCl_3$): δ (ppm)=27.55 ($OC(CH_3)_3$), 28.03 ($OC(CH_3)_3$), 38.84 (C-4), 44.35 (C-3), 49.41 (C-5), 61.22 (C-2), 64.04 (C-6), 80.39 ($OC(CH_3)_3$), 81.56 ($OC(CH_3)_3$), 156.18 (C=O), 160.37 (C=O, aziridine). IR (KBr): ν (cm^{-1})=3440 (OH,NH), 2970, 2920, 2890, 2860, 1730, 1720, 1670 (C=O). $[\alpha]_D^{20}$ −44 (*c*=0.3, CH_2Cl_2). MS (70 eV), *m/z* (%): 284 (4)[M^+-CH_2OH+1], 228 (4), 185 (8), 171 (15) [M^+-CH_2OH, −2×Boc+2], 127 (31), 83 (19), 67 (16), 68 (11), 57 (100), 41 (33). $C_{15}H_{26}N_2O_5$ (314.4) calcd. C 57.31, H 8.32, N 8.91; found C 57.38, H 8.01, N 8.63.

cis-*1*-tert.*Butoxycarbonyl-3,4*-tert.*butoxycarboxepimino*-L-*proline*

(2S,3S,4R)-3,6-Di-tert.*butoxycarbonyl-3,6-diazabicyclo[3.1.0]hexan-2-carboxylic acid* ***23***

H_2O (22.5 ml) and $NaIO_4$ (1.41 g, 6.6 mmol) were added to a solution of **22** (943 mg, 3 mmol) in MeCN (30 ml) and CCl_4 (15 ml). After complete dissolution $RuCl_3 \times H_2O$ (14.8 mg, 0.073 mmol) was added and the reaction mixture was stirred vigorously at ambient temperature for 70 minutes. Dichloromethane (100 ml) and 0.5 N H_2SO_4 (100 ml) were added, the two layers were separated and the aqueous layer was extracted with dichloromethane (100 ml × 2). The combined organic layers were dried over Na_2SO_4, filtered and extracted with dilute $NaHCO_3$ solution (200 ml × 3). The combined aqueous solutions were adjusted to pH 1–2 with 0.5 N H_2SO_4 and extracted with dichloromethane (500 ml × 3). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to yield a colourless powdery residue, that was recrystallized from CH_2Cl_2/PE. Yield: 344 mg (35%), colourless powder, R_f=0.1 (EtOAc), m.p. 178°C. ^{1}H NMR ($CDCl_3/CD_3OD$, 332 K): δ (ppm)=1.43 (s, 9 H, $OC(CH_3)_3$), 1.44 (s, 9 H, $OC(CH_3)_3$), 3.28 (dd, $J_{4,3}$=4.9 Hz, $J_{4,5a}$=3.2 Hz, 1 H, 4-H), 3.47–3.54 (m, 2 H, 3-H, 5-H_a), 3.82 (d, $J_{5a,5b}$=11.8 Hz, 1 H, 5-H_b), 4.36 (d, $J_{2,3}$=3.3 Hz, 1 H, 2-H). ^{13}C NMR ($CDCl_3/CD_3OD$, 332 K): δ (ppm)=27.57 ($OC(CH_3)_3$), 27.95 ($OC(CH_3)_3$), 41.07 (C-4), 44.09 (C-3), 48.46 (C-5), 60.06 (C-2), 80.88 ($OC(CH_3)_3$), 81.96 ($OC(CH_3)_3$), 154.35 (C=O), 160.29 (C=O, aziridine), 170.05 (COOH). IR (neat): ν (cm^{-1})=3000–2800 (broad, OH), 2600, 1720, 1700 (C=O, acid), 1630 (C=O, urethane). $[\alpha]_D^{20}$ −86 (*c*=0.1, CH_2Cl_2). MS (70 eV), *m/z* (%): 284 (0.3)[$M^+-COOH+1$], 227 (2) [M^+-COOH, −Boc+1], 171 (15) [M^+-COOH, −2xBoc+2], 127 (15), 83 (10), 67 (32), 68 (11), 57 (100), 44 (14), 41 (34). $C_{15}H_{24}N_2O_6$ (328.4) calcd. C 54.87, H 7.38, N 8.53; found C 54.54, H 6.99, N 8.26.

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