Enantioselective Syntheses of (*R*)- and (*S*)-Hexahydropyridazine-3-carboxylic Acid Derivatives[1]

Ulrich Schmidt,* Christine Braun, Heinz Sutoris
Institut für Organische Chemie und Isotopenforschung der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany
Received 7 August 1995

Appropriately protected optically active tetrahydropyridazine-3-carboxylic acid and hexahydropyridazine-3-carboxylic acid were prepared via ring closure of α-hydrazino- and δ-hydrazinopentanoates. Either optically active glutamic acid or an enantioselective catalytic hydrogenation was used to generate the chiral center. The numerous optically active intermediates are valuable starting materials for the synthesis of other unusual amino acids.

In recent years, many biologically active natural compounds containing tetrahydropyridazine-3-carboxylic acid (didehydropiperazic acid, ΔPiz) and hexahydropyridazine-3-carboxylic acid (piperazic acid, Piz) have been isolated. A summary of the literature up to 1993 is given in ref 2. ΔPiz has been found in the linear antrimycines[3] and cirratiomycines[4] and has been synthesized.[5,6,8,9] The (3*S*,4*S*)-4-hydroxy-ΔPiz has been recognized as a residue of luzopeptin[10] and has also been prepared.[11] Most of the peptides and depsipeptides that are known to contain Piz are cyclic. There are a number of hexapeptolides with 19-membered rings. The monamycins[12] contain two Piz of different configuration next to each other; L-156,602,[13] azinothricin,[14] A83586C,[15] IC 101,[16] citropeptin and variapeptin[17] contain two Piz separated by two amino acids; depsidomycin[18] contains two Piz of unknown configuration separated by one amino acid and verucopeptin[19] contains just one Piz. Another group of naturally occurring cyclic hexapeptides consists of 18-membered rings containing two directly attached Piz of different configuration. They are antagonists of oxytocin and vasopressin.[20] The only linear natural products, the matlystatins, contain one Piz.[21]

To date, only antrimycin D,[7] matlystatin A and B,[22,23] and L-156-602[24] have been prepared. The synthesis of racemic Piz[12b] and the separation of 1-Z-Piz into the enantiomers[25] as well as the reduction of ΔPiz[5,8,9] have been described. Optically active Piz has been prepared using the method of Evans.[26]

In the following sections, we describe three new pathways for the synthesis of optically active Piz and its derivatives. The intramolecular formation of hydrazones and intramolecular alkylation of α- or δ-hydrazinocarboxylic acids, which were prepared from α-amino acids, were used as ring-closure processes. The chiral center was formed by hydrogenation in the presence of Rh-DIPAMP or taken from optically active glutamic acid. Optically active derivatives of α-amino-δ-oxopentanoic acid, α-amino-δ-hydroxypentanoic acid, the corresponding α-hydroxycarboxylic acids and α-hydrazinocarboxylic acids were prepared in the course of these syntheses. They can be used for the preparation of optically active nonribosomal amino acids and hydroxy acids.

Piz via 4-Formyl-2-hydrazinobutyric Acid

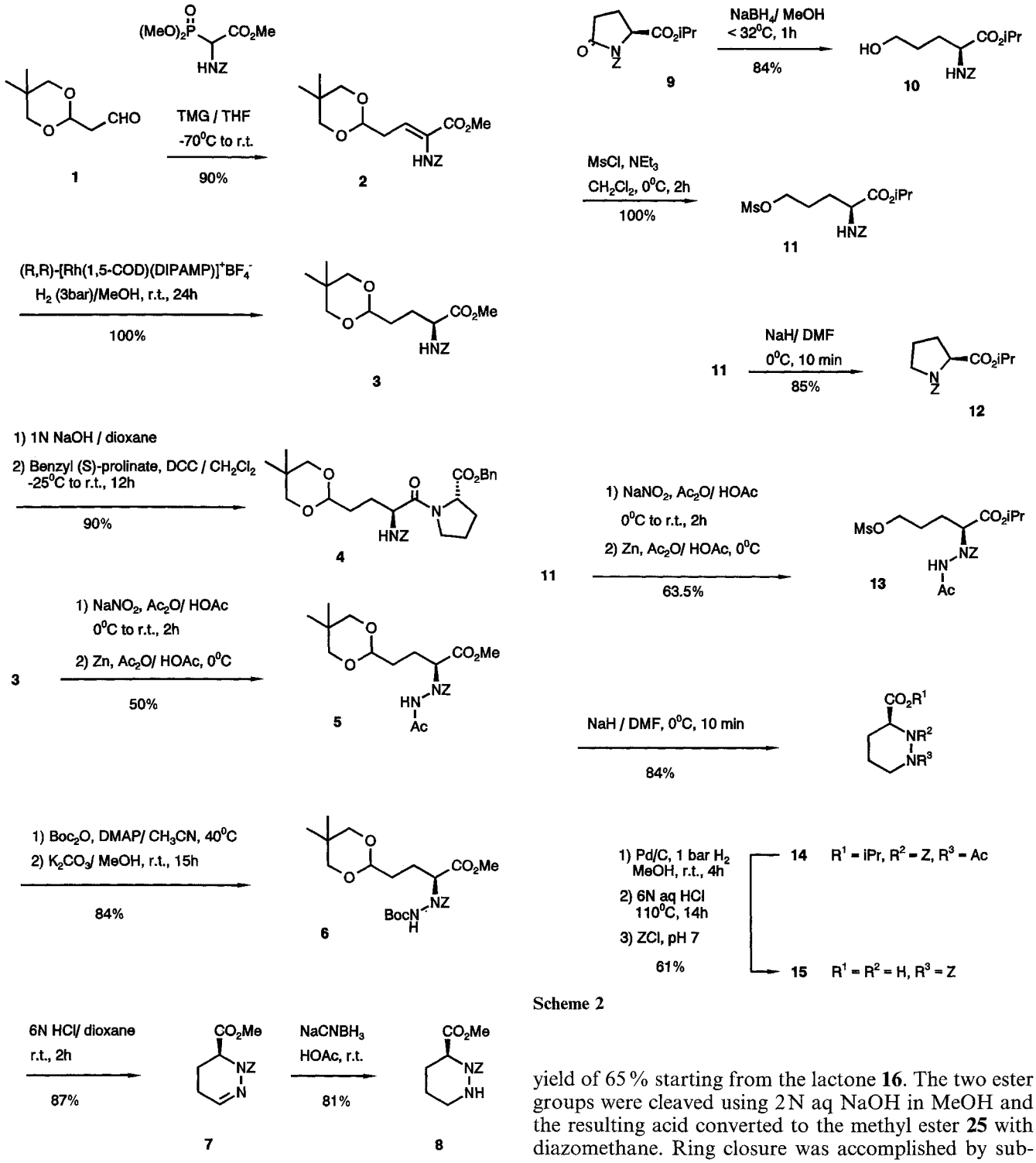
β,β-Dialkoxypropionaldehydes (malonic aldehyde dialkyl acetals) are easily accessible C_3-building blocks. For the following reactions, the 1,3-dioxane **1**[27] proved to be a suitable starting point. The (*Z*)-didehydroamino acid ester **2** was prepared in high yield by condensation of **1** with methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate[28] and tetramethylguanidine.[29] Hydrogenation in the presence of the optically active catalyst (*R,R*)-[Rh(1,5-COD)(DIPAMP)]$^+$[BF_4]$^-$ (COD = cyclooctadiene, DIPAMP = (*R,R*)-1,2-bis[2-(2-methoxyphenyl)phenylphosphanyl]ethane)[30] proceeded with high enantioselectivity (97% ee) to yield the amino acid ester **3**. The enantiomeric excess was estimated by determination of the d.r. (diastereomeric ratio) of the coupling product with benzyl (*S*)-prolinate by HPLC [saponification of **3** and DCC coupling of the resulting carboxylic acid to benzyl (*S*)-prolinate]. Amino acid ester **3** was transformed to the hydrazine **5** via nitrosation and reduction. The general procedure of Garcia and Vilarrasa[31] had to be modified and optimized: for the nitrosation, sodium nitrite[32] was used instead of nitrosyl sulfuric acid. The nitroso compound was added slowly to the suspension of the reducing reagent in Ac_2O/HOAc at 0°C. Using these conditions, 50% of the hydrazine product **5** was isolated together with approximately 30% of starting material **3** (formed by reductive cleavage of the N–N bond). Replacement of the acetyl by a *tert*-butoxycarbonyl group gave **6**, which was treated with 6N HCl in dioxane to give **7**. The reduction of the latter with sodium cyanoborohydride yielded Piz derivative **8** (Scheme 1).

Piz via Pyroglutamic Acid

Z-Pyroglutamic acid was easily prepared from glutamic acid by published procedures.[33] The isopropyl ester **9** was subsequently reduced with sodium borohydride to give the hydroxy compound **10** (ee > 90%). The enantiomeric purity was established by conversion of the methanesulfonic ester **11** into the proline derivative **12** and determination of the optical purity of this material. The nitrosation and reduction of **11** gave the hydrazine compound **13** which was transformed into the isopropyl (*S*)-2-acetyl-1-benzyloxycarbonylhexahydropyridazine-3-carboxylate **(14)** by intramolecular ring closure. Cleavage of the Z-group by hydrogenlysis, hydrolysis and reaction with benzyloxycarbonyl chloride[12f] gave rise to the Piz derivative **15** (Scheme 2), in high optical purity (> 92% ee) which is well-suited for the construction of Piz containing peptides.

Piz via 5-Oxotetrahydrofuran-2-carboxylic Acid

Both of the enantiomers of 5-oxotetrahydrofuran-2-carboxylic acid[34] are easily accessible by treating glutamic acid with sodium nitrite in dilute sulfuric acid. The *tert*-butyl ester **16** was reduced either with $NaBH_4$ (61% yield)[36] or with DIBAL (92% yield) to *tert*-butyl 2,5-

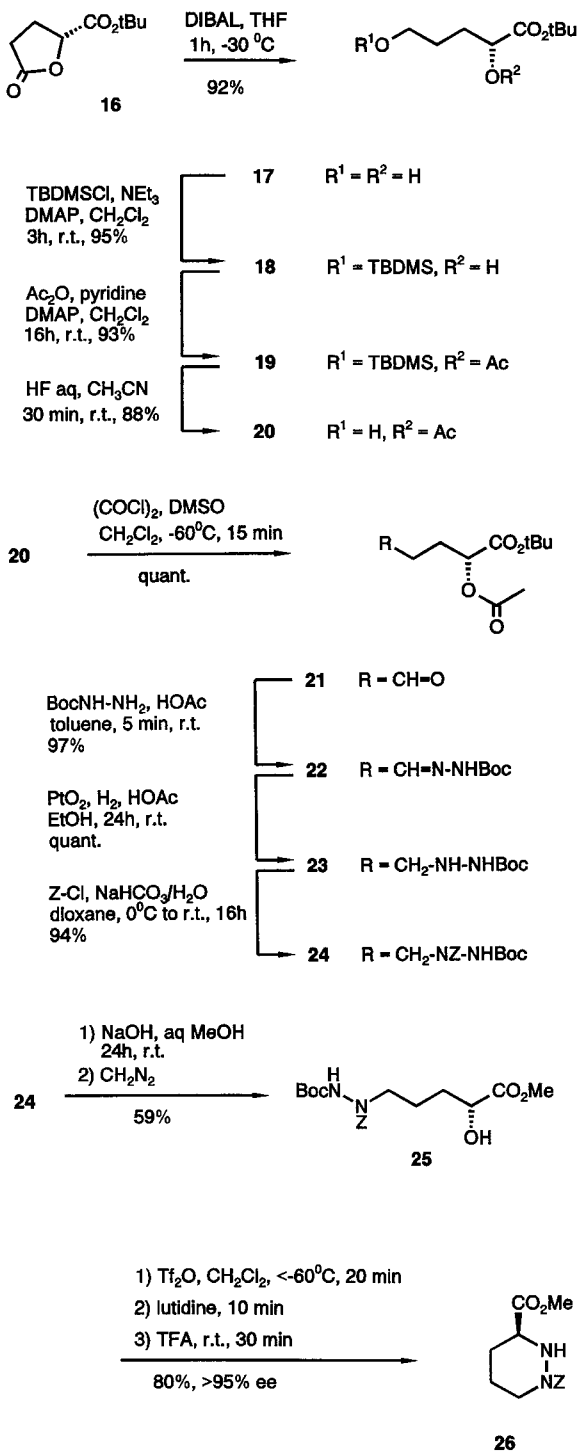


Scheme 1

Scheme 2

dihydroxypentanoate (**17**).[37] The primary OH group had to be protected as *tert*-butyldimethylsilyl ether **18** to allow the selective acetylation of the secondary OH group to afford **19**. The silyl ether of **19** was cleaved with aqueous HF to give *tert*-butyl 2-acetoxy-5-hydroxypentanoate (**20**).[38] The primary OH group was oxidized with oxalyl chloride/DMSO to the aldehyde **21**, which was condensed to the Boc-hydrazone **22**. This was hydrogenated and protected to give the Boc,Z-hydrazine **24** in an overall yield of 65% starting from the lactone **16**. The two ester groups were cleaved using 2N aq NaOH in MeOH and the resulting acid converted to the methyl ester **25** with diazomethane. Ring closure was accomplished by subsequent treatment with Tf_2O (trifluoromethanesulfonic acid anhydride), lutidine and TFA (Tf_2O/lutidine are known to be the best reagents for the reaction of methyl α-hydroxycarboxylates with *tert*-butyl carbazate[41]), to yield 2-Z-Piz-methyl ester **26** in high optical purity (95% ee). (Scheme 3).

^{1}H NMR spectra were recorded on a Bruker AC-F (250 MHz) with TMS as internal standard. Optical rotation values were determined with a Perkin-Elmer 241 polarimeter. TLC was performed on silica gel plates (Merck Silica 60 F_{254} sheets) and for MPLC, Merck LiChroprep Si 60 (15–25 μ) was used. HPLC was performed on a LKB instrument and a silica gel column Merck Hibar LiChrosorb



Scheme 3

(Si 60 7μ). GC was performed with a Carlo Erba HRGC 5300 MEGA on glass capillary columns (P22.2 (II), with permethyl-β-cyclodextrin, 19 m, prepared in the GC department of our institute). After an initial hold of 1 min at 50 °C, the column was temperature programmed at 4 °C/min to 200 °C. Hydrogen was employed as carrier gas. Satisfactory elemental analyses were obtained for compounds **2**, **3**, **4**-acid, **5**, 2-acetyl-**6**, **7**, **9**, **10**, **11**, **13**, **14**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25**, **26**: C ± 0.30, H ± 0.26, N ± 0.15, compds **11**, **13**: S ± 0.27.

Methyl 2-(Benzyloxycarbonylamino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pent-2-enoate (2):

5,5-Dimethyl-1,3-dioxane-2-acetaldehyde[27] (**1**; 10.52 g, 66.5 mmol) in anhyd THF (10 mL) was added through a dropping funnel to a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate[28] (26.43 g, 80 mmol) and tetramethylguanidine (9.20 g, 80 mmol) in anhyd THF (300 mL) at −70 °C. The mixture was allowed to warm to r.t. overnight. The solvent was removed under reduced pressure, the residue dissolved in EtOAc and washed with H_2O, 1 N aq HCl and H_2O, dried ($MgSO_4$) and evaporated in vacuo. Filtration through silica gel (eluent: hexane/EtOAc, 6:4) afforded a slightly yellow oil; yield: 21.75 g (90%) R_f 0.50 (hexane/EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 0.71 (s, 3H), 0.96 (s, 3H), 2.54–2.59 (m, 2H), 3.74 (s, 3H), 4.57 (t, 1H, J = 4.7 Hz), 5.14 (s, 2H), 6.58–6.67 (m, 2H), 7.26–7.38 (m, 5H).

Methyl (*S*)-2-(Benzyloxycarbonylamino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoate (3):

Pentenoate **2** (25.80 g, 71 mmol) in anhyd MeOH (30 mL) was hydrogenated (3 bar, r.t.) in the presence of (*R,R*)-[Rh(1,5-COD)(DIPAMP)]$^+BF_4^-$ for 2 d. The solvent was evaporated under reduced pressure and the product purified by filtration through silica gel (eluent: hexane/EtOAc, 6:4); yield: 25.95 g (100%); yellow oil; R_f 0.50 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ + 3.9 (*c* = 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.70 (s, 3H), 1.16 (s, 3H), 1.65–2.03 (m, 4H), 3.39 (d, 2H, J = 10.9 Hz), 3.64 (d, 2H, J = 11.1 Hz), 3.73 (s, 3H), 4.33–4.46 (m, 2H), 5.1 (s, 2H), 5.45 (d, 1H, J = 8.1 Hz), 7.26–7.35 (m, 5H).

Benzyl (*S*)-1-[(*S*)-Benzyloxycarbonylamino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoyl]prolinate (4):

(S)-2-(Benzyloxycarbonylamino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoic Acid:

Pentanoate **3** (1.25 g, 3.43 mmol) in dioxane (15 mL) was saponified by titration with 1 N aq NaOH (3.5 mL). When the reaction was complete (TLC control), the dioxane was removed by distillation and the remaining aqueous solution washed with Et_2O (2 × 20 mL). The aqueous layer was acidified and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure; yield: 1.19 g (100%) colorless oil; $[\alpha]_D^{20}$ + 9.2 (*c* = 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.70 (s, 3H), 1.74–2.12 (m, 4H), 3.39 (d, 2H, J = 10.7 Hz), 3.59 (d, 2H, J = 10.9 Hz), 4.39–4.48 (m, 2H), 5.10 (s, 2H), 5.60 (d, 1H, J = 8 Hz), 7.26–7.34 (m, 5H), 10.3 (br, 1H).

Benzyl (S)-1-[(S)-2-(Benzyloxycarbonylamino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoyl]prolinate (**4**):

A solution of (*S*)-2-(benzyloxycarbonylamino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoic acid (878 mg, 2.5 mmol) and (*S*)-proline benzyl ester (310 mg, 2.5 mmol) in anhyd THF (15 mL) was cooled to −25 °C. DCC (516 mg, 2.5 mmol) was added in one portion. The reaction mixture was allowed to come up to r.t. overnight, the urea was filtered off and the solvent removed under reduced pressure. The resulting residue was dissolved in EtOAc (30 mL) and washed successively with 10% aq citric acid, sat. aq $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The pure product (1.21 g, 90%, colorless oil) was obtained by flash chromatography (hexane/EtOAc, 6:4); R_f 0.27 (hexane/EtOAc, 6:4); $[\alpha]_D^{20}$ −46.9 (*c* = 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.70 (s, 3H), 1.16 (s, 3H), 1.61–2.21 (m, 8H), 3.30–3.73 (m, 6H), 4.40–4.60 (m, 3H), 5.02–5.21 (m, 4H), 5.30 (d, 1H, J = 8.6 Hz), 7.25–7.38 (m, 10H).

Methyl (*S*)-2-(2-Acetyl-1-benzyloxycarbonylhydrazino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoate (5):

$NaNO_2$ (3.79 g, 55 mmol) was added to a solution of **3** (10.01 g, 27.4 mmol) in HOAc (30 mL) and Ac_2O (15 mL) at 0 °C. When nitrosation was complete (TLC control), the reaction mixture was filtered. The filtrate was added dropwise (over 45 min) to a vigorously stirred suspension of Zn powder (10 g) in HOAc (150 mL) and Ac_2O (50 mL) at 0 °C. After 3 h at 0 °C, Zn powder (2 g) and HOAc (20 mL) were added. After 5 min the Zn salts were filtered off and washed with Et_2O (100 mL). The combined organic layers

were evaporated in vacuo. The residue was dissolved in Et_2O/EtOAc, 2:1. After filtration, the solvent was evaporated under reduced pressure. Traces of HOAc and Ac_2O were removed by adding toluene and evaporation in vacuo. This procedure was repeated twice. The pure product **5** (5.76 g, 50%) and some starting compound **3** (3.50 g, 35%) were obtained by flash chromatography (hexane/EtOAc, 1:1); R_f 0.15 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ −0.5 (c = 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.70 (s, 3H), 1.16 (s, 3H), 1.79–2.17 (m, 7H), 3.37–3.70 (m, 7H), 4.44 (m, 1H), 4.48–5.25 (m, 3H), 7.27–7.44 (m, 6H).

Methyl (*S*)-2-(1-Benzyloxycarbonyl-2-*tert*-butoxycarbonylhydrazino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoate (6):

Methyl (S)-2-(2-Acetyl-1-benzyloxycarbonyl-2-tert-butoxycarbonylhydrazino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoate **(2-Acetyl-6)**:

Di-*tert*-butyl dicarbonate (Boc_2O, 4.84 g, 22.2 mmol) and DMAP (400 mg) were added to a solution of **5** (4.69 g, 11.1 mmol) in anhyd CH_3CN (50 mL) at 40 °C. After 10 min, the solvent was removed under reduced pressure. The pure 2-acetyl-2-*tert*-butoxycarbonyl derivative (4.87 g, 84%, yellow oil) was obtained by flash chromatography (hexane/EtOAc, 1:1); R_f 0.56 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ −18.6 (c = 1.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.68–0.70 (m, 3H), 1.13–1.16 (m, 3H), 1.37–1.91 (m, 13H), 2.45–2.55 (m, 3H), 3.31–3.40 (m, 2H), 3.51–3.72 (m, 5H), 4.33–4.44 (m, 1H), 4.62–4.83 (m, 1H), 4.97–5.31 (m, 2H), 7.24–7.37 (m, 5H).

Methyl (S)-2-(1-Benzyloxycarbonyl-2-tert-butoxycarbonylhydrazino)-5,5-(2,2-dimethylpropane-1,3-diyldioxy)pentanoate **(6)**:

K_2CO_3 (100 mg) was added to a solution of the 2-acetyl-2-*tert*-butoxycarbonyl derivative **2-acetyl-6** (4.08 g, 7.8 mmol) in anhyd MeOH. The reaction mixture was stirred at r.t. for 15 h and then neutralized with 1N aq HCl. The solution was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed successively with sat. aq $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo; yield: 3.75 g (100%) yellow oil; R_f 0.54 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ −3.8 (c = 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.70 (s, 3H), 1.17 (s, 3H), 1.38–1.51 (m, 9H), 1.85–2.42 (m, 4H), 3.37–3.75 (m, 7H), 4.45 (br, 1H), 4.70–4.92 (m, 1H), 5.09–5.24 (m, 2H), 6.34–6.57 (m, 1H), 7.27–7.33 (m, 5H).

Methyl (*S*)-2-Benzyloxycarbonyl-2,3,4,5-tetrahydropyridazine-3-carboxylate (7):

Pentanoate **6** (3.51 g, 7.28 mmol) was dissolved in 6N HCl/dioxane (30 mL) and allowed to stand at r.t. under Ar for 2 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc and washed successively with sat. aq $NaHCO_3$ and twice with brine. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure; yield: 1.75 g (87%); yellow oil; R_f 0.28 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ −19.8 (c = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.89–2.46 (m, 4H), 3.72–3.76 (m, 3H), 5.06 (s br, 1H), 5.25–5.39 (m, 3H), 6.98 (s br, 1H), 7.26–7.41 (m, 5H).

Methyl (*S*)-2-Benzyloxycarbonylhexahydropyridazine-3-carboxylate (8):

$NaCNBH_3$ (742 mg, 1.7 mL) was added to a solution of **7** (700 mg, 2.8 mmol) in anhyd CH_3CN (20 mL) and HOAc (2.7 mL). The solution was kept at r.t. for 36 h. The solvent was evaporated in vacuo. The resulting residue was dissolved in Et_2O and washed with sat. aq $NaHCO_3$. The solvent was evaporated in vacuo to yield 605 mg (85%) of a slightly yellow oil; $[\alpha]_D^{20}$ −29.3 (c = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.37–1.48 (m, 1H), 1.57–1.65 (m, 1H), 1.86–1.97 (m, 1H), 2.19–2.45 (m, 1H), 2.76–2.91 (m, 1H), 3.03–3.10 (m, 1H), 3.75 (s, 3H), 3.88 (br, 1H), 4.97 (br, 1H), 5.20 (s, 2H), 7.32–7.37 (m, 5H).

***N*-Benzyloxycarbonyl-L-pyroglutamic Acid Isopropyl Ester (9):**

N-Benzyloxycarbonylpyroglutamic acid chloride[33] (41.97 g, 149 mmol) was added dropwise to a vigorously stirred solution of *i*-PrOH (18.03 g, 300 mmol) and anhyd pyridine (15.2 mL, 187.5 mmol) in anhyd CH_2Cl_2 at −30 °C. The mixture was allowed to come up to r.t. overnight. The solvent was removed under reduced pressure. The resulting residue was dissolved in EtOAc and filtered. The filtrate was washed successively with 1N aq HCl, sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. The pure product (colorless oil) was obtained by flash chromatography (EtOAc); yield: 40.94 g (90%); R_f 0.56 (EtOAc); $[\alpha]_D^{20}$ −24.5 (c = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.16 (d, 3H, J = 5.9 Hz), 1.18 (d, 3H, J = 5.9 Hz), 1.98–2.09 (m, 1H), 2.25–2.72 (m, 3H), 5.01 (h, 1H, J = 2.5 Hz), 5.2–5.31 (m, 2H), 7.32–7.46 (m, 5H).

Isopropyl (*S*)-2-(Benzyloxycarbonylamino)-5-hydroxypentanoate (10):

$NaBH_4$ (700 mg, 19 mmol) was added in portions over 1 h to a vigorously stirred mixture of **9** (800 mg, 2.6 mmol) and KH_2PO_4 (2.6 g) in MeOH (25 mL) and H_2O (5 mL). The temperature was kept between 22 °C and 32 °C. HOAc (20 mL) was added and stirring was continued for 10 min. The mixture was filtered. The filtrate was concentrated in vacuo. The resulting residue was dissolved in Et_2O and washed with H_2O (3×). The organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure; yield: 677 mg (84%) colorless oil; R_f 0.17 (hexane/EtOAc, 6:4); $[\alpha]_D^{20}$ +8.6 (c = 1.3 $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.22–1.27 (m, 6H), 1.54–1.94 (m, 5H), 3.62–3.68 (m, 2H), 4.31–4.39 (m, 1H), 5.02–5.19 (m, 3H), 5.54 (d, 1H, J = 7.8 Hz), 7.30–7.36 (m, 5H).

Isopropyl (*S*)-2-(Benzyloxycarbonylamino)-5-(methanesulfonyloxy)-pentanoate (11):

A solution of methanesulfonyl chloride (10.0 g, 87.3 mmol) in anhyd CH_2Cl_2 (20 mL) was added dropwise to a solution of **10** (13.49 g, 43.6 mmol) and NEt_3 (12.1 mL, 87.3 mmol) in anhyd CH_2Cl_2 (120 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The solvent was removed under reduced pressure, the resulting residue dissolved in EtOAc and washed successively with 1N aq HCl, sat. aq $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The pure product (colorless oil) was obtained by flash chromatography (hexane/EtOAc, 3:7); yield: 16.89 g (100%); R_f 0.45 (hexane/EtOAc, 3:7); $[\alpha]_D^{20}$ +9.9° (c = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.24–1.28 (m, 6H), 1.69–2.17 (m, 4H), 2.99 (s, 3H), 4.21–4.39 (m, 3H), 5.0–5.11 (m, 3H), 5.40 (d, 1H, J = 7.7 Hz), 7.26–7.44 (m, 5H).

Isopropyl (*S*)-2-(2-Acetyl-1-benzyloxycarbonylhydrazino)-5-(methanesulfonyloxy)pentanoate (13):

Preparation according to the procedure described for **5** starting from **11** (21.70 g, 56 mmol); yield: 17.2 g (69%, colorless oil); some starting material **11** (6.8 g, 31%) was also recovered. R_f 0.13 (hexane/EtOAc, 6:4); $[\alpha]_D^{20}$ +12.1 (c = 1.3, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.25 (d, 6H, J = 3.9 Hz), 1.67–2.22 (m, 7H), 2.99 (s, 3H), 4.26 (s br, 2H), 4.7–5.26 (m, 4H), 7.27–7.42 (m, 5H), 7.50 (s br, 1H).

Isopropyl (*S*)-1-Acetyl-2-benzyloxycarbonylhexahydropyridazine-3-carboxylate (14):

NaH (54 mg, 2.25 mmol) was added to a solution of **13** (1.00 g, 2.25 mmol) in anhyd DMF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. 1N aq HCl (10 mL) and EtOAc (20 mL) were added. The organic layer was washed successively with 1N aq HCl, sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was filtered (silica gel, eluent: EtOAc); yield: 660 mg (84%); colorless oil; R_f 0.37 (hexane/EtOAc, 6:4); $[\alpha]_D^{20}$ −26.9 (c = 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.25 (d, 6H, J = 6.3 Hz), 1.58–1.69 (m, 3H), 2.11–2.20 (m, 1H), 2.14 (s, 3H), 2.70 (br, 1H), [4.47 (t, J = 4.0 Hz), 4.53 (t, J = 3.8 Hz), 1H], 5.02–5.34 (m, 4H), 7.36 (s, 5H).

(*S*)-1-Benzyloxycarbonylhexahydropyridazine-3-carboxylic Acid (15):
Pd(0) (30 mg) was added to a solution of **14** (11.40 g, 32.7 mmol) in anhyd MeOH (10 mL). It was hydrogenated (1 bar, r.t.) for 4 h. The catalyst was filtered off and the solvent was evaporated in vacuo. 6 N aq HCl (200 mL) was added and the mixture kept at 110 °C for 14 h. The reaction mixture was concentrated under reduced pressure. The residue was converted to **15** according to the procedure described by Hassall[34]; yield: 5.21 g (61 %) colorless solid; $[\alpha]_D^{20}$ − 32.3 (c = 0.5, MeOH). By comparison with reported values of optical rotation[34] an optical purity > 92 % ee was found.

***tert*-Butyl (*R*)-5-Oxotetrahydrofuran-2-carboxylate (16):**
(*R*)-5-Oxotetrahydrofuran-2-carboxylic acid chloride[35] (14.8 g, 100 mmol) was added slowly to a vigorously stirred solution of anhyd pyridine (10.1 mL, 125 mmol) and anhyd *t*-BuOH (18.8 mL, 200 mmol) in anhyd CH_2Cl_2 (100 mL) at − 30 °C. The mixture was allowed to come up to r.t.. The pyridinium salts were filtered off using a short column of silica gel. The column was washed with hexane/EtOAc (8:2). The solvent was removed under reduced pressure, the resulting dark violet residue dissolved in EtOAc and washed successively with 10 % aq citric acid, sat. aq $NaHCO_3$, and brine. The solution was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Bulb-to-bulb distillation (110–120 °C/0.001 Torr) afforded colorless crystals; yield: 16.9 g (91 %); R_f 0.48 (hexane/EtOAc, 1:1); mp 55–56 °C; $[\alpha]_D^{20}$ − 6.8 (c = 1, CH_2Cl_2); GC: 98 % ee.

^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 9 H), 2.21–2.34 (m, 1 H), 2.44–2.68 (m, 3 H), 4.79–4.84 (m, 1 H).

***tert*-Butyl (*R*)-2,5-Dihydroxypentanoate (17):**
a) 1 N DIBAL in hexane (55 mL) was added to a stirred solution of **16** (4.65 g, 25 mmol) in anhyd THF (60 mL), which was kept under N_2 atmosphere at − 40 °C. The solution was stirred for 1 h, quenched with MeOH (7.5 mL) and allowed to come to r.t. It was poured onto a stirred mixture of EtOAc/10 % citric acid and extracted several times with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The pure product (colorless oil) was obtained by chromatography (silica gel, hexane/EtOAc, 1:1); yield: 4.36 g (92 %); R_f 0.24 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ + 6.7 (c = CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 9 H), 1.64–1.94 (m, 4 H), 2.17 (m, 1 H), 3.25 (d, 1 H, J = 5.0 Hz), 3.67–3.69 (m, 2 H), 4.07–4.13 (m, 1 H).

b) $NaBH_4$ (3.8 g, 100 mmol) was suspended in ice water (12 mL) and added in one portion to a vigorously stirred solution of **16** (4.65 g, 25 mmol) in THF (25 mL). More $NaBH_4$ (1.9 g, 50 mmol) was added in small portions. During the reaction time (about 30 min, TLC) the temperature was kept below 25 °C by adding crushed ice. It was diluted with Et_2O/sat. aq $NaHCO_3$ and extracted several times with Et_2O. The ethereal solution was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Chromatography (silica gel, hexane/EtOAc, 1:1) gave a colorless oil; yield: 2.92 g (61 %); GC: 96.5 % ee; The analytical data was identical with that in a).

***tert*-Butyl (*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-hydroxypentanoate (18):**
DMAP (30 mg), anhyd NEt_3 (2.3 mL, 16.5 mmol) and TBDMSCl (2.49 g, 16.5 mmol) were added to a stirred solution of **17** (2.92 g, 15 mmol) in anhyd CH_2Cl_2 (30 mL). The mixture was stirred for 3 h, washed with 1 N aq HCl, sat. aq $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The colorless oily product was obtained by chromatography (silica gel, hexane/EtOAc, 8:2); yield: 4.34 g (95 %); R_f 0.45 (hexane/EtOAc, 8:2); $[\alpha]_D^{20}$ + 3.0 (c = 1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$*): δ = 0.00 (s, 6 H), 0.84 (s, 9 H), 1.43 (s, 9 H), 1.49–1.70 (m, 3 H), 1.71–1.85 (m, 1 H), 2.98 (d, br, 1 H, J = 4.6 Hz), 3.60 (t, 2 H, J = 6.0 Hz), 3.96–4.02 (m, 1 H).
* without TMS.

***tert*-Butyl (*R*)-2-Acetoxy-5-(*tert*-butyldimethylsilyloxy)pentanoate (19):**
DMAP (28 mg), anhyd pyridine (1.7 mL, 21 mmol), and Ac_2O (2.0 mL, 21 mmol) were added to a stirred solution of **18** (4.34 g, 14.2 mmol) in anhyd CH_2Cl_2 (30 mL). The solution was kept at r.t. for 16 h, washed with 1 N aq HCl, sat. aq $NaHCO_3$ and brine. It was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (silica gel, hexane/EtOAc, 8:2) to afford a colorless oil; yield: 4.88 g (93 %); R_f 0.55 (hexane/EtOAc, 8:2), $[\alpha]_D^{20}$ + 21.4 (c = 1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$*): δ = 0.00 (s, 6 H), 0.84 (s, 9 H), 1.41 (s, 9 H), 1.51–1.66 (m, 2 H); 1.71–1.94 (m, 2 H), 2.07 (s, 3 H), 3.58 (t, 2 H, J = 6.1 Hz), 4.83 (dd, 1 H, J = 7.5, 5.0 Hz).
* without TMS.

***tert*-Butyl (*R*)-2-Acetoxy-5-hydroxypentanoate (20):**
Pentanoate **19** (4.58 g, 13.2 mmol) was dissolved in CH_3CN (27 mL) and 40 % aq HF (3 mL, 60 mmol). After 15 min at r.t., $NaHCO_3$ (12.7 g, 150 mmol) was added. It was stirred for 30 min, diluted with Et_2O and filtered. The solution was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Chromatography (silica gel, hexane/EtOAc, 1:1) yielded the pure product as a colorless oil; yield: 2.7 g (88 %); R_f 0.42 (hexane/EtOAc, 1:1), $[\alpha]_D^{20}$ + 39.2 (c = 1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9 H), 1.60–1.74 (m, 2 H), 1.86–2.02 (m, 2 H), 2.13 (s, 3 H), 3.68 (t, 2 H, J = 6.3 Hz), 4.99 (dd, 1 H, J = 7.2, 5.0 Hz).

***tert*-Butyl (*R*)-2-Acetoxy-5-oxopentanoate (21):**
DMSO (1.9 mL, 26.8 mmol) in anhyd CH_2Cl_2 (7 mL) was added to a stirred solution of oxalyl chloride (1.15 mL, 13.4 mmol) in anhyd CH_2Cl_2 (27 mL) at − 50 to − 60 °C. The reaction mixture was stirred for 2 min and the (*R*)-2-acetoxy-5-hydroxy derivative **20** (2.7 g, 11.6 mmol) in anhyd CH_2Cl_2 (13.5 mL) was added over 5 min. Stirring was continued for an additional 15 min. NEt_3 (8.4 mL) was added, the reaction mixture stirred for 5 min and then allowed to come to r.t. The solution was washed with 1 N aq HCl, sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The oily product (2.7 g, ~ 100 %) was used without further purification. Bulb-to-bulb distillation (90–100 °C/0.001 Torr) reduced the yield (2.2 g, 83 %); R_f 0.63 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ + 34.4 (c = 1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9 H), 2.12 (s, 3 H), 2.07–2.30 (m, 2 H), 2.52–2.64 (m, 2 H), 4.90 (dd, 1 H, J = 7.3, 5.0 Hz), 9.79 (s, 1 H).

***tert*-Butyl (*R*)-2-Acetoxy-5-(*tert*-butoxycarbonylhydrazono)pentanoate (22):**
Aldehyde **21** (2.2 g, 9.6 mmol) and *tert*-butyl carbazate (1.27 g, 9.6 mmol) were dissolved in toluene (10 mL) and HOAc (10 µL). The product separated immediately as a colorless oil. The solvent was evaporated under reduced pressure and the crude product chromatographed (silica gel) using hexane/EtOAc (8:2) as eluent for sulfur containing byproducts and hexane/EtOAc (1:1) to gain the pure product; yield: 3.2 g (97 %); colorless oil; R_f 0.41 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ + 14.4 (c = 1, CH_2Cl_2); E/Z mixture.

^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 7.2 H), 1.48 (s, 1.8 H), 1.50 (s, 7.2 H), 1.53 (s, 1.8 H), 2.12 (s, 2.4 H), 2.15 (s, 0.6 H), 1.98–2.25 (m, 1.6 H), 2.18–2.33 (m, 0.4 H), 2.38–2.46 (m, 1.6 H), 2.49–2.60 (m, 0.4 H), 4.82 (dd, 0.8 H, J = 7.0, 5.3 Hz), 4.88 (dd, 0.2 H, J = 7.0, 5.3 Hz), 6.64 (t, 0.2 H, J = 4.9 Hz), 7.20 (t, 0.8 H, J = 4.9 Hz), 7.77 (s, 0.8 H), 7.83 (s, 0.2 H).

***tert*-Butyl (*R*)-2-Acetoxy-5-(2-*tert*-butoxycarbonylhydrazino)pentanoate (23):**
Hydrazone **22** (3.2 g, 9.3 mmol) was dissolved in EtOH (10 mL) and HOAc (1 mL) and hydrogenated in the presence of PtO_2 (90 mg) at 3 bar/r.t. for 24 h. The catalyst was filtered off and the solvent removed under reduced pressure, the residue was dissolved in CH_2Cl_2 and washed with 1 N aq NaOH. It was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield a colorless oil; yield: 3.2 g (~ 100 %); R_f 0.40 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ + 21.4 (c = 1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 18 H), 1.50–1.64 (m, 2 H), 1.82–1.90 (m, 2 H), 2.13 (s, 3 H), 2.92 (t, 2 H, J = 7.1 Hz), 4.86 (t, 1 H, J = 6.2 Hz), 5.50–6.50 (br, 2 H).

tert-Butyl (_R_)-2-Acetoxy-5-(1-benzyloxycarbonyl-2-_tert_-butoxycarbonylhydrazino)pentanoate (24):

Z–Cl (1.65 mL, 11.6 mmol) was added through a dropping funnel to a well-stirred and cooled (0 °C) mixture of **23** (3.2 g, 9.3 mmol) in dioxane (12 mL) and 1 N aq $NaHCO_3$ (12 mL). The mixture was allowed to come up to r.t. and was stirred for an additional 12 h. The dioxane was removed under reduced pressure and the aqueous solution extracted several times with EtOAc. The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Chromatography (silica gel, hexane/EtOAc, 8:2 to 6:4) afforded a colorless oily product; yield: 4.18 g (94%); R_f 0.38 (hexane/EtOAc, 7:3); R_f 0.18 (hexane/EtOAc, 8:2); $[\alpha]_D^{20}$ +15.5 (c = 1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 18 H), 1.60–1.90 (m, 4 H), 2.11 (s, br, 3 H), 3.55 (br, 2 H), 4.80–4.90 (m, 1 H), 5.15 (s, br, 2 H), 6.26 and 6.47 (s, br, 1 H), 7.25–7.37 (m, 5 H).

Methyl (_R_)-5-(1-Benzyloxycarbonyl-2-_tert_-butoxycarbonylhydrazino)-2-hydroxypentanoate (25):

Hydrazinopentanoate **24** (4.18 g, 8.7 mmol) was dissolved in MeOH (30 mL). The acetoxy group was carefully saponified by very slow addition of 1 N aq NaOH (8.7 mL). 2 N aq NaOH (8.7 mL) was added in one portion and the mixture kept at r.t. for 24 h. It was neutralized with 1 N aq HCl and the MeOH removed under reduced pressure. The aqueous solution was diluted with 1 N aq NaOH and washed with Et_2O. The aqueous solution was acidified by adding citric acid (pH 2). It was extracted several times with EtOAc, dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was dissolved in Et_2O and converted to the methyl ester using CH_2N_2. After evaporation of the solvent, the crude product was purified by chromatography (silica gel, hexane/EtOAc, 1:1) to yield a colorless oil; yield: 2.03 g (59%); R_f 0.24 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ –1.5 (c = 1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.41 (br, 9 H), 1.60–1.90 (m, 4 H), 3.00 (br, 1 H), 3.56 (br, 2 H), 3.76 (s, 3 H), 4.20 (br, 2 H), 5.15 (s, br, 2 H), 6.58 (br, 1 H), 7.33 (s, 5 H).

Methyl (_S_)-1-Benzyloxycarbonylhexahydropyridazine-3-carboxylate (26):

Methyl ester **25** (400 mg, 1 mmol) was dissolved in anhyd CH_2Cl_2 (2 mL) and cooled under N_2 to –80 °C. Tf_2O (180 µL, 1.1 mmol) was added in one portion. The mixture was allowed to reach –60 °C over 20 min; during that time, the Tf_2O dissolved. Lutidine (290 µL, 2.5 mmol) in anhyd CH_2Cl_2 (2 mL) was added through a dropping funnel. After 10 min of stirring, the mixture was allowed to warm to 0 °C (ice bath) and TFA (6 mL) was added. After 5 min, the ice bath was removed and the solution kept at r.t. for 30 min. The solvent was evaporated under reduced pressure and the residue dissolved in EtOAc. The solution was washed with ice cold 2 N aq NaOH (several times, till pH > 7) and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the remaining lutidine at 0.001 Torr. The crude product was purified by chromatography (silica gel, hexane/EtOAc, 1:1) to yield a slightly yellow oil (228 mg, 80%); R_f 0.30 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ –28.4 (c = 1, CH_2Cl_2). The optical rotation of the free acid (after saponification) was compared to the values published[34] and revealed an optical purity of >95% ee. This means that there was no significant change after the NaBH reduction.

^{1}H NMR ($CDCl_3$): δ = 1.56–1.80 (m, 3 H), 2.04–2.09 (m, 1 H), 3.13 (t br, 1 H, J = 11.6 Hz), 3.51–3.59 (m, 1 H), 3.72 (s, 3 H), 4.03 (d br, 1 H, J = 11.6 Hz), 4.60–5.00 (br, NH), 5.18 (s, 2 H), 7.38–7.27 (m, 5 H).

Support of this research work by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

(1) Amino acids and peptides 100; part 99: Schmidt, U.; Weinbrenner, S. *Synthesis* **1996**, 28.
(2) Rutjes, F.P.J.T.; Teerhuis, N.M.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron* **1993**, *49*, 8605.
(3) (a) Shimada, N.; Morimoto, K.; Naganawa, H.; Takita, T.; Hamada, M.; Maeda, K.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 1613.
(b) Morimoto, K.; Shimada, N.; Naganawa, H.; Takita, T.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 1615.
(c) Morimoto, K.; Shimada, N.; Naganawa, H.; Takita, T.; Umezawa, H. *J. Antibiot.* **1982**, *35*, 378.
(4) (a) Shiroza, T.; Ebisawa, N.; Furihata, K.; Endo, T.; Seto, H.; Otake, N. *Agric. Biol. Chem.* **1982**, *46*, 865.
(b) Shiroza, T.; Ebisawa, N.; Kojima, A.; Furihata, K.; Endo, T.; Seto, H.; Otake, N. *Agric. Biol. Chem.* **1982**, *46*, 1885.
(c) Shiroza, T.; Ebisawa, N.; Furihata, K.; Endo, T.; Seto, H.; Otake, N. *Agric. Biol. Chem.* **1982**, *46*, 1891.
(5) Nakamura, Y.; Shin, C. *Chem. Lett.* **1991**, 1953.
(6) Schmidt, U.; Riedl, B. *Synthesis* **1993**, 809.
(7) Schmidt, U.; Riedl, B. *Synthesis* **1993**, 815.
(8) Nelson, W.R. Ph. D. Thesis, Utah State University, Logan, Utah/USA, 1987.
(9) Aspinall, I.H.; Cowley, P.M.; Mitchell, G.; Stoodley, R.J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179.
(10) (a) Konishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Am. Chem. Soc.* **1981**, *103*, 1241.
(b) Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 1243.
(11) Hughes, P.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 3260.
(12) (a) Hassall, C.H.; Morton, R.B.; Ogihara, Y.; Thomas, W.A. *J. Chem. Soc., Chem. Commun.* **1969**, 1079.
(b) Bevan, K.; Davies, J.S.; Hassall, C.H.; Morton, R.B.; Phillips, D.A.S. *J. Chem. Soc. (C)* **1971**, 514.
(c) Hassall, C.H.; Ogihara, Y.; Thomas, W.A. *J. Chem. Soc. (C)* **1971**, 522.
(d) Hassall, C.H.; Morton, R.B.; Ogihara, Y.; Phillips, D.A.S. *J. Chem. Soc. (C)* **1971**, 526.
(e) Hassall, C.H.; Thomas, W.A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2369.
(f) Hassall, C.H.; Johnson, W.H.; Theobald, C.J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1451.
(13) (a) Hurley, T.R.; Bunge, R.H.; Willmer, N.E.; Hokanson, G.C.; French, J.C. *J. Antibiot.* **1986**, *39*, 1651.
(b) Hensens, O.D.; Borris, R.P.; Koupal, L.R.; Caldwell, C.G.; Currie, S.A.; Haidri, A.A.; Homnick, C.F.; Honeycutt, S.S.; Lindenmayer, S.M.; Schwartz, C.D.; Weissberger, B.A.; Woodruff, H.B.; Zink, D.L.; Zitano, L.; Fieldhouse, J.M.; Rollins, T.; Springer, M.S.; Springer, J.P. *J. Antibiot.* **1991**, *44*, 249.
(14) Maehr, H.; Liu, C.-M.; Palleroni, N.J.; Smallheer, J.; Todaro, L.; Williams, T.H.; Blount, J.H. *J. Antibiot.* **1986**, *39*, 17.
(15) Smitka, T.A.; Deeter, J.B.; Hunt, A.H.; Mertz, F.P.; Ellis, R.M.; Boeck, L.D.; Yao, R.C. *J. Antibiot.* **1988**, *41*, 726.
(16) Ueno, M.; Amemiya, M.; Someno, T.; Masuda, T.; Iinuma, H.; Naganawa, H.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1993**, *46*, 1658.
(17) (a) Nakagawa, M.; Hayakawa, Y.; Furihata, K.; Seto, H. *J. Antibiot.* **1990**, *43*, 477.
(b) Nakagawa, M.; Hayakawa, Y.; Adachi, K.; Seto, H. *Agric. Biol. Chem.* **1990**, *54*, 791.
(18) Isshiki, K.; Sawa, T.; Naganawa, H.; Koizumi, Y.; Matsuda, N.; Hamada, M.; Takeuchi, T.; Iijima, M.; Osono, M.; Masuda, T.; Ishizuka, M. *J. Antibiot.* **1990**, *43*, 1195.
(19) Sugawara, K.; Toda, S.; Moriyama, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1993**, *46*, 928.
(20) (a) Bock, M.G.; Freidinger, R.M.; DiPardo, R.M.; Merck & Co, Inc. U.S.-Patent 5026703; *Chem. Abstr.* **1991**, *115*, 256660n.
(b) Goetz, M.A.; Schwartz, C.D.; Koupal, L.R.; Liesch, J.M.; Hansens, O.D.; Freidinger, R.; Anderson, P.S.; Pettibone, D.J.; Woodruff, B.H.; Merck & Co, Inc. Eur. Patent 0327744 A1; *Chem. Abstr.* **1990**, *112*, 215199p.

(21) Ogita, T.; Sato, A.; Enokita, R.; Suzuki, K.; Ishii, M.; Negishi, T.; Okazaki, T.; Tanaki, K.; Tanzawa, K. *J. Antibiot.* **1992**, *45*, 1723.
(22) Tamaki, K.; Ogita, T.; Tanzawa, K.; Sugimura, Y. *Tetrahedron Lett.* **1993**, *34*, 683.
(23) Tamaki, K.; Kurihura, S.; Sugimura, Y. *Tetrahedron Lett.* **1993**, *34*, 8477.
(24) (a) Caldwell, C.G.; Rupprecht, K.M.; Bondy, S.S.; Davis, A.A. *J. Org. Chem.* **1990**, *55*, 2355.
(b) Durette, P.L.; Baker, F.; Barker, P.L.; Boger, J.; Bondy, S.S.; Hammond, M.L.; Lanza, T.J.; Pessolano, A.A.; Caldwell, C.G. *Tetrahedron Lett.* **1990**, *31*, 1237.
(c) Kopka, I.E. *Tetrahedron Lett.* **1990**, *31*, 4711.
(25) Oki, K.; Suzuki, K.; Tuchida, S.; Saito, T.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2554.
(26) Hale, K.J.; Delisser, V.M.; Manaviazar, S. *Tetrahedron Lett.* **1992**, *33*, 7613.
(27) Shi-Qi, P.; Winterfeld, E. *Liebigs Ann. Chem.* **1989**, 1045.
(28) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.
(29) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487.
(30) Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D.; Weinkauff, D.J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.
(31) Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* **1987**, *28*, 341.
(32) White, E.H. *J. Am. Chem. Soc.* **1955**, *77*, 6008.
(33) Gibian, H.; Klieger, E. *Liebigs Ann. Chem.* **1961**, *640*, 145.
(34) Okabe, M.; Sun, R.-C.; Tam, S.Y.-K.; Todaro, L.J.; Coffen, D.L. *J. Org. Chem.* **1988**, *53*, 4780.
(35) Eguchi, C.; Kakuta, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1704.
(36) A large excess of $NaBH_4$ had to be used to accelerate the reaction because in the alkaline aqueous solution the lactone was opened to the carboxylate which does not react further.
(37) There are several publications (for example refs 34, 39 and 40) using 2-hydroxy-5-(hydroxymethyl)tetrahydrofuran in organic syntheses, all of them using disiamylborane or DIBAL for reduction of the lactone to the lactol. We tried also to stop the reduction at the stage of the lactol using DIBAL in THF. We got only about 30% yield as further reduction to the diol could not be avoided.
(38) If tetrabutylammonium fluoride was used acetyl migration to the δ-position took place.
(39) Farina, V.; Benigi, D.A. *Tetrahedron Lett.* **1988**, *29*, 1239.
(40) Wilson, L.J.; Liotta, D. *Tetrahedron Lett.* **1990**, *31*, 1815.
(41) Hoffman, R.V.; Kim, H.-O. *Tetrahedron Lett.* **1990**, *31*, 2953.