Enantioselective and Diastereoselective Formation of *syn*-3-Hydroxy-4-amino Acids (*syn*-Statines) via Tetramic Acids[1]

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Enantiomerically pure pyrrolidine-2,4-diones (tetramic acids) which can be diastereoselectively hydrogenated to *syn*-statines (4-amino-3-hydroxy-6-methylheptanoic acids) have been prepared by catalytic hydrogenation of 4-(benzyloxycarbonylamino)-3-oxocarboxylic acid esters.

Statine – (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid – is the characteristic constituent of the naturally occurring peptide antibiotic Pepstatin, which functions as an unselective inhibitor of acid proteases such as renin, pepsin and cathepsin D. (3*S*,4*R*)-4-Amino-3-hydroxy-5-methylhexanoic acid and its homolog are residues of the highly cancerostatic and immunsuppressive cyclodepsipeptides didemnine A, B, C and nordidemnine A, B, C. Numerous methods[2-39] for the construction of *syn*- and *anti*-statines have been reported because renin inhibitors are of great interest in the treatment of hypertension and congestive heart failure. However, many of these syntheses are not sufficiently stereoselective or are rather tedious. Two main types can be recognized:

- acylation of ester enolates or magnesium malonates with acylamino acid derivatives to give β-oxo esters and subsequent diastereoselective reduction,[3-13]
- stereoselective aldol condensation of ester enolates and α-acylamino aldehydes.[3,14-23]

Syntheses via the latter route suffer from the notorious tendency of the aldehydes, especially *tert*-butoxycarbonyl (Boc) amino aldehydes, towards racemization. The non-diastereoselective condensation can be regulated to give *syn*-diastereomers by chelation control[20] or with the help of optically active enolates.[21-23]

Acylation reactions of lithium ester enolates or magnesium enolates of malonic esters with activated acylamino acids were very successful but the subsequent reduction gave mainly the *anti*-statines. *N*-(9-Fluorenyl)methoxycarbonyl (FMoc) derivatives in particular are recommended because they crystallize very well.[9,10] A highly stereoselective conversion to the *syn*-statine has been achieved by yeast reduction,[12] by catalytic hydrogenation with optically active Wilkinson catalysts[11] and by sodium borohydride reduction of the dibenzylamino β-oxo esters.[13]

Several authors have prepared *syn*-statines via tetramic acids.[35-39] A highly diastereoselective reduction of these compounds was first described by Katsuki,[35] but the construction of the tetramic acids themselves by the Dieckmann condensation led to partial or complete racemization at C-5. By optimizing the reaction conditions Klutchko[37] was able to prepare a cyclohexyltetramic acid with 80% ee and Jouin and Castro found that optically pure tetramic acids are accessible from Boc-amino acids, Meldrum's acid and isopropenyl chlorofor-

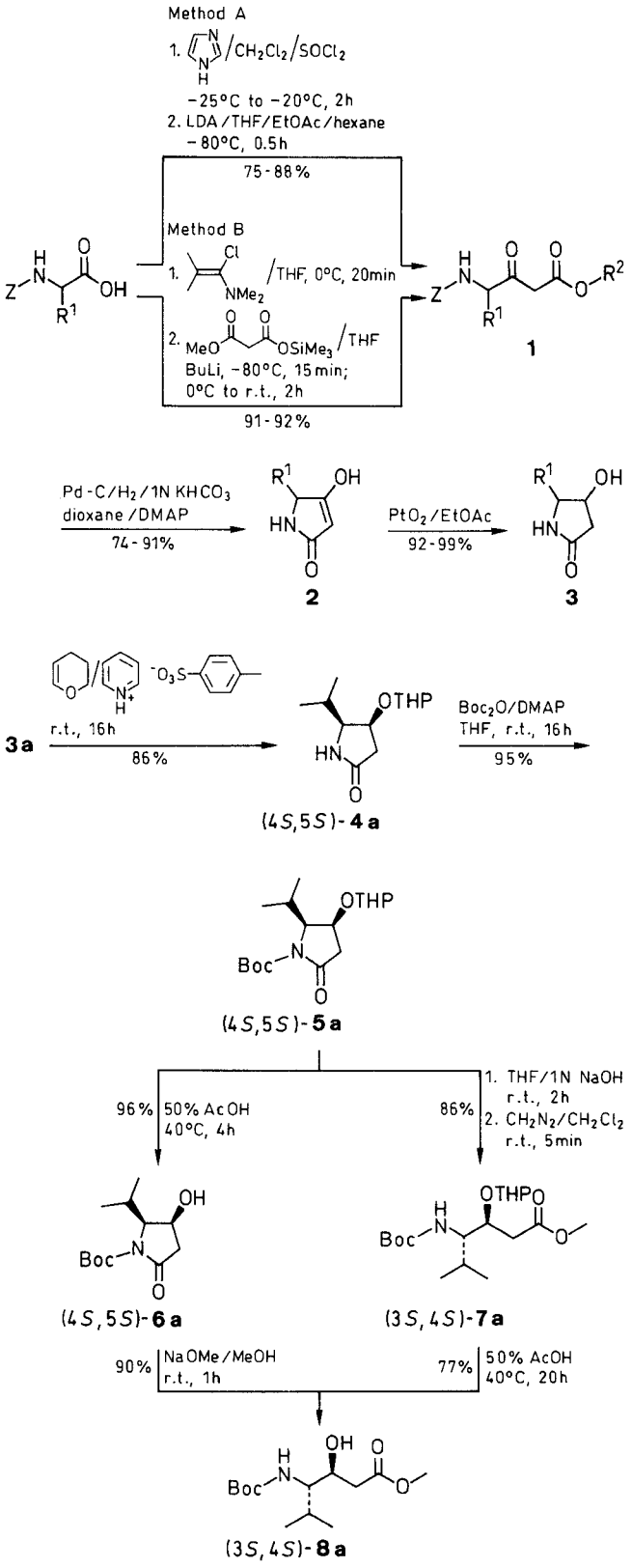


Table 1. Formation of 4-Acylamino-3-oxo Esters **1**

Product[a]	R^1	R^2	Method (Yield %)	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)[b]
(*S*)-**1a**	*i*-Pr	Et	A (88)	−28.7° (1.22)	A: 7.40 (s, 5H), 5.40 (br, 1H), 5.15 (s, 2H), 4.40–4.50 (m, 1H), 4.20 (q, *J* = 7, 2H), 3.55 (s, 2H), 2.10–2.30 (m, 1H), 1.30 (t, *J* = 7, 3H), 1.05 (d, *J* = 7, 3H), 0.80 (d, *J* = 7, 3H)
(*R*)-**1a'**	*i*-Pr	Me	B (92)	+18° (1.98)	A: 7.35 (s, 5H), 5.70 (d, *J* = 8, 1H), 5.10 (s, 2H), 4.25–4.50 (m, 1H), 3.70 (s, 3H), 3.55
(*S*)-**1a'**	*i*-Pr	Me	B (91)	−17.6° (2.86)	(s, 2H), 2.00–2.40 (m, 1H), 1.00 (d, *J* = 7, 3H), 0.80 (d, *J* = 7, 3H)
(4*S*,5*S*)-**1c**	*s*-Bu	Et	A (80)	+18.5° (1.42)	B: 7.35 (s, 5H), 5.39 (d, *J* = 9, 1H), 5.10 (s, 2H), 4.40–4.46 (m, 1H), 4.18 (d, *J* = 7.2, 2H), 3.53 (s, 2H), 1.95–1.99 (m, 1H), 1.35–1.87 (m, 2H), 1.26 (t, *J* = 7.2, 3H), 1.01 (d, *J* = 6.8, 3H), 0.91 (d, *J* = 7.1, 3H)
(4*R*,5*S*)-**1c**	*s*-Bu	Et	A (75)	−19° (0.7)	B: 7.30 (s, 5H), 5.39 (d, *J* = 9, 1H), 5.08 (s, 2H), 4.55–4.60 (m, 1H), 4.17 (d, *J* = 7.2, 2H), 3.51 (s, 2H), 1.92–1.97 (m, 1H), 1.37–1.70 (m, 2H), 1.24 (t, *J* = 7.2, 3H), 0.75–1.00 (m, 6H)
(*S*)-**1d**	*i*-Bu	Et	A (75)	−5.4° (1.14)	A: 7.30 (s, 5H), 5.05–5.30 (m, 1H), 5.10 (s, 2H), 4.10–4.65 (m, 3H), 3.53 (s, 2H), 1.25–1.80 (m, 3H), 1.25 (t, *J* = 7, 3H), 0.90 (d, *J* = 6, 6H)

[a] Satisfactory microanalyses obtained: C ±0.24, H ±0.14, N ±0.21. [b] A: 80 MHz, B: 250 MHz.

Table 2. Pyrrolidine-2,4-diones **2**

Product[a]	Educt	Yield (%)	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)	mp (°C)	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)[b]
(*S*)-**2a**	(*S*)-**1a**	90	−85.60° (0.97)	145	A: 8.40 (br, 1H), 3.90 (d, *J* = 4, 1H), 3.00 (s, 2H), 1.90–2.40 (m, 1H), 1.10 (d,
(*R*)-**2a**	(*R*)-**1a'**	91	+84.57° (0.66)	145	*J* = 7, 3H), 0.90 (d, *J* = 7, 3H)
(*S*)-**2c**	(4*S*,5*S*)-**1c**	74	−72.1° (0.62)	114	B: 8.15 (br, 1H), 3.90 (d, *J* = 4, 1H), 2.95 (s, 2H), 1.80–1.90 (m, 1H), 1.27–1.37 (m, 2H), 1.00 (d, *J* = 7, 3H), 0.90 (d, *J* = 7, 3H)
(*R*)-**2c**	(4*R*,5*S*)-**1c**	76	+106.51° (0.73)	135–138	B: 7.35 (br, 1H), 4.0–4.06 (m, 1H), 2.98 (s, 2H), 1.91–1.98 (m, 1H), 1.25–1.30 (m, 2H), 0.97 (d, *J* = 7, 3H), 0.86 (d, *J* = 7, 3H)
(*S*)-**2d**	(*S*)-**1d**	70	−40.8° (0.87)	99–101	A: 7.55 (br, 1H), 3.90–4.15 (m, 1H), 3.05 (s, 2H), 1.40–2.00 (m, 3H), 0.97 (d, *J* = 7, 6H)

[a] Satisfactory microanalyses obtained: C ±0.22, H ±0.15, N ±0.22. [b] A: 80 MHz, B: 250 MHz.

Table 3. Hydrogenation of Pyrrolidine-2,4-diones

Product[a]	Educt	Yield (%)	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)	mp (°C)	^1H NMR (250 MHz, $CDCl_3$/TMS) δ, *J* (Hz)
(4*S*,5*S*)-**3a**	(*S*)-**2a**	98	−12 (0.45)	131	7.27 (d, *J* = 5.25, 1H), 4.31–4.35 (m, 1H), 3.70 (br, 1H), 3.15 (dd, *J* = 9.9, 3.9, 1H), 2.30–2.60 (m, 2H), 1.95–2.02 (m, 1H), 1.02 (d, *J* = 6.6, 3H), 0.97 (d, *J* = 6.6, 3H)
(4*R*,5*R*)-**3a**	(*R*)-**2a**	96	+11.5 (0.9)	135	6.96 (s, 1H), 4.38 (t, *J* = 4.6, 1H), 3.18 (dd, *J* = 9.9, 4.0, 1H), 3.00 (br, 1H), 2.62 (dd, *J* = 17.2, 5.3, 1H), 2.33–2.40 (m, 1H), 1.93–2.07 (m, 1H), 1.00 (d, *J* = 6.7, 3H), 0.99 (d, *J* = 6.6, 3H)
(*S*)-**3c**	(*S*)-**2c**	99	−13.04 (1.0)	91	6.78 (s, 1H), 4.38 (t, *J* = 4.5, 1H), 3.26 (dd, *J* = 17.2, 3.9 Hz, 1H), 3.00–3.40 (br, 1H), 2.61 (dd, *J* = 17.2, 5.3, 1H), 2.36 (d, *J* = 17.2, 1H), 1.76–1.90 (m, 1H), 1.49–1.65 (m, 1H), 1.13–1.31 (m, 1H), 0.97 (d, *J* = 6.6, 3H), 0.94 (t, *J* = 7.3, 3H)
(*R*)-**3c**	(*R*)-**2c**	99	+8.9 (0.89)	85	6.93 (s, 1H), 4.42 (br, 1H), 3.29 (dd, *J* = 9.60, 4.1, 2H), 2.62 (dd, *J* = 7.20, 5.5, 1H), 2.37 (dd, *J* = 7.2, 0.7, 1H), 2.00–2.10 (m, 1H), 1.75–1.86 (m, 1H), 1.56–1.72 (m, 1H), 1.01 (d, *J* = 6.6, 3H), 0.96 (t, *J* = 7.3, 3H)
(*S*)-**3d**	(*S*)-**2d**	92	−12.2 (1.08)	145	6.64 (s, 1H), 4.37 (t, *J* = 4.5, 1H), 4.08–4.16 (m, 1H), 3.67–3.74 (m, 1H), 2.62 (dd, *J* = 7.2, 5.7, 1H), 2.33 (dd, *J* = 7.1, 1.5, 1H), 1.31–1.79 (m, 3H), 0.97 (d, *J* = 5.7, 3H), 0.94 (d, *J* = 5.1, 3H)

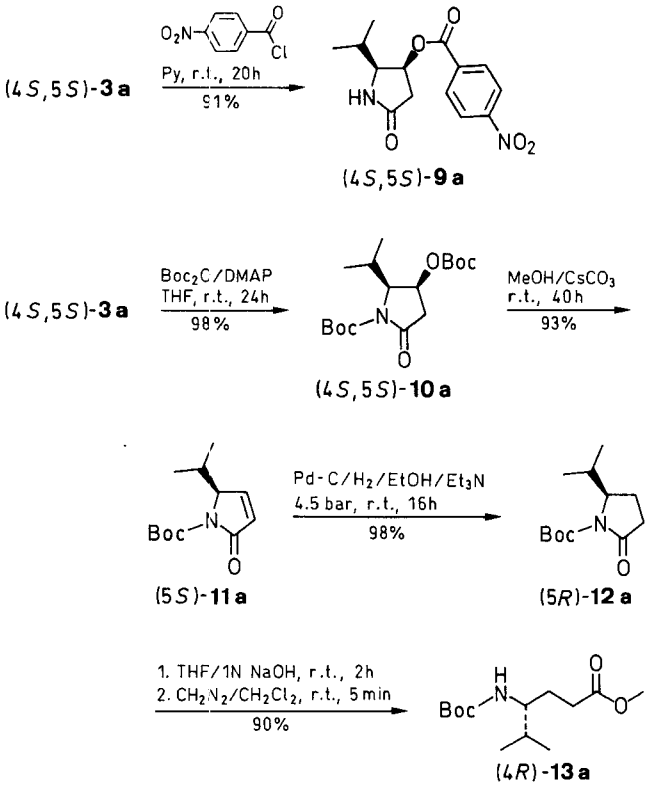
[a] Satisfactory microanalyses obtained: C ±0.13, H ±0.13, N ±0.10.

mate.[36] However, the latter reagent is very expensive and the reaction conditions are rather elusive.

We have now observed that the hydrogenolytic deprotection of γ-benzyloxycarbonyl(Z)amino-β-oxocarboxylic esters **1** in sodium hydrogen carbonate solution in the presence of 4-dimethylaminopyridine[40] smoothly gives rise to tetramic acid salts (Table 2). The γ-Z-amino-β-oxo acid esters **1** were prepared by acylation of the lithium enolates of ethyl acetate or methyl trimethylsilyl malonate with activated Z-amino acids. The use of the imidazolides[3,7] and chlorides[41] is especially recommended (Table 1). The construction of the β-oxo esters **1** and their transformation to tetramic acids **2** were examined with regard to the diastereomeric purity for the example of the isobutyl compounds from L-isoleucine and D-allo-isoleucine, respectively, because the diastereomeric tetramic acids can be separated by HPLC [LiChrosorb Si 60, 7 μ

(Merck), CH_2Cl_2/*i*-PrOH, 96 : 4]. No diastereomer has been found indicating a stereoselective formation of the β-oxo ester and of the tetramic acid.

The steric course of the reduction **2** → **3** was examined for the example of the isopropyl compound by HPLC of its 4-nitrobenzoic ester **9a** and found to give 98% (4*S*/5*S*)-**3a** and 2% (4*S*/5*R*)-**3a** (Table 3). This high purity was achieved by catalytic hydrogenation of **2** in ethyl acetate or ethanol with the Adams catalyst. The sodium borohydride reduction is inferior in terms of yield and diastereomeric purity.



The nucleophilic opening of *N*-Boc-dihydrotetramic acids has been described repeatedly.[36,37] The isopropyl compound (4*S*,5*S*)-**3a** was reacted with dihydropyran and then *N*-protected with the *tert*-butoxycarbonyl group to give (4*S*,5*S*)-**5a**, the tetrahydropyranyl protecting group of which can be split off giving (4*S*,5*S*)-**6a**. Opening of the pyrrolidinones **5a** and **6a** gave rise to the protected statines **7a** and **8a**, respectively. This sequence represents a highly diastereoselective method for the synthesis of optically pure *syn*-statines in good yield and on a large scale.

The di-Boc-compound **10a** forms by treatment with caesium carbonate pyrrol-2-(5*H*)-one **11a**, which can be hydrogenated to pyrrolidinone **12a**, the opening of which represents a way to optically active γ-amino acid derivative **13a**.

^{1}H NMR spectra are recorded on a Bruker Spectrospin 80 MHz and a Bruker AC-F (250 MHz) spectrometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Melting points (Reichert microscope) are uncorrected. TLC was done on silica gel (Merck silica 60 F_{254} sheets).

Ethyl (4*S*)-4-(Benzyloxycarbonylamino)-5-methyl-3-oxohexanoate (S)-1a; Typical Procedures:

Method A: To a stirred solution of imidazole (20.85 g, 306 mmol) in anhydr. CH_2Cl_2 (150 mL) $SOCl_2$ (9.12 g, 75 mmol) was added at − 25 °C. After 10 min a solution of Z-L-Val-OH (14.85 g, 59.4 mmol) in CH_2Cl_2 (240 mL) was added slowly and the mixture was stirred for further 2 h at − 20 °C. The organic layer was washed successively with 1 N H_2SO_4, 1 N $NaHCO_3$ and H_2O. After drying ($MgSO_4$) and evaporation of the solvent under reduced pressure the product was obtained as a colourless oil. The imidazolide was used immediately without further purification.

To a freshly prepared solution of LDA (122 mmol) in anhydr. THF/hexane (129 mL/80 mL) EtOAc (10.7 g, 11.9 mL, 122 mmol) in anhydr. THF (43 mL) and (*S*)-*N*-(benzyloxycarbonyl)valylimidazolide (59.4 mmol) in anhydr. THF (60 mL was added slowly under nitrogen at − 80 °C and the mixture was stirred for further 30 min. The reaction was quenched with 1 N HCl (200 mL) and allowed to warm up to r.t. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography on silica gel (hexane/EtOAc, 7 : 3) gave pure product (*S*)-**1a** (Table 1); yield: 19.1 g (88%).

Method B [for (*S*)-**1a'**]: To a stirred solution of Z-L-Val-OH (20.95 g, 84 mmol) in anhydr. THF (110 mL) 1-chloro-2-methyl-*N*,*N*-dimethyl-1-propenylamine[42] (11.74 mL) was added and the mixture was stirred for 20 min at 0 °C.

To a solution of methyl trimethylsilylmalonate (35 mL, 183 mmol) in anhydr. THF (200 mL), a solution of BuLi in hexane (110 mL, 182 mmol) was added slowly followed by the above prepared solution (84 mmol) of the chloride in anhydr. THF (110 mL), while the temperature of the mixture was maintained at − 80 °C. After stirring for 15 min at − 80 °C, 90 min at 0 °C and 30 min at r.t. the mixture was quenched by the addition of 2 N H_2SO_4 (140 mL). The THF was removed under reduced pressure and the resulting aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with 1 N $NaHCO_3$ (150 mL) and brine (100 mL). Drying ($MgSO_4$), evaporating and flash chromatography (eluent hexane/EtOAc, 7 : 3) gave (*S*)-**1a'** as a colourless oil (Table 1); yield: 23.5 g (91%).

(*S*)-5-Isopropylpyrrolidine-2,4-dione [(*S*)-2a]; Typical Procedure:

A solution of ethyl (4*S*)-4-(benzyloxycarbonylamino)-5-methyl-3-oxohexanoate [(*S*)-**1a**; 16.9 g, 52.5 mmol) and 4-(dimethylamino)-pyridine (DMAP, 1.6 g, 13.1 mmol) in dioxane/1 N aq $KHCO_3$ (105 mL/150 mL) was hydrogenated at r.t. in the presence of Pd-C (2.6 g, 5%) at 1.1 bar H_2 for 5 h. After filtration and evaporation of the dioxane the residue was acidified with 5 N H_2SO_4 (41 mL). The aqueous solution was extracted thoroughly with $CHCl_3$, the combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from EtOAc/hexane affording (S)-**2a**; yield: 6.7 g (90%); mp 145 °C; $[\alpha]_D^{20}$ − 80.7° (*c* = 0.97, CH_2Cl_2).

(4*S*,5*S*)-5-Isopropyl-4-hydroxypyrrolidin-2-one [(4*S*,5*S*)-3a]; Typical Procedure:

A solution of (S)-**2a** (6.25 g, 44 mmol) in EtOAc (70 mL) was hydrogenated in the presence of 250 mg PtO_2 at 30 bar H_2 for 1 d. After filtration and evaporation of the solvent the residue was purified by filtration through silica gel (Si 60; 63-200 μ; eluent: EtOAc) and dried in vacuo (0.001 mbar) to give (4*S*,5*S*)-**3a**; yield: 6.17 g (98%); mp 131 °C, $[\alpha]_D^{20}$ − 12.0° (*c* = 0.45, $CHCl_3$).

(4*S*,5*S*)-5-Isopropyl-4-(tetrahydropyran-2-yloxy)pyrrolidin-2-one (4*S*,5*S*)-4a]:

A solution of (4*S*,5*S*)-**3a** (600 mg, 4.2 mmol) and 3,4-dihydro-2*H*-pyran in anhydr. CH_2Cl_2 (14 mL) was treated with pyridinium *p*-toluenesulfonate (100 mg) and stirred for 16 h at r.t. After evaporation the residue was dissolved in Et_2O, washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (eluent: EtOAc) to give (4*S*,5*S*)-**4a** as a colourless oil; yield: 820 mg (86%).

$C_{12}H_{21}NO_3$	calc.	C 63.41	H 9.32	N 6.16
(227.3)	found	63.55	9.36	5.94

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90–1.07 (m, 6H), 1.53–1.79 (m, 6H), 1.90–2.21 (m, 1H), 2.35–2.71 (m, 2H), 3.34–3.41 (m, 1H), 3.50–3.54 (m, 1H), 3.83–3.92 (m, 1H), 4.30–4.55 (m, 1H), 4.59–4.69 (m, 1H), 7.18 (s, 1H).

(4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5-isopropyl-4-(tetrahydropyran-2-yloxy)pyrrolidin-2-one [(4*S*,5*S*)-5a]:

A solution of (4*S*,5*S*)-**4a** (0.72 g, 3.15 mmol) and DMAP (0.35 g, 3.15 mmol) in anhydr. THF (20 mL) was treated with Boc_2O (1.37 g, 6.3 mmol) and stirred for 14 h at r.t. After evaporation the residue was dissolved in EtOAc, washed with 1 N H_2SO_4 and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent: hexane/EtOAc 7 : 3) to give (4*S*,5*S*)-**5a** as a pale yellow oil; yield: 939 mg (95%); R_f = 0.33 (hexane/EtOAc, 7 : 3). The product was used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01–1.26 (m, 6H), 1.53 (s, 9H), 1.56–1.83 (m, 1H), 2.19–2.39 (m, 1H), 2.50–2.76 (m, 2H), 3.49–3.58 (m, 1H), 3.76–3.90 (m, 1H), 4.19–4.26 (m, 1H), 4.44–4.58 (m, 1H), 4.61–4.70 (m, 1H).

(4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-5-isopropylpyrrolidin-2-one [(4*S*,5*S*)-6a)]:

A solution of (4*S*,5*S*)-**5a** (230 mg, 0.73 mmol) in 50% AcOH (5 mL) was stirred at 40°C for 4 h. After removing the solvent, the crude product was purified by flash chromatography (EtOAc) to give (4*S*,5*S*)-**6a** as a colourless solid; yield: 0.16 g (96%); mp 96°C; $[\alpha]_D^{20}$ + 58.4° (*c* = 0.9, CH_2Cl_2).

$C_{12}H_{21}NO_4$	calc.	C 59.24	H 8.70	N 5.76
(243.3)	found	58.97	8.67	5.63

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ = 1.04 (d, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.52 (s, 9H), 2.28–2.39 (m, 1H), 2.51–2.68 (m, 3H), 4.12 (dd, *J* = 7.5, 5.0 Hz, 1H), 4.68 (q, *J* = 8.6 Hz, 1H)

Methyl (3*S*,4*S*)-4-*tert*-Butoxycarbonyl-5-methyl-3-(tetrahydropyran-2-yloxy)hexanoate [3*S*,4*S*)-7a]:

A solution of (4*S*,5*S*)-**5a** (350 mg, 1.12 mmol) in THF (6 mL) was treated with 1 N NaOH (2.8 mL) and stirred at r.t. until no more starting material was detected (TLC, about 2 h). The mixture was diluted with EtOAc (20 mL), acidified by the addition of 1 N H_2SO_4 (6 mL) and stirred for 5 min. The organic layer was separated and the aqueous layer was washed with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was diluted with CH_2Cl_2 (10 mL) and converted into the methyl ester (3*S*,4*S*)-**7a** by the addition of CH_2N_2. The crude product was purified by flash chromatography (eluent: hexane/EtOAc 7 : 3) to give (3*S*,4*S*)-**7a** as a colourless oil; yield: 330 mg (86%), R_f = 0.44 (hexane/EtOAc; 7 : 3).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93–1.03 (m, 6H), 1.44 (s, 9H), 1.50–1.93 (m, 7H), 2.45–2.84 (m, 2H), 3.16–3.32 (m, 1H, 3.38–3.59 (m, 1H), 3.67 (s, 3H), 3.83–3.92 (m, 1H), 4.27–4.38 (m, 1H), 4.40–4.63 (m, 1H), 4.76 (dd, *J* = 10.3, 4.2 Hz, 1H).

Methyl (3*S*,4*S*)-4-*tert*-Butoxycarbonylamino-3-hydroxy-5-methylhexanoate [(3*S*,4*S*)-8a] from (4*S*,5*S*)-6a:

A solution of (4*S*,5*S*)-**6a** (120 mg, 0.5 mmol) in anhydr. MeOH (2 mL) was treated with NaOMe (28 mg, 0.52 mmol) and stirred for 1 h at r.t. After removing the MeOH the residue was dissolved in EtOAc (20 mL) and washed with H_2O and brine. After drying the crude product was purified by flash chromatography (eluent: hexane/EtOAc, 7 : 3) to give (3*S*,4*S*)-**8a** as a colourless oil; yield: 124 mg (90%).

Methyl (3*S*,4*S*)-4-*tert*-Butoxycarbonylamino-3-hydroxy-5-methylhexanoate [(3*S*,4*S*)-8a] from (3*S*,4*S*)-7a:

A solution of (3*S*,4*S*)-**7a** (200 mg, 0.6 mmol) in 50% AcOH (5 mL) was stirred for 20 h at 40°C. After removing the AcOH under reduced pressure the crude product was purified by flash chromatography (eluent: hexane/EtOAc, 7 : 3) to give (3*S*,4*S*)-**8a** as a colourless oil; yield: 128 mg (77%), R_f = 0.32 (hexane/EtOAc, 7 : 3), $[\alpha]_D^{20}$ − 37.9 (*c* = 1.9, CH_2Cl_2).

$C_{13}H_{25}NO_5$	calc.	C 56.50	H 9.48	N 5.07
(275.3)	found	56.58	9.19	5.00

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 1.48–1.62 (br, 1H), 1.77–1.94 (m, 1H), 2.42–2.62 (m, 2H), 3.11–3.19 (m, 1H), 3.71 (s, 3H), 4.24–4.30 (m, 1H), 4.97 (d, *J* = 10.2 Hz, 1H)

(4*S*,5*S*)-5-Isopropyl-4-(4-nitrobenzoyloxy)pyrrolidin-2-one [4*S*,5*S*-(9a)]:

To a stirred solution of (4*S*,5*S*)-5-isopropyl-4-hydroxypyrrolidin-2-one [(4*S*,5*S*)-**3a**; 40 mg, 0.28 mmol] in CH_2Cl_2 (2 mL) 4-nitrobenzoyl chloride (52 mg, 0.28 mmol) and pyridine (0.025 mL) were added at r.t. and the mixture was stirred for 20 h. The solution was diluted with EtOAc (20 mL), washed with aq 1 N $KHSO_4$ (10 mL) and brine (10 mL) dried ($MgSO_4$) and evaporated in vacuo. The resulting 4-nitrobenzoyloxypyrrolidone was dried in vacuo (0.001 mbar) to yield (4*S*,5*S*)-**9a** (de 96%): 75 mg (91%); HPLC: $t_{R(4S5S)}$ = 6.05 min, $t_{R(4S5R)}$ = 4.00 min (eluent: EtOAc; Merck Hibar, LiChroSorb Si 60 7 μ); mp 171°C; $[\alpha]_D^{20}$ + 16.6° (*c* = 1.0, CH_2Cl_2).

$C_{14}H_{16}N_2O_5$	calc.	C 57.53	H 5.52	N 9.58
(292.3)	found	57.39	5.55	9.45

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 2.04 (m, 1H), 2.48 (dd, *J* = 17.8, 1.4 Hz, 1H), 2.83 (dd, *J* = 17.8, 5.9 Hz, 1H), 3.53 (dd, *J* = 9.2, 4.7 Hz, 1H), 5.64 (m, 1H), 7.30 (br s, 1H), 8.13 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H).

The (4*S*,5*R*)-**9a** compound was prepard analogously; (4*S*,5*R*)-**3a** was separated from the product of the $NaBH_4$ reduction of (*S*)-**2a**.

(4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-4-*tert*-butoxycarbonyloxy-5-isopropylpyrrolidin-2-one [(3*S*,4*S*)-10a]:

To a solution of (3*S*,4*S*)-**3a** (1.1 g, 7.7 mmol) and DMAP (90 mg, 0.8 mmol) in anhydr. THF (70 mL) Boc_2O (3.71 g, 17 mmol) was added and stirred for 24 h at r.t. THF was removed under reduced pressure, the residue was dissolved in EtOAc (30 mL) and washed successively with 1 N H_2SO_4, 1 N $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was removed under reduced pressure and the crude product was purified by filtration through silica gel (eluent: EtOAc/hexane, 2 : 8) to yield (4*S*,5*S*)-**10a**: 2.6 g (98%). $[\alpha]_D^{20}$ + 31.8° (*c* = 1.1, CH_2Cl_2).

$C_{17}H_{29}NO_6$	calc.	C 59.46	H 8.51	N 4.08
(343.5)	found	59.50	8.54	3.91

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ = 1.00 (d, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.50 (s, 9H), 1.53 (s, 9H), 2.15–2.28 (m, 1H), 2.75–2.79 (m, 2H), 4.36 (dd, *J* = 7.6, 4.5 Hz, 1H), 5.24–5.34 (m, 1H).

(5*S*)-*N*-*tert*-Butoxycarbonyl-5-isopropylpyrrolin-2(5*H*)-one [(5*S*)-11a]:

A solution of (4*S*,5*S*)-**10a** (2.5 g, 7.3 mmol) in MeOH (100 mL) was treated with $CsCO_3$ (484 mg, 1.46 mmol) and stirred for 40 h at r.t. After removing the solvent in vacuo the crude product was purified by filtration through silica gel (eluent: hexane/EtOAc, 7 : 3) to give (5*S*)-**11a** as a colourless solid; yield: 1.53 g (93%); mp 65°C; $[\alpha]_D^{20}$ + 183° (*c* = 1.0, CH_2Cl_2).

$C_{12}H_{18}NO_3$	calc.	C 63.98	H 8.50	N 6.22
(225.3)	found	63.85	8.57	5.93

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ = 0.67 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 7.1 Hz, 3H), 1.56 (s, 9H), 2.54–2.79 (m, 1H), 4.45–4.58 (m, 1H), 6.14 (dd, *J* = 6.2, 1.6 Hz, 1H), 7.13 (dd, *J* = 6.2, 2.1 Hz, 1H).

(5*R*)-*N*-*tert*-Butoxycarbonyl-5-isopropylpyrrolidin-2-one [(5*R*)-12a]:

A solution of (5*S*)-**11a** (500 mg, 2.2 mmol) in EtOH (10 mL) was treated with Pd-C (45 mg) and Et_3N (3 drops). The mixture was hydrogenated under pressure (4.5 bar) for 16 h. The catalyst was

filtered off, washed (EtOH, 50 mL) and the filtrate was evaporated in vacuo. The crude product was purified by flash chromatography (eluent: hexane/EtOAc 1 : 1) to give (5*R*)-**12a** as a colourless oil; yield: 500 mg (88%). $[\alpha]_D^{20}$ +57.6 (c = 1.0, $CHCl_3$), R_f = 0.35 (hexane/EtOAc, 7 : 3).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.08 (ddd, J = 6.8, 4.4, 2.4 Hz, 1 H), 2.37–2.60 (m, 2 H), 2.26 (dd, J = 4.4, 2.5 Hz, 1 H), 1.90–2.12 (m, 1 H), 1.76–1.88 (m, 1 H), 1.53 (s, 9 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H).

Methyl (4*R*)-4-*tert*-Butoxycarbonylamino-5-methylhexanoate [(4*R*)-13a]:

A solution of (5*R*)-**12a** (300 mg, 1.3 mmol) in THF (10 mL) was treated with 1 N NaOH (2 mL) and stirred for 2 h at r.t. After diluting with EtOAc (20 mL) the mixture was acidified by the addition of 1 N H_2SO_4 (5 mL). After separating the organic layer, the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the EtOAc was removed under reduced pressure. The free acid was converted into the methyl ester (4*R*)-**13a** by the addition of CH_2N_2. The crude product was purified by flash chromatography (eluent: hexane/EtOAc, 7 : 3) to give (4*R*)-**13a** as a colourless solid; yield: 300 mg (90%); R_f = 0.58 (hexane/EtOAc, 7 : 3), mp 65 °C, $[\alpha]_D^{20}$ +2.6 (c = 1.1, $CHCl_3$).

$C_{13}H_{25}NO_4$	calc.	C 60.21	H 9.72	N 5.40
(259.3)	found	60.07	9.67	5.19

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.6 Hz, 3 H), 1.43 (s, 9 H), 1.59–1.91 (m, 3 H), 2.37 (t, J = 7.5 Hz, 2 H), 3.37–3.49 (m, 1 H), 3.67 (s, 3 H), 4.3 (d, J = 9.9 Hz, 1 H).

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