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Stereoselective Syntheses of Deuterated Pipecolic Acids as Tools to Investigate the Stereoselectivity of the Hydroxylase GetF

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Members of the GE81112 family are interesting candidates for the development of antibiotics. The configuration of the OH group on the pipecolic acid moiety plays a pivotal role in antibiotic activity. To investigate the stereoselectivity of the corresponding hydroxylase GetF, involved in the biosynthetic pathway, we synthesized the two deuterium-labeled pipecolic acid diastereomers in a highly stereoselective fashion via chelate-enolate Claisen rearrangement. The stereochemical outcome of the enzymatic hydroxylation step could easily be determined by analysis of mass differences between the products.

Introduction

GE81112, a natural product complex comprising of three tetrapeptide congeners (Figure 1, A, B and B1), was initially identified as a translation inhibitor via in vitro protein synthesis assays employing extracts from *Streptomyces* sp..[1] Each isolated congener exhibits activities against a panel of Gram-positive and Gram-negative pathogens.[1,2] Further investigations revealed its novel mechanism of action in which GE81112 inhibits the translation initiation complex formation process by interacting with the 30S small ribosomal subunit in a different manner than other antibiotics.[3] The biosynthesis of GE81112 has been reported to be directed by a nonribosomal peptide synthetase (NRPS) involving the formation of various precursors and corresponding assembly steps.[4–6]

The understanding of the biosynthetic route enabled a recent chemoenzymatic synthesis of congener B1 including a panel of derivatives.[7] The ensuing structure-activity relationship (SAR) study revealed the key pharmacophore of the structure. Among the key chemical moieties, the hydroxyl group of the 3-hydroxypipecolic acid moiety (3-HyPip) is essential for activity.[6]

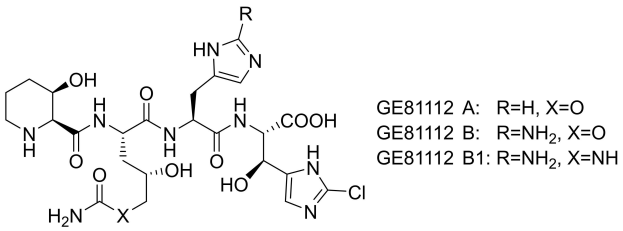
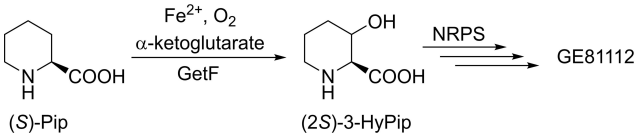


Figure 1. Tetrapeptides of the GE81112 family.

The previous biosynthetic studies suggested that probably free (2*S*,3*R*)-3-HyPip serves as the first building block for the biosynthetic pathway of GB81112. The 3-HyPip is formed from (*S*)-Pip due to catalysis of the iron- and α-ketoglutarate-dependent hydroxylase GetF,[4,6] but little is known about the stereoselectivity of the GetF-mediated hydroxylation (Scheme 1). Therefore, we decided to investigate this process in more detail.

Results and Discussion

We started our investigations on the stereoselectivity of this enzymatic oxidation step soon after the report of the biosynthesis of the GE81112 antibiotics.[8] At that time, the configuration at the hydroxy-group of 3-HyPip was not unambiguously clear. Therefore, we decided to develop a stereoselective



Scheme 1. GetF-mediated hydroxylation of (*S*)-pipecolic acid.

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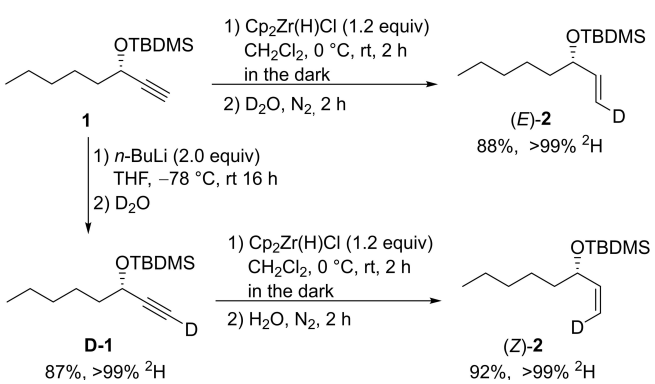
synthesis of the two diastereomeric 3-deuterated pipecolic acids and subject them to GetF-mediated hydroxylation. This should allow to determine the stereochemical outcome of the reaction either by NMR or by GC.

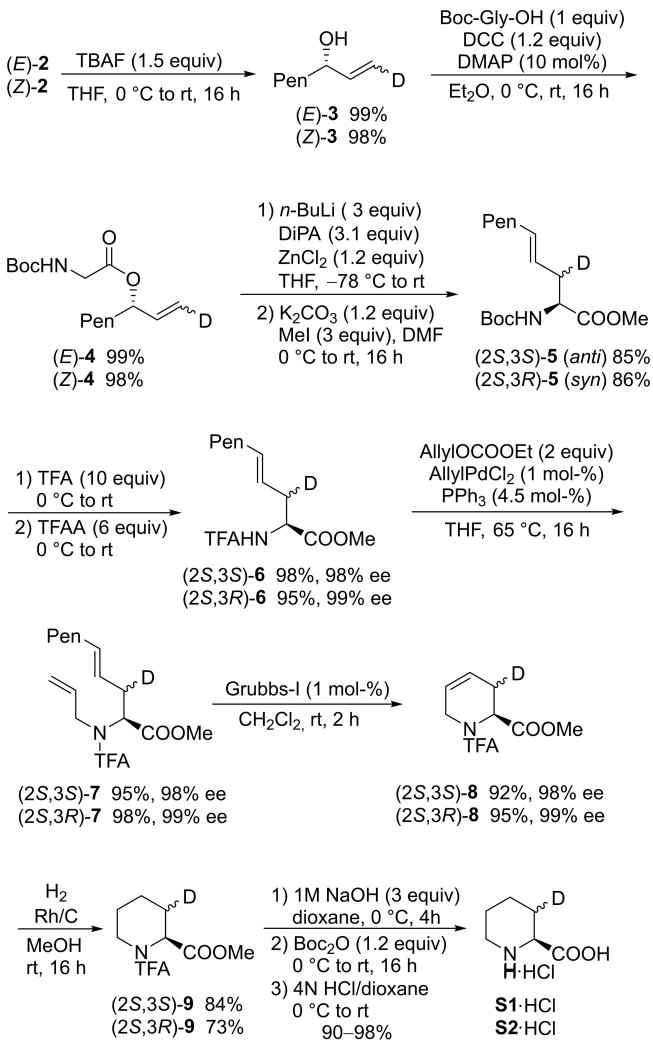
We decided to use a chelate-enolate Claisen rearrangement as a key step of our synthesis,[9] which is especially well suited for the stereoselective synthesis of substituted γ,δ-unsaturated amino acid derivatives.[10] Subsequent *N*-allylation and ring-closing metathesis allows for the synthesis of cyclic amino acid derivatives.[11]

To introduce the desired deuterium atoms stereoselectively, we started with the known silyl protected (*S*)-1-octyn-3-ol (**1**),[12] which had to be converted into the (*E*)- and (*Z*)-deuterated protected allyl alcohol **2** (Scheme 2). For the synthesis of (*E*)-**2** we decided to apply a regioselective hydrozirconation using Schwartz reagent,[13] and to trap the vinyl zirconium intermediate with D_2O. Best results were obtained using THF as the solvent, and it is worth mentioning that the reaction should be carried out in the dark under nitrogen to ensure high levels of deuteration. For the synthesis of the corresponding (*Z*)-isomer the acetylenic hydrogen was replaced by deuterium and the deuterated alkyne **D-1** was first subjected to a Lindlar hydrogenation. Although a wide range of reaction conditions was evaluated, the desired product (*Z*)-**2** was only obtained in trace amounts. Therefore, we decided to use the successful hydrozirconation approach also in this case. Subsequent protonation provided the desired product in high yield and a deuteration grade $>99\,\%$.

After desilylation, both alcohols **3** were reacted according to Neises and Steglich[14] with Boc-protected glycine, and the resulting allylic esters **4** were subjected to a chelate-enolate Claisen rearrangement (Scheme 3).[9,10] Double deprotonation and addition of zinc chloride generates a (*Z*)-configured chelated enolate, which undergoes a stereoselective Claisen rearrangement via a chair-like transition state to the desired unsaturated amino acid derivatives **5**. While the (*E*)-configured allylic ester **4** provides the *anti*-deuterated amino acid derivative **5**, the corresponding *syn*-isomer is obtained from (*Z*)-**2**. In the NMR spectra, a single set of signals was observed for both diastereomers.



Scheme 2. Stereoselective synthesis of silylated deuterated allyl alcohols **2**.



Scheme 3. Stereoselective syntheses of β-deuterated pipecolic acids.

Unfortunately, we were not able to determine the enantiomeric excess of **5**, neither by HLPC nor by GC using chiral phases. Therefore, the Boc-protecting group was replaced by a trifluoroacetyl (TFA) group, enabling the amino acid esters **6** to be nicely analyzed by GC. An excellent chirality transfer was observed from the allyl esters **4** onto the two new stereogenic centers of the amino acids.[15] The TFA protecting group was not only used for analytical purposes, it also allowed a subsequent *N*-allylation via palladium-catalyzed allylic alkylation.[16] With allyl carbonates this reaction proceeded under completely neutral conditions and without epimerization of the relatively labile stereogenic α-center, since only catalytic amounts of alcoholate are formed to deprotonate the TFA-amide. The *N*-allylated products **7** were then subjected to a ring-closing metathesis using Grubbs first generation catalyst.[17] The subsequent hydrogenation of the double bond in **8** was carried out with rhodium on carbon to avoid a migration of the double bond under the hydrogenation conditions, a side reaction observed with Pd/C and which resulted in a partial loss of the deuterium label. Both protecting groups could be removed

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from **9** in one step, but it was impossible to purify the free amino acid. Therefore, we protected it again with Boc, purified the Boc-protected amino acid and then removed the Boc protecting group. The pure HCl-salts of **S1** and **S2** were used in the bioassays.

To investigate the stereochemical outcome of the enzymatic hydroxylation step, we first incubated GetF with α-ketoglutarate, $FeSO_4$, ascorbate and undeuterated (*S*)-pipecolic acid. After Fmoc chloride (Fmoc-Cl) derivatization, Fmoc-HyPip (**11**) with *m/z* value of 368.15 was observed at the retention time (RT) of 9.3 min (Figure 2, in red), as reported before.[6] A second new peak (**12**) with *m/z* value of 590.22 was detected at RT of 14.3 min, which is assumed to be di-Fmoc-HyPip with the second Fmoc on the new introduced hydroxyl group, also supporting the hydroxylation of (*S*)-Pip. However, these data gave us no information on the stereoselectivity of the hydroxylation step.

Therefore, the two deuterium-substituted (*S*)-Pip salts, **S1**·HCl and **S2**·HCl, were assayed and derivatized using the same conditions. In the **S1** assay, products with identical mass spectra and RTs to both **11** and **12** were detected (Figure 2, green), suggesting the substitution of the deuterium atom with a hydroxyl group on C-3. In addition, a huge amount of Fmoc-protected deuterated pipecolic acid **13** was observed, indicating that the hydroxylation was much slower compared to the previous reaction with undeuterated (*S*)-Pip, where almost no unhydroxylated **10** could be determined. In the **S2** assay, two new products with *m/z* values of 369.15 (**15**) and 591.22 (**16**) were detected also at RTs of 9.3 min and 14.3 min, respectively (Figure 1, blue).

Both of these products are 1 Dalton heavier than their counterparts (**11** and **12**) in the (*S*)-Pip and the **S1** assays, indicating the presence of the deuterium atom on C-3 of 3-HyPip. The turnover rate of **S2** was much higher as in the case of **S1** and comparable to the reference reaction with unlabeled (*S*)-Pip.

These observations corroborate the stereochemistry of the product of GetF to be (2*S*,3*R*)-3-HyPip, which is in agreement with the results of recent biosynthetic studies.[6,7] In the meantime, researchers at Sanofi succeeded in the total synthesis of GE81112 A, which also confirmed this configurational assignment that resulted in a revision of the original structural proposal, postulating a (2*S*,3*S*)-configuration.[18]

Conclusions

In summary, we could show that stereoselective chelate-enolate Claisen rearrangements are powerful tools for the syntheses of deuterium labeled amino acids, which can be used in biosynthetic studies. The hydroxylase GetF, an essential enzyme in the biosynthesis of the tetrapeptide antibiotics GE81112 hydroxylates (S)-pipecolic acid in a highly stereoselective fashion selectively at the β-position to (2*S*,3*R*)-3-hydroxypipecolic acid.

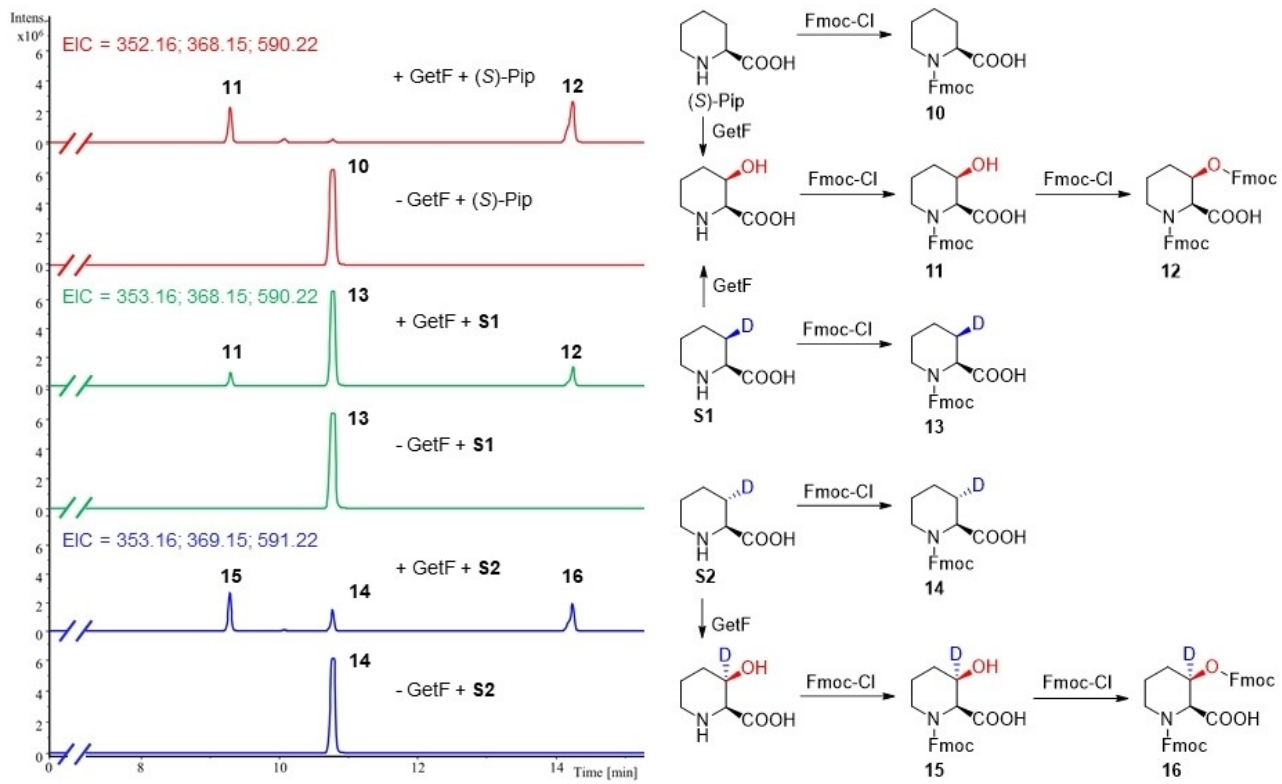

Figure 2. In vitro assay of GetF mediated hydroxylation. Extracted ion chromatograms (EICs) of derivatized substrates and the corresponding products are shown in the left panel. Illustration of enzymatic reaction and derivatization of each compound is shown in the right panel.

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Experimental Section

General remarks: All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of nitrogen. Dried solvents were distilled before use: THF was distilled from $LiAlH_4$, dichloromethane was dried with CaH_2 before distillation and DMF was purchased from Sigma-Aldrich. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel 60, 0.063–0.2 mm). Mixtures of ethyl acetate and hexane were generally used as eluents. Analytical TLC was performed on pre-coated silica gel plates (Fluka). Visualization was accomplished with UV-light and $KMnO_4$ or Ninhydrin solution. Melting points were determined with a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$, unless otherwise specified. Chemical shifts are reported in ppm relative to TMS, and $CHCl^+$ was used as the internal standard. Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. The diastereomeric ratios were determined by NMR and GC. Enantiomeric ratios were determined by GC using chiral columns (Chirasil-Dex-CB or Chirasil-Val-CB). Mass spectra were recorded with a Finnigan MAT 95 spectrometer using the CI technique. Elemental analyses were performed at the Saarland University.

(*R*)-3-(*O*-*tert*-Butyldimethylsilyl)-1-deutero-1-octyne (D-1):[19] A solution of silyl ether **1** [12] (6.01 g, 25.0 mmol) in THF (90 mL) was cooled to −78 °C before *n*-BuLi (31.3 mL, 1.6 M in Hexan, 50.0 mmol) was added and the mixture was allowed to warm to room temperature overnight. D_2O (20 mL) was added, and the aqueous layer was extracted trice with ether. The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica, hexanes/ethyl acetate 9:1) giving rise to deuterated alkyne **D-1** as a colorless liquid (5.25 g, 21.7 mmol, 87%, 99% ^2H). R_f (**D-1**) = 0.63 (hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.34 (t, *J* = 6.5 Hz, 1 H), 1.67 (m, 2 H), 1.49–1.25 (m, 6 H), 0.92–0.88 (m, 12 H), 0.14 (s, 3 H), 0.12 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.8 (d), 38.6 (t), 31.4 (t), 25.8 (q), 24.8 (t), 22.6 (t), 18.2 (s), 14.0 (q), −4.6 (q), −5.1 (q), (alkyne C's could not be detected) ppm. HRMS (CI) *m/z* for $C_{14}H_{28}DOSi$ $[M+H]^+$: calcd. 242.2045; found: 242.2048. Elemental analysis calcd (%) for $C_{14}H_{27}DOSi$ (241.47): C 69.64, H 12.11; found: C 69.38, H 12.13.

(*S*,*E*)-3-(*O*-*tert*-Butyldimethylsilyl)-1-deutero-1-octene ((*E*)-2): According to Ball et al.[20] a solution of alkyne **1** (3.61 g, 15.0 mmol) in THF (60 mL) was cooled to 0 °C before a solution of Schwartz reagent (4.64 g, 18.0 mmol) was added in the dark. The cooling bath was removed after 30 min and the solution was stirred at room temperature for 2 h. D_2O (30 mL) was added and stirring continued for another 2 h. The layers were separated, and the aqueous layer was extracted trice with ether. The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was filtered via celite and purified by flash chromatography (silica, hexanes) giving rise to deuterated alkene **(*E*)-2** as a colorless liquid (3.12 g, 13.2 mmol, 88%, 99% ee, >99% ^2H). R_f ((*E*)-**2**) = 0.61 (hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.81 (dd, *J* = 17.1, 6.0 Hz, 1 H), 5.12 (dd, *J* = 17.1, 1.3 Hz, 1 H), 4.08 (tdd, *J* = 6.5, 6.5, 1.3 Hz, 1 H), 1.59–1.22 (m, 8 H), 0.92–0.88 (m, 3 H), 0.91 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9 (d), 113.1 (t, *J* = 24 Hz), 73.9 (d), 38.1 (t), 31.8 (t), 25.9 (s), 24.9 (t), 22.6 (t), 18.3 (q), 14.0 (q), −4.4 (q), −4.8 (q) ppm. GC (Chirasil-Dex-CB, T_0 [3 min] = 80 °C, 2 °C/min bis T = 200 °C [3 min], Inj.: 250 °C, Det.: 275 °C): **(*S*/*E*)-2**: t_R = 18.00 min, **(*R*/*E*)-2**: t_R = 18.25 min. HRMS (CI) *m/z* for $C_{14}H_{30}DOSi$ $[M+H]^+$: calcd. 244.2201; found: 244.2181. Elemental analysis calcd (%) for $C_{14}H_{29}DOSi$ (243.48): C 69.06, H 12.83; found: C 68.94, H 13.33.

(*S*,*Z*)-3-(*O*-*tert*-Butyldimethylsilyl)-1-deutero-1-octene ((*Z*)-2): According to Ball et al. [20] a solution of deuterated alkyne **D-1** (2.41 g, 10.0 mmol) in THF (40 mL) was cooled to 0 °C before a solution of Schwartz reagent (3.09 g, 12.0 mmol, 1.2 equiv) was added in the dark. The cooling bath was removed after 30 min and the solution was stirred at room temperature for 2 h. H_2O (30 mL) was added and stirring continued for another 2 h. The layers were separated, and the aqueous layer was extracted trice with dichloromethane. The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was filtered via celite and purified by flash chromatography (silica, hexanes) giving rise to deuterated alkene **(*Z*)-2** as a colorless liquid (2.24 g, 9.20 mmol, 92%, 99% ee, 99% ^2H). R_f ((*Z*)-**2**) = 0.61 (hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.80 (m, 1 H), 5.00 (dd, *J* = 10.4, 1.1 Hz, 1 H), 4.09 (dt, *J* = 6.0, 6.0 Hz, 1 H), 1.56–1.23 (m, 8 H), 0.92–0.88 (m, 3 H), 0.91 (s, 9 H) 0.06 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9 (d), 113.1 (t, *J* = 24 Hz), 73.9 (d), 38.1 (t), 31.4 (t), 25.9 (s), 24.9 (t), 22.6 (t), 18.3 (q), 14.0 (q), −4.4 (q), −4.8 (q) ppm. GC (Chirasil-Dex-CB, T_0 [3 min] = 80 °C, 2 °C/min bis T = 200 °C [3 min], Inj.: 250 °C, Det.: 275 °C): **(*S*/*Z*)-2**: t_R = 18.00 min, **(*R*/*Z*)-2**: t_R = 18.25 min. HRMS (CI) *m/z* for $C_{14}H_{30}DOSi$ $[M+H]^+$: calcd. 244.2201; found: 244.2201. Elemental analysis calcd (%) for $C_{14}H_{29}DOSi$ (243.48): C 69.06, H 12.83; found: C 68.77, H 13.21.

(*S*,*E*)-1-Deutero-1-octen-3-ol ((*E*)-3): According to Korthals et al. [21] a solution of tetrabutylammonium fluoride (1 M in THF, 15.0 mL, 15.0 mmol) was added to a stirred solution of **(*S*,*E*)-2** (2.43 g, 10.0 mmol) in THF (80 mL) at 0 °C and the mixture was warmed to room temperature. After complete conversion (TLC) the reaction mixture was diluted with H_2O and the aqueous layer was extracted trice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica, hexanes/ethyl acetate 8:2) giving rise to **(*E*)-3** (1.26 g, 9.86 mmol, 99%) as a colorless liquid. R_f ((*E*)-**3**) = 0.31 (hexanes/ethyl acetate 8:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.87 (dddd, *J* = 17.3, 6.2, 1.3, 1.3 Hz, 1 H), 5.21 (dd, *J* = 17.1, 1.3 Hz, 1 H), 4.09 (m, 1 H), 1.55–1.29 (m, 8 H), 1.30 (bs, 1 H, OH), 0.90 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2 (d), 114.2 (t, *J* = 24 Hz), 73.3 (d), 37.0 (t), 31.7 (C-6), 25.0 (t), 22.6 (t), 14.0 (q) ppm.

(*S*,*Z*)-1-Deutero-1-octen-3-ol ((*Z*)-3):[22] In analogy to **(*E*-3)**, **(*Z*)-3** was obtained from **(*Z*)-2** (2.92 g, 12.0 mmol) and tetrabutylammonium fluoride (1 M in THF, 15.6 mL, 15.6 mmol) in 98% yield (1.52 g, 11.8 mmol). R_f ((*E*)-**3**) = 0.31 (hexanes/ethyl acetate 8:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.87 (m, 1 H), 5.09 (dd, *J* = 10.3, 1.0 Hz, 1 H), 4.10 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H), 1.58–1.24 (m, 9 H, OH), 0.87 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2 (d), 114.2 (t, *J* = 24 Hz), 73.2 (d), 37.0 (t), 31.7 (t), 25.0 (t), 22.6 (t), 14.0 (q) ppm.

(*S*,*E*)-Oct-1-en-3-yl-1-deutero-(*tert*-butoxycarbonylamino)acetate ((*E*)-4): DCC (1.81 g, 8.76 mmol) was added to a solution of **(*E*)-3** (0.94 g, 7.29 mmol), Boc-Gly-OH (1.28 g, 7.29 mmol) and DMAP (89.0 mg, 0.73 mmol) in ether (45 mL) at 0 °C. The reaction mixture was warmed to room temperature overnight and filtered. The clear solution was washed with 1 M $KHSO_4$, sat. $NaHCO_3$-Lösung and brine, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica, hexanes/ethyl acetate 9:1) giving rise to **(*E*)-4** (2.08 g, 7.28 mmol, 99%) as a colorless liquid. R_f ((*E*)-**4**) = 0.35 (hexanes/ethyl acetate 8:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.76 (dd, *J* = 17.3, 6.5 Hz, 1 H), 5.31–5.21 (m, 2 H), 5.01 (bs, 1 H, NH), 3.92 (m, 2 H), 1.60 (m, 2 H), 1.46 (s, 9 H), 1.34–1.26 (m, 6 H), 0.88 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (s), 155.6 (s), 135.9 (d), 116.9 (t, *J* = 25 Hz), 79.9 (s), 76.1 (d), 42.6 (t), 34.0 (t), 31.5 (t), 28.3 (q), 24.6 (t), 22.4 (t), 13.9 (q) ppm. HRMS (CI) *m/z* for $C_{15}H_{27}DNO_4$ $[M+H]^+$: calcd. 287.2076; found: 287.2075. Elemental analysis calcd (%) for

$C_{15}H_{26}DNO_4$ (286.39): C 62.91, H 9.85, N 4.89; found: C 63.26, H 10.34, N 5.05.

(*S*,*Z*)-Oct-1-en-3-yl-1-deutero-(*tert*-butoxycarbonylamino)acetate ((*Z*)-7): In analogy to **(*E*-4)**, **(*Z*)-4** was obtained from **(*Z*)-3** (0.95 g, 7.46 mmol). DCC (1.85 g, 8.95 mmol), Boc-Gly-OH (1.31 g, 7.46 mmol) and DMAP (92.0 mg, 0.75 mmol) in 98% yield (2.09 g, 7.31 mmol). R_f (**(*Z*)-4**) = 0.35 (hexanes/ethyl acetate 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (m, 1 H), 5.28 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H), 5.16 (dd, *J* = 10.5, 1.0 Hz, 1 H), 5.01 (bs, 1 H, NH), 3.91 (m, 2 H), 1.60 (m, 2 H), 1.45 (s, 9 H), 1.32–1.24 (m, 6 H), 0.88 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (s), 155.6 (s), 135.9 (d), 116.9 (t, *J* = 24 Hz), 79.9 (s), 76.1 (d), 42.6 (t), 34.0 (t), 31.5 (t), 28.3 (q), 24.6 (t), 22.4 (t), 13.9 (q) ppm. HRMS (CI) *m/z* for $C_{15}H_{27}DNO_4$ $[M+H]^+$: calcd. 287.2076; found: 287.2073. Elemental analysis calcd (%) for $C_{15}H_{26}DNO_4$ (286.39): C 62.91, H 9.85, N 4.89; found: C 63.04, H 10.05, N 5.18.

(2*S*,3*S*,*E*)-2-(*tert*-Butoxycarbonylamino)-3-deutero-4-decenoic acid methylester (*anti*-5): A fresh LDA solution was prepared by adding *n*-BuLi (10.9 mL, 1.6 M in Hexan, 17.4 mmol) to a solution of diisopropylamine (2.5 mL, 18.0 mmol) in THF (18 mL) at −20 °C. After stirring for 20 min at this temperature, the solution was cooled to −78 °C before it was added to a solution of **(*E*)-4** (1.72 g, 6.0 mmol) and $ZnCl_2$ (0.98 g, 7.20 mmol) in THF (30 mL) at −78 °C. The clear solution was allowed to warm to room temperature overnight before it was diluted with ether and hydrolyzed with 1 M $KHSO_4$. The aqueous layer was extracted trice with ethyl acetate, the combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo*. The crude product was dissolved in DMF (20 mL) and cooled to 0 °C. K_2CO_3 (1.00 g (7.20 mmol) and MeI (1.13 mL, 18.0 mmol) were added and the mixture was warmed to room temperature overnight. The reaction mixture was poured into H_2O (60 mL), sat. NH_4Cl (9.0 mL) were added, and vigorous stirring continued for 20 min. The aqueous layer was extracted trice with ethyl acetate, the combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography (silica, hexanes/ethyl acetate 8:2) giving rise to ***anti*-5** (1.53 g, 5.11 mmol, 85%) as a colorless liquid. R_f (***anti*-5**) = 0.39 (hexanes/ethyl acetate 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (m, 1 H), 5.27 (dd, *J* = 15.2, 7.4 Hz, 1 H), 5.00 (d, *J* = 7.5 Hz, 1 H, NH), 4.33 (dd, *J* = 7.5, 5.8 Hz, 1 H), 3.74 (s, 3 H), 2.40 (m, 1 H), 1.99 (dt, *J* = 7.1, 7.1 Hz, 2 H), 1.45 (s, 9 H), 1.39–1.19 (m, 6 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (s), 135.6 (d), 123.2 (d), 79.7 (s), 53.1 (d), 52.1 (q), 32.4 (t), 31.2 (t), 28.9 (t), 28.2 (q), 22.4 (t), 14.0 (q), (the signals of the trifluoroacetyl group could not be detected). HRMS (CI) *m/z* for $C_{16}H_{29}DNO_4$ $[M+H]^+$: calcd. 301.2232; found: 301.2238. Elemental analysis calcd (%) for $C_{16}H_{28}DNO_4$ (300.42): C 63.97, H 10.07, N 4.66; found: C 64.06, H 10.32, N 5.07.

(2*S*,3*R*,*E*)-2-(*tert*-Butoxycarbonylamino)-3-deutero-4-decenoic acid methylester (*syn*-5): Amino acid derivative ***syn*-5** was obtained in analogy to ***anti*-5** from **(*Z*)-4** (1.43 g, 5.0 mmol). Yield: 1.29 g (4.30 mmol, 86%). R_f (***syn*-5**) = 0.39 (hexanes/ethyl acetate 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 (dtd, *J* = 15.1, 6.9, 1.0 Hz, 1 H), 5.25 (dd, *J* = 15.3, 7.5 Hz, 1 H), 5.01 (d, *J* = 5.5 Hz, 1 H, NH), 4.33 (dd, *J* = 7.7, 5.1 Hz, 1 H), 3.73 (s, 3 H), 2.48 (dd, *J* = 6.1, 6.1 Hz, 1 H), 2.00 (dt, *J* = 6.9, 6.9 Hz, 2 H), 1.44 (s, 9 H), 1.37–1.21 (m, 6 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (s), 135.7 (d), 123.2 (d), 79.8 (s), 53.1 (d), 52.1 (q), 32.5 (t), 31.3 (t), 28.9 (t), 28.3 (q), 22.5 (t), 14.0 (q), (the signals of the trifluoroacetyl group could not be detected). HRMS (CI) *m/z* for $C_{16}H_{29}DNO_4$ $[M+H]^+$: calcd. 301.2232; found: 301.2218. Elemental analysis calcd (%) for $C_{16}H_{28}DNO_4$ (300.42): C 63.97, H 10.07, N 4.66; found: C 63.83, H 10.22, N 4.83.

(2*S*,3*S*,*E*)-2-(2,2,2-Trifluoroacetamido)-3-deutero-4-decenoic acid methylester (*anti*-6): Trifluoroacetic acid (2.90 mL, 37.3 mmol) was added to ***anti*-5** (1.11 g, 3.72 mmol) at 0 °C. After cleavage of the Boc-group was complete (TLC) trifluoroacetic anhydride (3.15 mL, 22.3 mmol) was added, and the mixture was warmed to room temperature overnight. The solvent was removed *in vacuo*, and the crude product was dissolved in dichloromethane and neutralized with sat. $NaHCO_3$. The aqueous layer was extracted trice with dichloromethane, the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica, hexanes/ethyl acetate 9:1) giving rise to ***anti*-6** (1.08 g, 3.65 mmol, 98%, 98% ee) as a pale yellow liquid. R_f (***anti*-6**) = 0.22 (hexanes/ethyl acetate 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (d, *J* = 5.5 Hz, 1 H, NH), 5.56 (dtd, *J* = 15.1, 6.9, 1.0 Hz, 1 H), 5.22 (dd, *J* = 15.3, 7.5 Hz, 1 H), 4.64 (dd, *J* = 7.7, 5.1 Hz, 1 H), 3.81 (s, 3 H), 2.52 (dd, *J* = 6.1, 6.1 Hz, 1 H), 2.00 (dt, *J* = 6.9, 6.9 Hz, 2 H), 1.37–1.20 (m, 6 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (s), 137.2 (d), 121.8 (d), 52.8 (d), 52.2 (q), 34.6 (t, *J* = 20 Hz), 32.4 (t), 31.2 (t), 28.9 (t), 22.4 (t), 14.0 (q) ppm, (the signals of the trifluoroacetyl group could not be detected). GC (Chirasil-Val-CB, T_0 [3 min] = 80 °C, 1 °C/min to T = 150 °C, 10 °C/min to T = 180 °C, Inj.: 250 °C, Det.: 275 °C): **(2*R*)-8**: t_R = 42.21 min, **(2*S*)-8**: t_R = 44.01 min. HRMS (CI) *m/z* for $C_{13}H_{20}DF_3NO_3$ $[M+H]^+$: calcd. 297.1536; found: 297.1531. Elemental analysis calcd (%) for $C_{13}H_{19}DF_3NO_3$ (296.31): C 52.70, H 7.14, N 4.73; found: C 53.17, H 7.42, N 4.65.

(2*S*,3*R*,*E*)-2-(2,2,2-Trifluoroacetamido)-3-deutero-4-decenoic acid methylester (*syn*-6): Amino acid derivative ***syn*-6** was obtained in analogy to ***anti*-6** from ***syn*-5** (0.53 g, 1.76 mmol). Yield: 0.50 g (1.67 mmol, 95%, 99% ee). R_f (***syn*-6**) = 0.22 (hexanes/ethyl acetate 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (m, 1 H, NH), 5.56 (dtd, *J* = 15.1, 7.0, 1.3 Hz, 1 H), 5.22 (dd, *J* = 15.3, 6.8 Hz, 1 H), 4.64 (dd, *J* = 7.4, 5.9 Hz, 1 H), 3.80 (s, 3 H), 2.60 (dd, *J* = 6.3, 6.3 Hz, 1 H), 2.00 (dt, *J* = 7.0, 7.0 Hz, 2 H), 1.39–1.21 (m, 6 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (s), 137.2 (d), 121.7 (d), 52.8 (d), 52.2 (q), 34.4 (t, *J* = 20 Hz), 32.4 (t), 31.2 (t), 28.9 (t), 22.4 (t), 13.9 (q), (the signals of the trifluoroacetyl group could not be detected) ppm. GC (Chirasil-Val-CB, T_0 [3 min] = 80 °C, 1 °C/min to T = 150 °C, 10 °C/min to T = 180 °C, Inj.: 250 °C, Det.: 275 °C): **(2*R*)-6**: t_R = 42.21 min, **(2*S*)-6**: t_R = 44.01 min. HRMS (CI) *m/z* for $C_{13}H_{19}DF_3NO_3$ $[M]^+$: calcd. 296.1458; found: 296.1465. Elemental analysis calcd (%) for $C_{13}H_{19}DF_3NO_3$ (296.31): C 52.70, H 7.14, N 4.73; found: C 52.96, H 7.66, N 4.92.

(2*S*,3*S*,*E*)-2-(*N*-Allyl-2,2,2-trifluoroacetamido)-3-deutero-4-decenoic acid methylester (*anti*-7): Allylpalladium chloride (11.0 mg, 0.03 mmol) and PPh_3 (35.4 mg, 0.14 mmol) were dissolved in THF (3.0 mL) before allyl ethyl carbonate (0.78 g, 6.00 mmol) was added and the solution stirred for 30 min at room temperature. A solution of ***anti*-6** (0.89 g, 3.00 mmol) was added, and the mixture was heated to reflux overnight. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (silica, hexanes/ethyl acetate 9:1) giving rise to ***anti*-7** (0.96 g, 2.85 mmol, 95%, 98% ee) as a colorless oil. R_f (***anti*-7**) = 0.22 (hexanes/ethyl acetate 9:1). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 5.51 (dtd, *J* = 15.3, 7.0, 1.5 Hz, 1 H), 5.33–5.25 (m, 3 H), 4.17–4.01 (m, 2 H), 3.95 (m, 1 H), 3.72 (s, 3 H), 2.71 (dd, *J* = 5.0, 5.0 Hz, 1 H), 1.98 (dt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 6 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (s), 135.3 (d), 132.3 (d), 124.3 (d), 119.8 (t), 116.1 (q, *J* = 288 Hz), 60.1 (d), 52.4 (q), 51.7 (q, *J* = 4 Hz), 32.5 (t), 31.3 (t), 30.9 (t, *J* = 21 Hz), 28.9 (t), 22.5 (t), 14.0 (q), (CF_3CO could not be detected) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (m, 1 H), 5.23–5.17 (m, 16-H), 4.53 (d, *J* = 6.0 Hz, 1 H), 3.73 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (s), 136.1 (d), 131.9 (d), 123.0 (d), 118.1 (t), 59.7 (d), 52.5 (q), 47.6 (t), 32.4 (t), 31.2 (t), 28.7 (t) ppm. HPLC

(Reprosil 100 Chiral-NR, hexanes:*i*PrOH = 95:5, 1 mL/min): **(2*R*)-7**: t_R = 6.69 min, **(2*S*)-7**: t_R = 8.64 min. HRMS (CI) *m/z* for $C_{16}H_{24}DF_3NO_3$ $[M+H]^+$: calcd. 337.1844; found: 337.1838. Elemental analysis calcd (%) for $C_{16}H_{23}DF_3NO_3$ (336.37): C 57.13, H 7.49, N 4.16; found: C 57.30, H 7.41, N 4.66.

(2*S*,3*R*,*E*)-2-(*N*-Allyl-2,2,2-trifluoroacetamido)-3-deutero-4-decenoic acid methylester (*syn*-7): Amino acid derivative ***syn*-7** was obtained in analogy to ***anti*-7** from ***syn*-6** (0.16 g, 0.53 mmol). Yield: 0.18 g (0.52 mmol, 98%, 99% ee). R_f (***syn*-7**) = 0.22 (hexanes/ethyl acetate 9:1). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 5.55 (m, 1 H), 5.34–5.17 (m, 3 H), 4.18–4.03 (m, 2 H), 3.72 (s, 3 H), 2.75 (dd, *J* = 9.3, 9.3 Hz, 1 H), 1.99 (m, 2 H), 1.36–1.23 (m, 6 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (s), 135.3 (d), 132.3 (d), 124.3 (d), 119.8 (t), 60.1 (d), 52.5 (q), 32.5 (t), 31.3 (t), 30.9 (t, *J* = 21 Hz), 28.9 (t), 22.5 (t), 14.0 (q), (the signals of the trifluoroacetyl group could not be detected) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52 (d, *J* = 8.5 Hz, 1 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 118.2 (t), 51.7 (q), 28.8 (t), 22.4 (t) ppm. HRMS (CI) *m/z* for $C_{16}H_{24}DF_3NO_3$ $[M+H]^+$: calcd. 337.1844; found: 337.1838. Elemental analysis calcd (%) for $C_{16}H_{23}DF_3NO_3$ (336.37): C 57.13, H 7.49, N 4.16; found: C 57.54, H 7.96, N 4.46.

(2*S*,3*S*)-1-(2,2,2-Trifluoroacetyl)-3-deutero-1,2,6-trihydropyridine-2-carboxylic acid methylester (*anti*-8): Benzylidenbis(tricyclohexylphosphan)dichlorruthenium (17.4 mg, 0.02 mmol) was added to a solution of ***anti*-7** (0.59 g, 1.76 mmol) in dichloromethane (18 mL) and the solution was stirred at room temperature until complete conversion (TLC). The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (silica, hexanes/ethyl acetate 9:1) giving rise to ***anti*-8** (0.39 g, 1.62 mmol, 92%, 98% ee) as a colorless oil. R_f (***anti*-8**) = 0.19 (hexanes/ethyl acetate 9:1). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (m, 1 H), 5.66 (m, 1 H), 5.45 (d, *J* = 6.8 Hz, 1 H), 4.27–4.14 (m, 2 H), 3.75 (s, 3 H), 2.76 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (s), 123.1 (d), 122.0 (d), 113.5 (q, *J* = 288 Hz), 52.8 (d), 50.6 (q), 42.5 (q, *J* = 4 Hz), 25.4 (t, *J* = 21 Hz), (CF_3CO could not be detected) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 5.75 (m, 1 H), 4.83 (d, *J* = 6.3 Hz, 1 H), 4.40 (ddd, *J* = 19.1, 3.1, 3.1 Hz, 1 H), 3.87 (d, *J* = 19.1 Hz, 1 H), 3.77 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (s), 123.1 (d), 122.1 (d), 53.7 (q, *J* = 4 Hz), 53.0 (d), 42.2 (q, *J* = 4 Hz), 26.6 (t, *J* = 21 Hz) ppm. GC (Chirasil-Dex-CB, T_0 [3 min] = 80 °C, 0.5 °C/min to T = 140 °C, 10 °C/min to T = 200 °C, Inj.: 250 °C, Det.: 275 °C): **(2*R*)-8**: t_R = 37.72 min, **(2*S*)-8**: t_R = 41.95 min. HRMS (CI) *m/z* for $C_9H_{10}DF_3NO_3$ $[M+H]^+$: calcd. 239.0748; found: 239.0745. Elemental analysis calcd (%) for $C_9H_9DF_3NO_3$ (238.18): C 45.38, H 4.65, N 5.88; found: C 45.47, H 4.89, N 5.72.

(2*S*,3*R*)-1-(2,2,2-Trifluoroacetyl)-3-deutero-1,2,6-trihydropyridine-2-carboxylic acid methylester (*syn*-8): Amino acid derivative ***syn*-8** was obtained in analogy to ***anti*-8** from ***syn*-7** (0.37 g, 1.10 mmol). Yield: 0.25 g (1.04 mmol, 95%, 99% ee). R_f (***syn*-8**) = 0.19 (hexanes/ethyl acetate 9:1). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddt, *J* = 10.3, 5.9, 2.3 Hz, 1 H), 5.67 (m, 1 H), 5.45 (m, 1 H), 4.28–4.15 (m, 2 H), 3.75 (s, 3 H), 2.52 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0 (s), 157.0 (q, *J* = 36 Hz), 123.1 (d), 122.0 (d), 116.3 (q, *J* = 288 Hz), 53.0 (d), 50.6 (q), 42.5 (q, *J* = 4 Hz), 25.5 (t, *J* = 21 Hz), (CF_3CO could not be detected) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (m, 1 H), 5.76 (m, 1 H), 4.83 (m, 1 H), 4.43 (m, 1 H), 3.88 (m, 1 H), 3.77 (s, 3 H), 2.58 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (d), 41.9 (t) ppm. HRMS (CI) *m/z* for $C_9H_{10}DF_3NO_3$ $[M+H]^+$: calcd. 239.0748; found: 239.0741. Elemental analysis calcd (%) for $C_9H_9DF_3NO_3$ (238.18): C 45.38, H 4.65, N 5.88; found: C 45.80, H 4.58, N 6.13.

(2*S*,3*S*)-1-(2,2,2-Trifluoroacetyl)-3-deutero-piperidinecarboxylic acid methylester (*anti*-9): Amino acid derivative ***anti*-8** (0.22 g, 0.94 mmol) was dissolved in methanol (5 mL) and after addition of 10% Rh/C (22.4 mg, 10 mol-%) the mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature overnight. The catalyst was filtered off, the solvent was removed *in vacuo* and the crude product was purified by flash chromatography (silica, hexanes/ethyl acetate 9:1) giving rise to ***anti*-9** (0.19 g, 0.80 mmol, 84%) as a colorless oil. R_f (***anti*-9**) = 0.19 (hexanes/ethyl acetate 9:1). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.26 (d, *J* = 6.0 Hz, 1 H), 3.94 (m, 1 H), 3.78 (s, 3 H), 3.34 (ddd, *J* = 13.4, 13.4, 3.0 Hz, 1 H), 1.80–1.69 (m, 3 H), 1.53 (m, 1 H), 1.40 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (s), 117.9 (q, *J* = 288 Hz), 53.3 (d), 52.6 (q), 43.7 (q, *J* = 4 Hz), 26.1 (t, *J* = 21 Hz), 25.0 (t), 20.6 (t), (CF_3CO could not be detected) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.72 (d, *J* = 5.3 Hz, 1 H), 4.48 (m, 1 H), 3.80 (s, 3 H), 2.97 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.2 (t), 24.3 (t), 20.5 (t) ppm. HRMS (CI) *m/z* for $C_9H_{12}DF_3NO_3$ $[M+H]^+$: calcd. 241.0905; found: 241.0917. Elemental analysis calcd (%) for $C_9H_{11}DF_3NO_3$ (240.20): C 45.00, H 5.45, N 5.83; found: C 45.59, H 5.80, N 6.01.

(2*S*,3*R*)-1-(2,2,2-Trifluoroacetyl)-3-deutero-piperidinecarboxylic acid methylester (*syn*-9): Amino acid derivative ***syn*-9** was obtained in analogy to ***anti*-9** from ***syn*-8** (0.26 g, 1.10 mmol). Yield: 0.19 g (0.80 mmol, 73%). R_f (***syn*-9**) = 0.19 (hexanes/ethyl acetate 9:1). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.26 (m, 1 H), 3.95 (m, 1 H), 3.78 (s, 3 H), 3.34 (ddd, *J* = 13.4, 13.4, 3.0 Hz, 1 H), 2.33 (m, 1 H), 1.76 (m, 2 H), 1.53 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (s), 116.4 (q, *J* = 288 Hz), 53.4 (d), 52.6 (q), 43.7 (q, *J* = 4 Hz), 26.2 (t, *J* = 20 Hz), 25.0 (t), 20.6 (t), (CF_3CO could not be detected) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (m, 1 H), 1.77 (m, 1 H), 3.80 (s, 3 H), 2.97 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (q), 41.2 (t), 24.3 (t), 20.5 (t) ppm. HRMS (CI) *m/z* for $C_9H_{12}DF_3NO_3$ $[M+H]^+$: calcd. 241.0905; found: 241.0914.

(2S,3S)-3-Deutero-piperidinecarboxylic acid hydrochloride (S2·HCl): A solution of ***anti*-9** (30 mg, 0.12 mmol) was dissolved in dioxane (0.5 mL) before 1 N NaOH (0.36 mL, 0.36 mmol) was added at 0 °C. After complete deprotection (TLC control) Boc_2O (30 mg, 0.14 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*, the residue was dissolved in ether and washed twice with ethyl acetate. The aqueous phase was acidified to pH 1 with 1 N HCl and extracted trice with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* giving rise to the Boc-protected amino acid (0.25 mg, 0.11 mmol, 90%) as colorless solid. This solid (15 mg, 0.07 mmol) was cooled to 0 °C before a 4 N solution of HCl in dioxane (0.3 mL, 1.2 mmol) was added. After the deprotection was complete (TLC control), the solvent was removed *in vacuo* and **S2**·HCl (11.6 mg, 0.07 mmol, 100%) was obtained as colorless solid. ^{1}H NMR (500 MHz, D_2O): δ = 3.85 (d, *J* = 11.8 Hz, 1 H), 3.41 (m, 1 H), 2.98 (dt, *J* = 12.4, 3.3 Hz, 1 H), 1.80–1.89 (m, 2 H), 1.50–1.72 (m, 3 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 175.1 (s), 60.0 (d), 46.9 (t), 28.5 (dt, *J* = 20.3 Hz), 24.3 (t), 24.3 (t) ppm. HRMS (CI) *m/z* for $C_6H_{11}DNO_2$ $[M+H–Cl]^+$: calcd. 131.0931; found: 131.0928.

(2S,3R)-3-Deutero-piperidinecarboxylic acid hydrochloride (S1·HCl): Amino acid salt **S1**·HCl was obtained in analogy to **S2**·HCl from ***syn*-9** (14.4 mg, 0.06 mmol). Yield: 10 mg (0.06 mmol, 98%). ^{1}H NMR (500 MHz, D_2O): δ = 3.84 (d, *J* = 3.5 Hz, 1 H), 3.40 (m, 1 H), 2.99 (dt, *J* = 12.4, 12.4, 3.3 Hz, 1 H), 2.22 (m, 1 H), 1.80–1.91 (m, 2 H), 1.51–1.67 (m, 2 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 175.1 (s), 60.0 (d), 46.7 (t), 28.4 (dt, *J* = 19.9 Hz), 24.2 (t), 24.2 (t) ppm. HRMS (CI) *m/z* for $C_6H_{11}DNO_2$ $[M+H–Cl]^+$: calcd. 131.0931; found: 131.0933.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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