Tandem Regioselective Rhodium-Catalyzed Hydroformylation–Enantioselective Aminocatalytic anti-Mannich Reaction

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I. General

All reactions were carried out in oven-dried glassware under an atmosphere of argon (Argon 5.0 from Sauerstoffwerke Friedrichshafen). All solvents were dried and distilled by standard procedures. Chromatographic purification of products was accomplished using flash chromatography[1] on MACHELEY-NAGEL silica gel 60® (230-400 mesh).

Melting points were measured on a Büchi melting point apparatus using open glass capillaries, and the values are uncorrected. Elementary analyses were performed on a Elementar vario (ELEMENTAR ANALYSENSYSTEME GmbH). Optical rotations were measured on a PERKIN-ELMER 241 polarimeter in 1.0 dm, 1.0 ml cells. The concentration in g/100 mL and the solvent are given in parentheses. Chiral HPLC analyses were performed on MERCK-HITACHI systems with Daicel Chiralpak AD-H (25 cm x 4.6 mm ID), Chiralpak AD-3 (15 cm x 4.6 mm ID), Chiralcel OD-H (25 cm x 4.6 mm ID), Chiralcel OJ-H (25 cm x 4.6 mm ID), Chiralcel OD-3 (15 cm x 4.6 mm ID), Chiralcel OJ-R (15 cm x 4.6 mm ID) or Chiralpak IA (25 cm x 4.6 mm ID) columns in n-heptane/iso-propanol or n-heptane/ethanol mixtures.

Nuclear magnetic resonance spectra were acquired on a BRUKER AMX 400 spectrometer (400.132 MHz and 100.626 MHz for 1H and 13C respectively) and referenced internally for 1H- and 13C-NMR according to residual proton solvent signals [CDCl3: 7.26 ppm (1H). 77.10 ppm (13C)].[2] Data for 1H-NMR are reported as follows: chemical shift (δ in ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; mC, symmetrical multiplet; br, broad signal), coupling constant (Hz), assignment, integration. Data for 13C-NMR are reported in terms of chemical shift, assignment, integration. Low resolution mass spectra were recorded on THERMO TSQ 700 spectrometers (EI: 70 eV; CI,NH3: 110 eV). High-resolution mass spectra were obtained on a Finnigan MAT 95XL instrument (EI: 70 eV; CI/NH3: 110 eV).

The following substrates were purchased from commercial sources: 1-octene (ACROS, destilled prior to use), 4-vinyl-1-cyclohexene (ACROS), 5-hexen-1-ol (MERCK), 5-hexen-2-one (ALFAAESAR), 3,3-dimethyl-1-butene (ALFAAESAR), 1,7-octadiene (ACROS), ethylglyoxylate (ALDRICH), benzylcarbamate (ALFAAESAR), K2HPO4 (RIEDEL-DE-HAÈN).
III. General procedure for hplc derivatization of domino hydroformylation/anti-Mannich-products

**General procedure for the O-benzyloximes 12a-l**[^3]

\[
\begin{align*}
\text{R} &\quad \text{NHBOc} \\
\text{O} &\quad \text{CO}_2\text{Me}^+ \\
\text{O} &\quad \text{NH}_2^+\text{HCl} \\
\text{CH}_2\text{Cl}_2, 4h \\
\end{align*}
\]

The aldehyde (1.0 equiv) was dissolved in CH\_2Cl\_2 (0.05 M) and O-benzylhydroxylamine hydrochlorid (2.6 eq.) and pyridine (12 equiv) were added. The reaction mixture was stirred for 4 h at rt, followed by filtration through a plug of silica and washed with CH\_2Cl\_2. After concentration in vacuo the residue was purified by flash column chromatography using mixtures of cyclohexane/ethyl acetate.

**General procedure for the reduction of the O-benzyloximes 12a-l to 13a-l**[^4]

\[
\begin{align*}
\text{O} &\quad \text{N} \\
\text{CO}_2\text{Et} \\
\text{NHBoc} \\
\text{R} \\
\end{align*}
\]

1. NaCNBH\_3
2. HCl

To a solution of the O-benzyloximes 12a-l (1.0 equiv) in EtOH (0.17 M) sodium cyanoborohydride (5.0 equiv) was added at rt. A drop of methylorange indicator was added followed by the addition of an aqueous solution of HCl (1.0 M) until the solution was pink and milky for at least 30 min. The reaction mixture was stirred at rt for 2-4 h. The solvent was removed in vacuo and the residue taken up in CH\_2Cl\_2 (5 ml). To the solution was added an aqueous solution of KOH (1.0 M) until the solution was alkaline. After separation of the layers the aqueous phase was extracted with CH\_2Cl\_2 (3 × 5 ml). The combined organic phases were dried over Na\_2SO\_4 and concentrated in vacuo. The residue was purified by flash column chromatography using mixtures of cyclohexane/ethyl acetate. The O-benzyloxyamines 13a-l were obtained as colorless oils.
(2S,3R)-2-tert-Butoxycarbonylamino-3-formyl-decanoic acid ethyl ester (4a):

\[
\begin{align*}
\text{BnO} & \quad \text{NH} & \quad \text{NH}_{\text{Boc}} & \quad \text{CO}_{2}\text{Et} \\
& \quad \text{12a} \\
\end{align*}
\]

(2S,3R)-3-(Benzyloxymimo-methyl)-2-tert-butoxycarbonylamino-decanoic acid ethyl ester (12a): The compound was prepared according to the general procedure with 4a (45 mg, 0.10 mmol, 1.0 equiv) CH$_2$Cl$_2$ (2.0 ml) and O-benzylhydroxylamine hydrochlorid (42 mg, 0.26 mmol, 2.6 equiv) and pyridine (97 µl, 95 mg, 1.2 mmol, 12 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 12a was obtained as a colorless oil (38 mg, 90 µmol, 86%). $^1$H-NMR (400.132 MHz, CDCl$_3$): $\delta$ [ppm] = 0.86 (t, $^3$J$_{Me,CH2}$ = 7.1 Hz, Me, 3H), 1.21 (t, $^3$J$_{Me,CH2}$ = 7.2 Hz, Me, 3H), 1.21-7.30 (m, CH$_2$, 10 H), 1.44 (s, t-Bu, 9H), 1.45-1.49 (m, CH$_2$, 2H), 2.85 (m, CH, 1H), [2.64 (m, CH, 1H)], 4.51 (q, $^3$J$_{OCH2,Me}$ = 7.1 Hz, CH$_2$, 2H), 4.44 (dd, $^3$J$_{CH,NH}$ = 4.6 Hz, $^3$J$_{CH,CH}$ = 9.5 Hz, CH, 1H), [4.32 (dd, $^3$J$_{CH,NH}$ = 5.4 Hz, $^3$J$_{CH,CH}$ = 8.0 Hz, CH, 1H)], 5.03 (s, CH$_2$, 2H), 5.16 (d, $^3$J$_{NH,CH}$ = 9.5 Hz, NH, 1H), 7.27-7.36 (m, Ar-H, NCH, 6H). $\delta$ = diastereomer. $^{13}$C-NMR (100.626 MHz, CDCl$_3$): $\delta$ [ppm] = 14.1 (Me, 1C), 14.2 (Me, 1C), 22.7 (CH$_2$, 1C), 27.0 (CH$_2$, 1C), 28.4 (CH$_2$, 1C), 28.4 (t-Bu, 3C), 29.2 (CH$_2$, 1C), 29.4 (CH$_2$, 1C), 29.6 (CH$_2$, 1C), 42.4 (CH, 1C), [54.9 (CH, 1C)], 61.4 (CH, 1C), 61.5 (CH$_2$-ester, 1C), 75.9 (CH$_2$, 1C), 127.9 (Ar-C, 2C), 128.4 (Ar-C, 2C), 137.7 (C(N), 1C), 150.7 (Ar-C, 1C), 151.2 (Ar-C, 1C), 155.9 (C(O), 1C), 171.5 (C(O), 1C). $\delta$ = diastereomer. CHN: calc. C: 66.94 H: 8.99 N: 6.24, found C: 66.72 H: 9.09 N: 6.02. $[\alpha]_D$ = +27.3 (c = 0.98, CHCl$_3$, 22 °C).

\[
\begin{align*}
\text{BnO} & \quad \text{NH} & \quad \text{NH}_{\text{Boc}} & \quad \text{CO}_{2}\text{Et} \\
& \quad \text{13a} \\
\end{align*}
\]

(2S,3R)-3-(Benzyloxymimo-methyl)-2-tert-butoxycarbonylamino-decanoic acid ethyl ester (13a): The compound was prepared according to the general procedure with 12a (38 mg, 90 µmol, 1.0 equiv) in EtOH (0.5 ml) and sodium cyanoborohydride (28 mg, 0.45 mmol, 5.0 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 13a was obtained as a colorless oil (40 mg, 90 µmol, >99%, 97% ee). $^1$H-NMR (400.132 MHz, CDCl$_3$): $\delta$ [ppm] = 0.87 (t, $^3$J$_{Me,CH2}$ = 7.1 Hz, Me, 3H), 1.23-1.30 (m, Me, CH$_2$, 15H), 1.45 (s, t-Bu, 9H), 2.14 (m, CH, 1H), 2.93 (d, $^3$J$_{CH2,CH2}$ = 5.2 Hz, CH$_2$, 2H), 4.51 (q, $^3$J$_{CH2,Me}$ = 7.1 Hz, CH$_2$, 2H), 4.37 (dd, $^3$J$_{CH,NH}$ = 3.2 Hz, $^3$J$_{CH,CH}$ = 8.9 Hz, CH, 1H), 4.68 (s, CH$_2$, 2H), 5.65 (d, $^3$J$_{NH,CH}$ = 8.5 Hz, NH, 1H), 7.27-7.37 (m, Ar-H, 5H). $^{13}$C-NMR (100.626 MHz, CDCl$_3$): $\delta$ [ppm] = 14.2 (Me, 1C), 14.3 (Me, 1C), 22.7 (CH$_2$, 1C), 27.0 (CH$_2$, 1C), 27.1 28.5 (t-Bu, 3C), 29.2 (CH$_2$, 1C), 29.7 (CH$_2$, 1C), 29.8 (CH$_2$, 1C), 38.7 (CH, 1C), 52.5 (CH$_2$, 1C), 55.6 (CH, 1C), 61.3 (CH$_2$-ester, 1C), 76.1 (CH$_2$, 1C), 128.0 (Ar-C, 1C), 128.5
(Ar-C, 2C), 128.7 (Ar-C, 2C), 137.6 (Ar-C, 1C), 156.1 (C(O), 1C), 172.7 (C(O), 1C). MS (Cl(NH3), C25H42N2O5, exact mass = 450.6 g/mol): m/z = 91.0 (12), 394.3 (15), 451.3 (100, M+H)+, 452.0 (22). HRMS (CI, (M+H)+) C25H43N2O5: calc.: 451.31720 found: 451.31680 (\(\Delta: 0.9\) ppm). The enantiomeric excess was determined by chiral HPLC (Chiralpak-AD-3 (15 cm \(\times\) 4.6 mm ID)), (\(n\)-Heptan/i-PrOH 97:3, 1.0 ml/min, \(\lambda = 210\) nm), \(\tau_{major} = 9.6\) min, \(\tau_{minor} = 18.9\) min. [\(\alpha\]D] = +2.9 (c = 1.25, CHCl3, 22 °C).

\((2S,3R)\)-2-tert-Butoxycarbonylamino-3-formyl-5,5-dimethyl-hexanoic acid ethyl ester (4c):

\((2S,3R)\)-3-(Benzyloxyimino-methyl)-2-tert-butoxycarbonylamino-5,5-dimethyl-hexanoic acid ethyl ester (12c): The compound was prepared according to the general procedure with 4c (59 mg, 0.14 mmol, 1.0 equiv) CH2Cl2 (2.8 ml) and O-benzylhydroxylamine hydrochloride (58 mg, 0.36 mmol, 2.6 equiv) and pyridine (136 \(\mu\)l, 133 mg, 1.70 mmol, 12 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 12c was obtained as a colorless oil (50 mg, 0.12 mmol, 85%). 1H-NMR (400.132 MHz, CDCl3): \(\delta [ppm] = 0.81\) (t, \(3J_{Me,CH2} = 7.1\) Hz, Me, 3H), 0.89 (s, t-Bu, 9H), 1.22 (dd, \(3J_{CH,CH} = 7.1\) Hz, \(3J_{CHA,CH} = 15.3\) Hz, CHA, 1H), 1.43 (dd, \(3J_{CHB,CH} = 7.0\) Hz, \(3J_{CHB,CHA} = 14.7\) Hz, CHB, 1H), 1.45 (s, t-Bu, 9H), 2.96 (mc, CH, 0.8H), [3.62 (mc, CH, 0.2H)], 4.20 (q, \(3J_{CH2,Me} = 7.1\) Hz, CH2, 2H), 4.35 (dd, \(3J_{CH,NH} = 4.9\) Hz, \(3J_{CH,CH} = 9.0\) Hz, CH, 0.9H), [4.25 (mc, CH, 0.1H)], 5.01 (s, CH2, 2H), [5.12 (s, CH2, 2H)], 5.40 (d, \(3J_{NH,CH} = 9.1\) Hz, NH, 1H), 7.25-7.40 (m, Ar-H, NCH, 6H). [] = diastereomer. 13C-NMR (100.626 MHz, CDCl3): \(\delta [ppm] = 14.2\) (Me, 1C), 29.7 (t-Bu, 3C), 29.9 (CH2, 1C), 30.9 (t-Bu, 3C), 42.6 (CH, 0.8C), [39.7 (CH, 0.2C)], 57.1 (CH, 1C), 61.5 (CH2-ester, 1C), 75.9 (CH2, 1C), 127.8 (Ar-C, 1C), 127.9 (Ar-C, 2C), 137.9 (C(N), 1C), 152.1 (Ar-C, 1C), 153.3 (Ar-C, 1C), 155.8 (C(O), 1C), 171.1 (C(O), 1C). CHN: calc. C: 65.69 H: 8.63 N: 6.66, found C: 65.35 H: 8.66 N: 7.00. [\(\alpha\]D] = +44.4 (c = 0.30, CHCl3, 22 °C).

\((2S,3R)\)-3-(Benzyloxyamino-methyl)-2-tert-butoxycarbonylamino-5,5-dimethyl-hexanoic acid ethyl ester (13c): The compound was prepared according to the general procedure with 12c (50 mg, 0.12 mmol, 1.0 equiv) in EtOH (0.7 ml) and sodium cyanoborohydride (38 mg, 0.60 mmol, 5.0 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 13c
was obtained as a colorless oil (47 mg, 0.11 mmol, 93%, >99% ee). $^1$H-NMR (400.132 MHz, CDCl$_3$): $\delta$ [ppm] = 0.92 (s, t-Bu, 9H), 1.03 (dd, $^3$J$_{CH,CH}$ = 5.2 Hz, $^2$J$_{CH,CH}$ = 14.5 Hz, CH$_2$, 2H), 1.25 (t, $^3$J$_{Me,CH_2}$ = 7.1 Hz, Me, 3H), 1.46 (s, t-Bu, 9H), 2.27 (m, CH, 1H), 2.92 (m, CH$_2$, 1.2H), [2.95 (m, CH, 0.8H)], 4.14 (q, $^3$J$_{CH_2,Me}$ = 7.1 Hz, CH$_2$, 1.2H), [4.12 (q, $^3$J$_{CH_2,Me}$ = 7.1 Hz, CH$_2$, 0.8H)], 4.36 (m, CH, 1H), 4.70 (s, CH$_2$, 1.2H), [4.71 (s, CH$_2$, 0.8H)], 5.60 (d, $^3$J$_{NH,CH}$ = 8.2 Hz, NH, 1H), 7.28-7.40 (m, Ar-H, 5H). $[^2]$ = diastereomer. $^{13}$C-NMR (100.626 MHz, CDCl$_3$): $\delta$ [ppm] = 14.3 (Me, 1C), 28.5 (CH, t-Bu, 3C), 29.6 (CH$_3$, t-Bu, 3C), 31.2 (CH, 1C), 42.6 (CH$_2$, 1C), 54.5 (CH$_2$, 1C), 57.0 (CH, 1C), 61.2 (CH$_2$-ester, 1C), 67.2 (CH$_2$, 1C), 128.0 (Ph-C, 1C), 128.5 (Ph-C, 2C), 128.7 (Ph-C, 2C), 137.7 (Ph-C, 1C), 156.2 (C=O), 1C), 172.4 (C=O), 1C). MS (Cl(NH$_3$), C$_{23}$H$_{38}$N$_2$O$_5$, exact mass = 422.6 g/mol): m/z = 321.3 (12), 366.3 (11), 423.4 (100, M$^+$+H). HRMS (Cl, (M+H)$^+$) C$_{23}$H$_{39}$N$_2$O$_5$: calc.: 423.28590 found: 423.28600 ($\Delta$: -0.2 ppm). The enantiomeric excess was determined by chiral HPLC (Chiralpak-AD-3 (15 cm × 4.6 mm ID)), (n-Heptan/i-PrOH 97:3, 1.0 ml/min, 22 °C, $\lambda$ = 210 nm), $\tau_{major}$ = 12.2 min, $\tau_{minor}$ = not observed. $[\alpha]_D$ = +18.2 ($c$ = 1.00, CHCl$_3$, 22 °C).

(2S,3R)-2-tert-Butyloxycarbonylamino-3-formyl-8-hydroxy-octanoic acid ethyl ester (4e):

The enantiomeric excess was determined by the corresponding benzoate 4i.

(2S,3R)-Benzoic acid 7-tert-butyloxycarbonylamino-7-ethoxycarbonyl-6-formyl-heptyl ester (4i):

![Diagram of reaction](image)

Aldehyde 4e (63 mg, 0.19 mmol, 1.0 equiv) was solved and benzoic acid (31 mg, 0.25 mmol, 1.3 equiv), triphenylphosphine (65 mg, 0.25 mmol, 1.3 equiv) and diisopropylazodicarboxylate (50 mg, 0.25 mmol, 1.3 eq.) were added subsequently. The reaction mixture was stirre for 4 h at rt. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of cyclohexane/ethyl acetate (CH/EE 10:1). Benzoate 4i was obtained as a colorless oil (68 mg, 0.16 mmol, 82%). $^1$H-NMR (400.132 MHz, CDCl$_3$): $\delta$ [ppm] = 1.30 (t, $^3$J$_{Me,CH_2}$ = 7.2 Hz, Me, 3H), 1.43 (s, t-Bu, 9H), 1.51 (m, CH$_2$, 4H), 1.78 (m, CH$_2$, 4H), 3.07 (m, CH, 0.7H), [2.75 (m, CH, 0.3H)], 4.20 (q, $^3$J$_{CH_2,Me}$ = 7.2 Hz, CH$_2$, 2H), 4.32 (t, $^3$J$_{CH_2,CH_2}$ = 6.9 Hz, CH$_2$, 2H), 4.58 (dd, $^3$J$_{CH,CH}$
= 3.8 Hz, $^{3} J_{CH,NH} = 9.3$ Hz, CH, 0.7H), [4.70 (dd, $^{3} J_{CH,CH} = 3.4$ Hz, $^{3} J_{CH,NH} = 8.0$ Hz, CH, 0.3H)], 5.25 (d, $^{3} J_{NH,CH} = 9.1$ Hz, NH, 1H), 7.44 (m, Ar-H, 2H), 7.55 (m, Ar-H, 1H), 8.04 (m, Ar-H, 2H), 9.62 (s, CH$_{Aldeh.}$, 0.7H), [9.69 (d, $^{3} J_{CH,CH} = 1.5$ Hz, CH$_{Aldeh.}$, 0.3H)]. $[] = \text{diastereomer.}$

$^{13}$C-NMR (100.626 MHz, CDCl$_{3}$): $\delta$ [ppm] = 14.1 (Me, 1C), 27.2 (CH$_{2}$, 1C), 28.3 (CH$_{2}$, 1C), 28.4 (t-Bu, 3C), 28.5 (CH$_{2}$, 1C), 28.6 (CH$_{2}$, 1C), 52.2 (CH, 1C), 53.1 (CH, 1C), 54.0 (CH, 1C), 61.9 (CH$_{2}$-ester, 1C), 64.9 (CH$_{2}$, 1C), 128.4 (Ph-C, 2C), 129.6 (Ph-C, 2C), 132.9 (Ph-C, 1C), 166.7 (Ph-C, 1C), 201.1 (C(O), 1C), 202.2 (C(O), 1C). MS (Cl(NH$_{3}$), C$_{23}$H$_{33}$NO$_{7}$, exact mass = 435.5 g/mol): m/z = 336.0 (23), 435.6 (98, M$^{+}$), 452.5 (100), 757.9 (18). CHN: calc. C: 63.43 H: 7.64 N: 3.22, found C: 63.68 H: 7.70 N: 3.47. The enantiotopic excess was determined by chiral HPLC (Chiralpak-AD-H and AD-3 (25 cm $\times$ 4.6 mm ID)), (n-Heptan/ EtOH 75:25, 1.0 ml/min, $\lambda$ = 214 nm), $\tau_{\text{major}}$ = 19.8 min, $\tau_{\text{minor}}$ = 18.2 min. $[\alpha]_{D} = +22.1$ (c = 1.01, CHCl$_{3}$, 22 °C).

$(2\text{S},3\text{R})$-8-Acetoxy-2-tert-butoxycarbonylaminoo-3-formyl-octanoic acid ethyl ester (4h):

$(2\text{S},3\text{R})$-8-Acetoxy-3-(benzyloxyimino-methyl)-2-tert-butoxycarbonylaminooctanoic acid ethyl ester (12h): The compound was prepared according to the general procedure with 4h (74 mg, 0.20 mmol, 1.0 equiv) CH$_{2}$Cl$_{2}$ (4.0 ml) and O-benzylhydroxylamine hydrochlorid (82 mg, 0.52 mmol, 2.6 equiv) and pyridine (194 µl, 190 mg, 2.40 mmol, 12.0 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 12h was obtained as a colorless oil (57 mg, 0.12 mmol, 58%). $^{1}$H-NMR (400.132 MHz, CDCl$_{3}$): $\delta$ [ppm] = 1.22 (t, $^{3} J_{Me,CH_{2}} = 7.1$ Hz, Me, 3H), 1.35 (m, CH$_{2}$, 4H), 1.45 (s, t-Bu, 9H), 1.47-1.66 (m, CH$_{2}$, 4H), 2.05 (s, Me, 3H), 2.87 (m, CH, 0.7H), [2.65 (m, CH, 0.3H)], 4.03 (m, CH$_{2}$, 2H), 4.25 (q, $^{3} J_{CH_{2},Me} = 7.1$ Hz, CH$_{2}$, 2H), 4.45 (dd, $^{3} J_{CH,NH} = 4.0$ Hz, $^{3} J_{CH,CH} = 9.5$ Hz, CH, 0.7H), [4.38 (m, CH, 0.3H)], 5.04 (s, CH$_{2}$, 0.5H), [5.04 (s, CH$_{2}$, 0.5H)], 5.15 (d, $^{3} J_{NH,CH} = 9.9$ Hz, NH, 1H), 7.13 (m, Ar-H, NCH, 6H). $[] = \text{diastereomer.}$ $^{13}$C-NMR (100.626 MHz, CDCl$_{3}$): $\delta$ [ppm] = 14.2 (Me, 1C), 14.3 (Me, 1C), 21.1 (CH$_{2}$, 1C), 25.8 (CH$_{2}$, 1C), 26.7 (CH$_{2}$, 1C), 28.4 (t-Bu, 3C), 29.4 (CH$_{2}$, 1C), 42.3 (CH, 1C), 61.4 (CH, 1C), 64.5 (CH$_{2}$-ester, 1C), 75.9 (CH$_{2}$, 1C), 128.2 (Ar-C, 1C), 128.4 (Ar-C, 2C), 128.5 (Ar-C, 2C), 137.6 (C(N), 1C), 150.6 (Ar-C, 1C), 171.3 (C(O), 1C), 171.4 (C(O), 1C). MS (Cl(NH$_{3}$), C$_{25}$H$_{38}$N$_{2}$O$_{7}$, exact mass = 478.6 g/mol): m/z = 277.2 (38), 379.2 (54), 423.2 (100), 479.3 (72, M$^{+}$+H). HRMS (Cl, (M$^{+}$+H)$^{+}$) C$_{25}$H$_{39}$N$_{2}$O$_{7}$: calc.: 479.27480 found: 479.27573 (Δ: 1.9 ppm). $[\alpha]_{D} = +20.3$ (c = 0.33, CHCl$_{3}$, 22 °C).
(2S,3R)-8-Acetoxy-3-(benzyloxyamino-methyl)-2-tert-butoxycarbonylaminooctanoic acid ethyl ester (13i): The compound was prepared according to the general procedure with 12i (57 mg, 0.12 mmol, 1.0 equiv) in EtOH (0.7 ml) and sodium cyanoborohydride (38 mg, 0.60 mmol, 5.0 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 13i was obtained as a colorless oil (51 mg, 0.12 mmol, 88%, 89% ee).

\[ ^1H\text{-NMR (400.132 MHz, CDCl}_3\text{): } \delta [ppm] = 1.26 (t, 3J_{Me,CH2} = 7.1 Hz, Me, 3H), 1.28-1.40 (m, CH2, 6H), 1.46 (s, t-Bu, 9H), 1.61 (m, CH2, 2H), 2.04 (s, Me, 3H), 2.16 (m, CH, 1H), 2.94 (m, CH2, 2H), 4.04 (t, 3J_{CH2,CH2} = 6.7 Hz, CH2, 2H), 4.16 (q, 3J_{CH2,Me} = 7.1 Hz, CH2, 2H), 4.37 (d, 3J_{CH,NH} = 5.2 Hz, CH, 0.7H), [4.48 (m, 3J_{CH,NH} = 8.9 Hz, CH, 0.3H)], 4.71 (s, CH2, 2H), 5.61 (d, 3J_{NH,CH} = 6.9 Hz, NH, 0.8H), [5.52 (d, 3J_{NH,CH} = 7.5 Hz, NH, 0.2H)], 7.25-7.48 (m, ArH, 5H). ] = diastereomer.

\[ ^13C\text{-NMR (100.626 MHz, CDCl}_3\text{): } \delta [ppm] = 14.3 (Me, 2C), 21.1 (CH2, 1C), 26.1 (CH2, 1C), 26.8 (CH2, 1C), 28.4 (t-Bu, 3C), 29.7 (CH2, 1C), 38.7 (CH, 1C), 52.4 (CH2, 1C), 61.4 (CH2, 1C), 64.5 (CH2-ester, 1C), 76.2 (CH2, 1C), 128.2 (Ar-C, 1C), 128.6 (Ar-C, 2C), 128.8 (Ar-C, 2C), 128.9 (Ar-C, 1C), 171.3 (C(O), 1C), 172.6 (C(O), 1C).

HRMS (CI, (M+H)\text{+}): calc.: 481.29138, found: 481.29080 (Ä: 1.2 ppm). The enantiotopic excess was determined by chiral HPLC (Chiralcel-OD-3 (15 cm x 4.6 mm ID)), (n-Heptan/i-PrOH 95:5, 1.0 ml/min, \( \lambda = 213 \text{ nm} \), \( \tau_{\text{major}} = 10.3 \text{ min} \), \( \tau_{\text{minor}} = 9.1 \text{ min} \). [\( \sigma \)]\text{D} = +1.2 (c = 0.90, CHCl3, 22 °C).

(2S,3R)-Benzoic acid 7-tert-butoxycarbonylaminoo-7-ethoxy-carbonyl-6-formyl-heptyl ester (4i): The compound was prepared according to the general procedure with hex-5-enyl benzoate (103 mg, 0.500 mmol, 1.4 equiv) and \( \alpha \)-amido sulfone 2a (129 mg, 0.360 mmol, 1.0 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 4i was obtained as a colorless oil (119 mg, 0.270 mmol, 76%, 93% ee). Analytical data: see above. The enantiotopic excess was determined by chiral HPLC (Chiralpak-AD-H (25 cm x 4.6 mm ID)), (n-Heptan/i-PrOH 90:10, 1.0 ml/min, \( \lambda = 214 \text{ nm} \), \( \tau_{\text{major}} = 14.8 \text{ min} \), \( \tau_{\text{minor}} = 17.6 \text{ min} \). [\( \sigma \)]\text{D} = +27.2 (c = 0.69, CHCl3, 22 °C).
(2S,3R)-2-tert-Butoxycarbonylamino-12-[1,3]dioxolan-2-yl-3-formyl-dodecanoic acid ethyl ester (4k):

(2S,3R)-3-(Benzyloxyimino-methyl)-2-tert-butoxycarbonylamino-12-[1,3]dioxolan-2-yl-dodecanoic acid ethyl ester (12k): The compound was prepared according to the general procedure with 4k (44 mg, 0.10 mmol, 1.0 equiv) CH₂Cl₂ (2.0 ml) and O-benzylhydroxylamine hydrochlorid (42 mg, 0.26 mmol, 2.6 equiv) and pyridine (97 µl, 95 mg, 1.2 mmol, 12 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 12k was obtained as a colorless oil (38 mg, 69 µmol, 69%). ¹H-NMR (400.132 MHz, CDCl₃): δ [ppm] = 1.22 (t, 3 JMe,CH₂ = 7.2 Hz, Me, 3H), 1.25-1.45 (m, CH₂, 16H), 1.46 (s, t-Bu, 9H), 1.65 (m, CH₂, 2H), 2.85 (m, CH, 0.8H), [2.62 (m, CH, 0.2H)], 3.85 (m, CH₂, 2H), 3.95 (m, CH₂, 2H), 4.10 (q, 3 JCH₂,Me = 7.1 Hz, CH₂, 2H), 4.43 (dd, 3 JCH,NH = 4.5 Hz, 3 JCH,CH = 9.4 Hz, CH, 0.8H), [4.32 (m, CH, 0.2H)], 4.84 (t, 3 JCH₂,CH₂ = 4.8 Hz, CH, 1H), 5.02 (s, CH₂, 1H), [5.07 (s, CH₂, 0.5H)], 5.16 (d, 3 JNH,CH = 9.5 Hz, NH, 1H), 7.26-7.37 (m, Ar-H, NCH, 6H). [Δ] = diastereomer. ¹³C-NMR (100.626 MHz, CDCl₃): δ [ppm] = 14.2 (Me, 1C), 24.2 (CH₂, 1C), 27.0 (CH₂, 1C), 28.1 (CH₂, 1C), 28.4 (tBu, 3C), 29.4 (CH₂, 2C), 29.5 (CH₂, 2C), 29.6 (CH₂, 2C), 34.0 (CH₂, 2C), 42.4 (CH, 1C), 54.9 (CH, 1C), 61.5 (CH₂-ester, 1C), 64.9 (CH₂, 2C), 75.9 (CH₂, 1C), 104.8 (CH, 1C), 127.9 (Ar-C, 2C), 128.1 (Ar-C, 2C), 128.3 (Ar-C, 1C), 137.7 (C(N), 1C), 151.2 (Ar-C, 1C), 155.9 (C(O), 1C), 171.5 (C(O), 1C). MS (Cl(NH₃)), C₃₀H₄₈N₂O₇, exact mass = 548.7 g/mol): m/z = 73.0 (29), 347.3 (42), 449.3 (69), 493.3 (100), 549.4 (95, M⁺+H). HRMS (Cl, (M+H)+) C₃₀H₄₉N₂O₇: calc.: 549.35398 found: 549.35340 (Δ: 1.1 ppm). [α]₀ = +24.4 (c = 0.82, CHCl₃, 22 °C).

(2S,3R)-3-(Benzyloxyamino-methyl)-2-tert-butoxycarbonylamino-12-[1,3]dioxolan-2-yl-dodecanoic acid ethyl ester (13k): The compound was prepared according to the general procedure with 12k (38 mg, 69 µmol, 1.0 equiv) in EtOH (0.4 ml) and sodium cyanoborohydride (22 mg, 0.35 mmol, 5.0 equiv). Purification was achieved by flash column chromatography using a mixture of cyclohexane/ethyl acetate (10:1). Compound 13k was obtained as a colorless oil (35 mg, 63 µmol, 92%, 97% ee). ¹H-NMR (400.132 MHz, CDCl₃): δ [ppm] = 1.25 (t, 3 JMe,CH₂ = 7.1 Hz, Me, 3H), 1.20-1.38 (m, CH₂, 16H), 1.45 (s, t-Bu, 9H), 1.61-1.69 (m, CH₂, 2H), 2.16 (m, CH, 1H), 2.90-3.01 (m, CH₂, 2H), 3.81-3.89 (m, CH₂, 2H),
3.91-4.01 (m, CH₂, 2H), 4.16 (q, JCH₂,Me = 7.1 Hz, CH₂, 2H), 4.36 (m, CH, 1H), 4.73 (s, CH₂, 2H), 4.84 (t, JCH,CH₂ = 4.8 Hz, CH, 1H), 5.65 (d, JNH,CH = 6.1 Hz, NH, 1H), 7.26-7.42 (m, Ar-H, 5H). ¹³C-NMR (100.626 MHz, CDCl₃): δ [ppm] = 14.2 (Me, 1C), 24.3 (CH₂, 1C), 27.1 (CH₂, 1C), 28.2 (CH₂, 1C), 28.4 (t-Bu, 3C), 29.4 (CH₂, 2C), 29.5 (CH₂, 2C), 29.6 (CH₂, 2C), 34.0 (CH₂, 2C), 38.9 (CH, 1C), 52.4 (CH₂, 1C), 55.6 (CH, 1C), 61.3 (CH₂-ester, 1C), 64.9 (CH₂, 2C), 76.2 (CH₂, 1C), 104.8 (CH, 1C), 128.2 (Ar-C, 2C), 128.4 (Ar-C, 2C), 128.5 (Ar-C, 1C), 128.6 (Ar-C, 1C), 156.1 (C(O), 1C), 172.7 (C(O), 1C). HRMS (CI, (M+H)⁺) C₃₀H₅₁N₂O₇: calc.: 551.36963 found: 551.36980 (Δ: -0.3 ppm). The enantiomeric excess was determined by chiral HPLC (Chiralpak-AD-H (25 cm × 4.6 mm ID)), (n-Heptan/i-PrOH 80:20, 1.0 ml/min, λ = 210 nm), τmajor = 8.9 min, τminor = 15.0 min. [α]D = +1.9 (c = 1.30, CHCl₃, 22 °C).
III.  NMR files of 4a-1

\(^1\)H-NMR (400.132 MHz, CDCl\(_3\)):

\(^1\)H-NMR (400.132 MHz, CDCl\(_3\)):

\(^13\)C-NMR (100.626 MHz, CDCl\(_3\)):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

\[ \text{Diagram of molecule 4e} \]

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):

\[ \text{Diagram of molecule 4e} \]
$^1$H-NMR (400.132 MHz, CDCl$_3$):

\[
\begin{align*}
\text{NHBoc} & \quad \text{CO$_2$Et} \\
\text{OBn} & \quad 4f
\end{align*}
\]

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
$^1$H-NMR (400.132 MHz, CDCl₃):

$^{13}$C-NMR (100.626 MHz, CDCl₃):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
$^1$H-NMR (400.132 MHz, CDCl$_3$):

$^{13}$C-NMR (100.626 MHz, CDCl$_3$):
IV. Representative HPLC traces

Vial: 182  Injection Volume (μL): 2

Vial: 181  Injection Volume (μL): 2
Vial: 192  Injection Volume (µl): 2

Vial: 191  Injection Volume (µl): 2
V. References