Supporting Information

A Stereoselective Synthesis of the ACE-Inhibitor Trandolapril

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1. General Experimental Conditions

All reactions were carried out under argon atmosphere. For sensitive reactions the glassware was flame-dried under vacuum before use and flooded with argon. Solids were added under argon counterflow. Syringes and cannula were purged with argon before use.

If not otherwise indicated, chemicals were employed without further purification. All solvents were dried and distilled before use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under argon. Dichloromethane was distilled from calcium hydride under argon. Dry acetonitrile was purchased from Acros (99.5%, Extra Dry over Molecular Sieve). NMR spectra were recorded at room temperature on a Bruker DPX 300, Avance II 300 or Avance II+ 600. Both, proton and $^{13}$C chemical shifts are reported in ppm downfield from TMS and are referenced to the non-deuterated impurities of the used solvents as internal standard: CDCl$_3$: $\delta$=7.28 ppm ($^1$H), $\delta$=77.00 ppm ($^{13}$C). The spectra are reported using the following abbreviations to express the multiplicities: s=singlet, d=doublet, t=triplet, dd=double doublet, m=multiplet. Most $^{13}$C NMR spectra were recorded using the DeptQ or APT sequence with complete proton decoupling. The non-trivial assignments were effected by H,H-COSY, HMQB, HMBC and NOESY spectra.

Infrared spectra (IR) were recorded at room temperature on a Paragon 100 FT-IR spectrometer or a Spectrum Two (UATR) FT-IR spectrometer (both from Perkin-Elmer). The absorptions are given in wave numbers (cm$^{-1}$) and are characterized by the abbreviations w (weak), middle (m) strong (s) and if necessary by br (broad).

Gas chromatography–mass spectrometry (GC-MS) was performed on an Agilent GC System, HP 6890 N Serie with Mass Selective Detector 5973 N. The used temperature program started at 50 °C and heated to 300 °C (25 °C/min; 0.7 bar; 2.7 ml/min).

High-resolution mass spectra were measured on a Finnigan MAT 900s. Low-resolution mass spectra were recorded either on a Finnigan MAT Incos 50 (EI) or a MAT 900s (ESI).

Melting points were determined with a Büchi B-545 or in open capillary tubes from Marienfeld (8.0 x 1.0 mm).

Analytical thin layer chromatography (TLC) was performed on silica coated alumina plates containing a fluorescent indicator, visualized by UV light or by using a potassium permanganate solution (0.5% solution in 1 M sodium hydroxide) followed by heating.

Flash column chromatography was conducted by using either silica gel DAVISIL®LC60A 40-63 µm from GRACE DIVISION or Allox N for column chromatography 50-200 µm, Brockmann I from Acros.

X-Ray measurements were carried out using a Bruker D8 Venture circle diffractometer.

Optical rotation was determined at 20.0 °C on a Perkin-Elmer Polarimeter 343 or a Anton Paar MCP 200 Polarimeter using a cuvette with a pathlength of 10 cm. Concentrations are given in g /100 ml of solvent.
2. Procedures and analytical data

2.1. (S)-tert-Butyl-5-oxopyrrolidine-2-carboxylate (16)

To a suspension of L-pyroglutamic acid 10 (50.0 g, 0.39 mol, 1.0 eq.) in tBuOAc (650 ml) was added dropwise HClO$_4$ (12.5 ml, 70 %) and the mixture was stirred at room temperature for 48 h. After a further addition of HClO$_4$ (12.5 ml, 70 %) stirring was continued for 48 hours. The reaction mixture was then quenched with saturated sodium bicarbonate solution (600 ml) and extracted with ethyl acetate (3 x 300 ml). The combined organic layers were dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The white residue was finally washed with Et$_2$O/nHexan (1:10) and concentrated to dryness to give pure 16 (64.7 g, 0.35 mol, 90 %) as a white crystalline solid.

M(C$_9$H$_{15}$NO$_3$) 185.22 g/mol.

R$_f$ 0.32 (EtOAc/CyHex, 1:2).

MP 97 °C.

$^1$H NMR (300 MHz, CDCl$_3$): δ [ppm] = 6.03 (s, 1H, NH), 4.15 - 4.11 (m, 1H, H-2), 2.45 - 2.35 (m, 3H, H-4, H-3'), 2.22 - 2.17 (m, 1H, H-3), 1.48 (s, 9H, H-8).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ [ppm] = 177.7 (C-5), 171.0 (C-6), 82.4 (C-7), 56.0 (C-2), 29.3 (C-4), 28.0 (C-8), 24.6 (C-3).

IR (ATR) $\nu$ (cm$^{-1}$) = 3451 (br), 3257(m), 3166 (w), 3086 (w), 2976 (m), 2930 (w), 2898 (w), 2838 (w) 1731 (s), 1658 (s), 1462 (m), 1425 (w), 1394 (m), 1368 (s), 1352 (m), 1281(s), 1246 (m), 1228 (s), 1143 (s), 1104 (m), 1045 (m), 1033 (w), 1002 (w), 912 (w), 844 (m), 809 (m), 54 (m), 727 (m).

GC-MS m/z (%) = 84 ([M]$^+$- CO$_2$Bu, 100), 57 (42).
\[ \alpha \propto \frac{20}{20} \quad (c = 1.000, \text{CHCl}_3): +100.1^\circ (334 \text{ nm}), +56.7^\circ (365 \text{ nm}), +30.6^\circ (405 \text{ nm}), +6.7^\circ (546 \text{ nm}). \]

2.2. (2S)-Di-tert-butyl-5-oxopyrrolidine-1,2-dicarboxylate (11)

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Bu} \\
\text{O} & \quad \text{CO}_2\text{Bu} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
& \quad \text{Boc}_2\text{O}, \text{DMAP} \\
\text{MeCN} & \quad \text{MeCN} \\
16 & \quad 11
\end{align*}
\]

To a solution of pyroglutamate 16 (5.00 g, 27.0 mmol, 1.00 eq.) in MeCN (50 ml) was added DMAP (0.16 g, 1.4 mmol, 0.05 eq.) and Boc\(_2\)O (6.5 ml, 29.7 mmol, 1.10 eq.). The resulting solution was stirred at room temperature for 18 h. The solvent was then removed under reduced pressure, the residue taken up in a EtOAc/CyHex mixture (100 ml, 1:1), filtered on silica and again evaporated to dryness. After chromatographic purification on silica (EtOAc/CyHex = 1:3) the protected pyroglutamate 11 (7.36 g, 25.8 mmol, 96 %) was obtained as a white crystalline solid.

\[ M (\text{C}_9\text{H}_{15}\text{NO}_3) = 285.16 \text{ g/mol}. \]

\[ R_f = 0.38 \text{ (EtOAc/CyHex, 1:1).} \]

\[ \text{Smp.} = 53^\circ \text{C.} \]

\[ H \text{ NMR} \quad (300 \text{ MHz, CDCl}_3): \delta [\text{ppm}] = 4.48 (\text{dd}, J = 9.4 \text{ Hz, 2.6 Hz, 1H, H-2}), 2.70 - 2.41 \text{ (m, 2H, H-3', H-4')}, 2.29 (\text{ddd}, J = 19.9 \text{ Hz, 13.2 Hz, 9.4 Hz, 1H, H-4}), 2.05 - 1.93 \text{ (m, 1H, H-3), 1.51 (s, 9H, H-11), 1.49 (s, 9H, H-8)}. \]

\[ C \text{ NMR} \quad (75 \text{ MHz, CDCl}_3): \delta [\text{ppm}] = 173.5 \text{ (C-5)}, 169.1 \text{ (C-6), 152.1 (C-9), 83.3 (C-7), 82.3 (C-10), 59.6 (C-2), 31.1 (C-4), 27.9 (C-8, C-11), 21.6 (C-3)}. \]

\[ IR \text{ (ATR)} \quad \nu [\text{cm}^{-1}] = 2976 \text{ (m), 2931 (w), 1789 (s), 1736 (s), 1714 (s), 1683 (w), 1476 \text{ (m), 1457 (m), 1419 (w), 1392 (m), 1366 (s), 1306 (s), 1280 (s), 1254 (s), 1222 (s), 1145 (s), 1045 (m), 1020 (m), 962 (m), 927 (w), 912 (m), 880 (m), 841 (m), 815 (m), 774 (m) 746 (m)}. \]
GC-MS \[ m/z \ (\%) = 84 ([M]^+ \cdot CO_2^tBu, 100), 57 (36). \]

\[ [\alpha]_{20}^\circ \]
\[ (c = 1.000, CHCl_3): -76.4^\circ (365 \text{ nm}), -74.4^\circ (334 \text{ nm}), -68.6^\circ (405 \text{ nm}), -40.4^\circ (546 \text{ nm}), -35.1^\circ (589 \text{ nm}). \]

2.3. Di-tert-butyl-4-allyl-5-oxopyrrolidine-1,2-dicarboxylate (9 & cis-9)

![Chemical structure of 11 and 9 + cis-9]

To a solution of pyroglutamate 11 (5.00 g, 17.5 mmol, 1.0 eq.) in THF (50 ml) was added a Lithium hexamethyldisilazide solution (22.4 ml, 20.2 mmol, 1.2 eq., 1.1 M in THF) at -78 °C. After 1 h TPPA (5.2 g, 17.5 mmol, 1.0 eq.) and subsequently allyl bromide (1.7 ml, 19.3 mmol, 1.1 eq.) were added. After 2 h of stirring at -78 °C the reaction mixture was quenched with saturated ammonium chloride solution (50 ml) and the aqueous layer was extracted three times with EtOAc. The combined organic layers were then washed with water and brine (250 ml), dried over Na_2SO_4, filtered and finally evaporated to dryness. The products were separated and purified through chromatographic purification on silica (EtOAc/CyHex = 1:4) to give white crystalline solids.

To a solution of the separated cis-alkylated pyroglutamate cis-9 (1.99 g, 6.1 mmol, 1.00 eq.) in THF (26 ml) stirred at room temperature was then added a TBAF solution (6.5 ml, 1.06 eq., 1 M in THF) before refluxing the mixture at 85 °C for 1.5 h. The reaction was then quenched with saturated ammonium chloride solution and the aqueous layer was extracted three times with EtOAc. The combined organic layers were then washed with water and brine (300 ml), dried over Na_2SO_4, filtered and finally evaporated to dryness. The trans-isomer 9 was separated through chromatographic purification on silica (EtOAc/CyHex = 1:4) as a white crystalline solid and was added to the previously isolated fraction (3.36 g, 10.33 mmol, 59%).
(2S,4R)-Di-tert-butyl-4-allyl-5-oxopyrrolidine-1,2-dicarboxylate (9)

**M(C$_{17}$H$_{27}$NO$_{5}$)** 325.40 g/mol.

**Yield** 34%$^1$ → 59%$^2$.

**R$_f$** 0.72 (EtOAc/CyHex, 1:2).

**Smp.** 65 °C.

**$^1$H NMR** (300 MHz, CDCl$_3$): $\delta$ [ppm] = 5.82-5.68 (m, 1H, H-13), 5.21-4.99 (m, 2H, H-14), 4.42 (dd, $J$ = 9.5 Hz, 1.6 Hz, 1H, H-2), 2.73-2.58 (m, 2H, H-4, H-12), 2.27-2.09 (m, 2H, H-12'/3), 2.04-1.92 (m, 1H, H-3’), 1.51 (s, 9H, H-11), 1.48 (s, 9H, H-8).

**$^{13}$C NMR** (75 MHz, CDCl$_3$): $\delta$ [ppm] = 174.5 (C-5), 170.3 (C-6), 149.4 (C-9), 134.4 (C-13), 117.6 (C-14), 83.2 (C-7), 82.2 (C-10), 57.8 (C-2), 41.1 (C-4), 34.5 (C-3/12), 27.9 (C-8/11).

**IR (ATR)** $\nu$ (cm$^{-1}$) = 3071 (w), 2976 (w), 2928 (w), 2848 (w), 1789 (s), 1755 (m), 1476 (w), 1456 (w), 1416 (w), 1392 (w), 1366 (w), 1312 (s), 1295 (l), 1225 (m), 1147 (s), 1092 (w), 1043 (w), 1011 (w), 995 (w), 962 (w), 918 (w), 846 (w), 808 (w), 776 (w), 742 (w), 724 (w).

**GC-MS** m/z (%) = 124 ([M$^+$-Boc, -CO$_2$Bu]), 96 (8), 82 (15), 57 (16).


$[\alpha]_{D}^{20}$ (c = 1.000, CHCl$_3$): -91.1° (365 nm), -76.8° (405 nm), -43.0° (546 nm), -36.9° (589 nm).

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$^1$ Isolated yield after initial $\alpha$-alkylation of 11.

$^2$ Overall yield of 9 after epimerization of cis-9 and second chromatographic separation.
(2S,4S)-Di-tert-butyl-4-allyl-5-oxopyrrolidine-1,2-dicarboxylate (cis-9):

\[ M(C_{17}H_{27}NO_5) = 325.40 \text{ g/mol}. \]

Yield \[ 35\% .^3 \]

Rf \[ 0.58 (\text{EtOAc/CyHex, 1:2}). \]

Smp. \[ 66 \degree C. \]

\[ ^1H \text{ NMR} \]
(300 MHz, CDCl\textsubscript{3}): \[ \delta \text{ [ppm]} = 5.82-5.66 (m, 1H, H-13), 5.06 (dd, \; J = 12.7 \text{ Hz}, 5.5 \text{ Hz}, 2H, H-14), 4.40 (dd, \; J = 9.3 \text{ Hz}, 5.7 \text{ Hz}, 1H, H-2), 2.70-2.53 (m, 2H, H-4, H-12), 2.44 (dt, \; J = 13.3 \text{ Hz}, 9.4 \text{ Hz}, 1H, H-12'), 2.32-2.11 (m, 1H, H-3), 1.83-1.60 (m, 1H, H-3'), 1.51 (s, 9H, H-11), 1.49 (s, 9H, H-8). \]

\[ ^{13}C \text{ NMR} \]
(75 MHz, CDCl\textsubscript{3}): \[ \delta \text{ [ppm]} = 174.8 (C-5), 170.6 (C-6), 149.5 (C-9), 134.8 (C-13), 117.6 (C-14), 83.4 (C-7), 82.1 (C-10), 58.1 (C-2), 42.1 (C-4), 35.4 (C-12), 27.9 (C-8/11), 26.3 (C-3). \]

\[ \text{IR (ATR)} \]
\[ \nu (\text{cm}^{-1}) = 3076 (\text{w}), 2976 (\text{w}), 2929 (\text{w}), 2903(w), 1787 (\text{w}), 1739 (m), 1715 (m), 1640 (w), 1476 (w), 1455 (w), 1414 (w), 1392 (m), 1366 (m), 1312 (s), 1302 (s), 1252 (s), 1222 (s), 1145 (s), 1070 (w), 1048 (w), 1041 (w), 1011 (m), 996 (m), 964 (w), 939 (w), 914 (m), 845 (m), 793 (w), 775 (m), 742 (w). \]

\[ \text{HR-MS} \]
(ESI): \[ m/z = [\text{M+Na}^+] \text{ calculated: 348.1781; detected: 348.1783}. \]

\[ ^3 \text{Isolated yield after initial } \alpha\text{-alkylation of 11.} \]
2.4. (2S,4R)-Di-tert-butyl-5-methoxy-4-ethylnpyrrolidine-1,2-dicarboxylate (12)

To a solution of pyroglutamate 9 (0.9 g, 2.8 mmol, 1.0 eq.) in THF (15 ml) stirred at -78 °C was added a Lithium triethylborohydride solution (2.8 ml, 2.8 mmol, 1.0 eq., 1 M in THF). After 2 h of stirring the reaction mixture was quenched with a saturated sodium bicarbonate solution and the aqueous layer was extracted three times with Et₂O. The combined organic layers were then dried over Na₂SO₄, filtered and finally evaporated to dryness. After dissolving the resulting clear oil in dry MeOH (9 ml), PPTS (0.02 g, 0.08 mmol, 0.02 eq.) was added. Stirring was continued for 16 h and the solvent removed under reduced pressure. After chromatographic purification on silica (EtOAC/CyHex = 1:3) the methoxyproline 12 (747 mg, 2.19 mmol, 81%) was obtained as a white crystalline solid.

\[
\text{M(C}_{18}\text{H}_{31}\text{NO}_{5}) = 341.45 \text{ g/mol.}
\]

**Yield** 81% (747 mg, 2.19 mmol).

**Rf** 0.76; 0.70 (EtOAC/CyHex, 1:2).

**HR-MS** (ESI): m/z = [M+Na]^+ calculated: 364.2094; detected: 364.2093.

**1H NMR** (300 MHz, CDCl₃, mixture of rotamers/diastereomers): \(\delta\) [ppm] = 5.84 - 5.61 (m, 1H, H-10), 5.13 - 4.87 (m, 3H, H-5/11), 4.35 - 4.11 (m, 1H, H-2), 3.50 - 3.33 (m, 3H, H-12), 2.23 - 2.10 (m, 2H, H-4/9), 2.09 - 1.97 (m, 2H, H-3/9'), 1.96 - 1.80 (m, 1H, H-3'), 1.46; 1.44 (2×s, 18H, H-8/15).

**13C NMR** (75 MHz, CDCl₃, mixture of rotamers/diastereomers): \(\delta\) [ppm] = 171.9; 171.7 (C-6), 154.8; 154.5 (C-13), 135.5; 135.4 (C-10), 117.8; 117.2 (C-11), 92.6 (C-5), 80.9; 80.4 (C-7/14), 59.2; 58.8 (C-2), 55.4; 55.0 (C-12), 44.4;
43.7 (C-4), 35.6; 35.3 (C-9), 32.3; 31.6 (C-3), 28.3; 28.1 (C-8/15).

**IR (ATR)**

\[ \nu \text{ (cm}^{-1}) = 3079 \text{ (w), 2978 (m), 2934 (m), 2834 (w), 1745 (m), 1705 \text{ (vs), 1642 (w), 1479 (m), 1456 (m), 1366 (vs), 1311 (m), 1256 (m), 1218 (m), 1151 (vs), 995 (m), 946 (m), 916 (m), 887 (m), 846 (m), 773 (m)}. \]

**GC-MS**

\[ m/z \text{ (%) = } 240 \text{ ([M]+ - CO}_2\text{Bu, 21), 140 \text{ ([M]+ - 2x CO}_2\text{Bu, 54), 108 \text{ ([M]+ - 2x CO}_2\text{Bu /OMe, 33), 57 (C}_4\text{H}_9, 100)}. \]

### 2.5. Di-tert-butyl-(2S,4R)-4,5-diallylpyrrolidine-1,2-dicarboxylate (8)

![Chemical Structure](image)

To a solution of 0.55 g (1.61 mmol, 1.0 eq.) methoxyproline 12 in 13 ml CH$_2$Cl$_2$ were added 0.64 ml (4.03 mmol, 2.5 eq.) allyl-TMS at -78 °C. Afterwards, 0.85 ml (3.22 mmol, 2 eq.) BF$_3$·OEt$_2$ (48 %) were added dropwise over 5 min. After 2 h of stirring at -78 °C, the reaction mixture was quenched with 5 ml of a saturated solution of NaHCO$_3$ and the aqueous layer extracted three times with 30 ml MTBE. The combined organic layers were washed two times with a saturated solution of sodium chloride, dried over MgSO$_4$, filtered and evaporated to dryness. After chromatographic separation of the diastereomeric mixture (17:1 „cis/trans“, as determined by $^1$H NMR) and purification on silica (EtOAc/CyHex = 1:4) of the diallylated proline 8 (0.42 g, 1.19 mmol, 74%) was obtained as a colourless oil.

**M(C$_{20}$H$_{33}$NO$_4$)** 351.49 g/mol.

**R$_f$** 0.59 (EtOAc/CyHex, 1:4).

**HR-MS** (ESI): \[ m/z = [M+Na]^+ \text{ calculated: 374.2302; detected: 374.2301}. \]
$^1$H NMR (300 MHz, CDCl$_3$, mixture of rotamers): $\delta$ [ppm] = 5.90 - 5.64 (m, 2H, H-10/13), 5.11 - 5.02 (m, 4H, H-11/14), 4.22 - 4.06 (m, 1H, H-2), 3.72 - 3.54 (m, 1H, H-5), 2.72 - 2.40 (m, 1H, H-4), 2.26 - 1.72 (m, 6H, H-3/9/12), 1.46;1.42 (2x, 18H, H-8).

$^{13}$C NMR (75 MHz, CDCl$_3$, mixture of rotamers): $\delta$ [ppm] = 172.3; 172.2 (C-6), 153.7; 153.1 (C-15), 136.5; 135.8; 135.4 (C-10/13), 116.8; 116.7; 115.9 (C-11/14), 80.8 (C-7), 79.7 (C-16), 63.0 (C-2), 59.5; 59.0 (C-5), 41.3; 40.2 (C-4), 38.9 (C-12) 38.2; 37.8 (C-9), 33.3; 32.4 (C-3), 28.3; 27.9 (C-8/17).

IR (ATR) $\nu$ (cm$^{-1}$) = 3078 (w), 2977 (m), 2932 (m), 1743 (s), 1697 (vs), 1641 (m), 1479 (m), 1456 (m), 1389 (vs), 1366 (vs), 1319 (m), 1298 (m), 1256 (m), 1217 (m), 1152 (vs), 1126 (s), 994 (m), 954 (m), 912 (s), 845 (m), 770 (m), 629 (w).

GC-MS $m/z$ (%) = 210 ([M]$^+$ - CO$_2$Bu/C$_3$H$_5$, 28), 154 (100), 108 ([M]$^+$ -2xCO$_2$Bu/C$_3$H$_5$, 11), 57 (C$_4$H$_9$, 59).

2.6. Di-tert-butyl-(2S,3aR,7aS)-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (7)

To a solution of 0.40 g (1.14 mmol, 1.00 eq.) diallylproline 8 in 35 ml DCM was added 0.05 g (0.06 mmol, 0.05 eq.) Grubbs II-catalyst and 0.02 g (0.09 mmol, 0.08 eq.) CuI at room temperature. After stirring for 2.5 h, the solution was evaporated under reduced pressure to dryness. After chromatographic purification on silica (CyHex/EtOAc = 4:1) the hexahydroindole 7 (0.35 g, 1.08 mmol, 95%) was obtained as colourless oil.
M(C$_{18}$H$_{29}$NO$_4$) 323.43 g/mol.

$R_f$ 0.58 (EtOAc/CyHex, 1:4).


$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ [ppm] = 5.72 - 5.62 (m, 2H, H-7/8), 4.37 - 4.11 (m, 1H, H-2), 3.25 - 1.65 (m, 8H, H-3/4/5/6/9), 1.41; 137 (2xs, 18H, H-12/15).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ [ppm] = 172.0 (C-10), 154.0 (C-13), 126.3; 124.8 (C-7/8), 80.6 (C-11), 79.4 (C-14), 60.8; 60.1 (C-2), 58.9; 58.6 (C-5), 53.8; 53.6 (C-4), 35.1; 34.3 (C-9), 34.0; 32.6 (C-6), 30.3; 27.4 (C-3), 28.3; 27.9 (C-12/15).

IR (ATR) $\nu$ (cm$^{-1}$) = 3026 (w), 2976 (m), 2932 (m), 2855 (w), 1742 (s), 1698 (vs), 1638 (w), 1478 (m), 1456 (m), 1399 (s), 1365 (vs), 1295 (m), 1256 (m), 1218 (s), 1170 (s), 1141 (vs), 1122 (vs), 1089 (m), 1063 (m), 997 (w), 954 (m), 931 (w), 868 (m), 847 (m), 813 (w), 769 (m), 665 (s).

$[\alpha]_{D}^{20}$ (c = 0.535, CHCl$_3$) = 146.9 $^\circ$ (365 nm), 97.9 $^\circ$ (436 nm), 58.2 $^\circ$ (546 nm), 50.4 $^\circ$ (579 nm), 45.4 $^\circ$ (589 nm).
2.7. Di-tert-butyl-(2S,3aR,7aS)-octahydro-1H-indole-1,2-dicarboxylate (13)

To a suspension of 19 mg 10wt% Pd/C in 1 ml EtOH was added 0.2 g (0.64 mmol, 1 eq.) hexahydroindole 7 in 7 ml EtOH. The suspension was stirred for 19 h at 24 Bar in a H₂-atmosphere at room temperature. The mixture was filtered over celite using EtOAc. The solution was evaporated to dryness under reduced pressure and the octahydroindole 13 (192 mg, 0.59 mmol, 95%) product obtained as a colourless oil.

\[ M(C_{18}H_{31}NO_4) \text{ g/mol.} \]

\[ R_f \text{ 0.60 (EtOAc/CyHex, 1:2).} \]

\[ \text{HR-MS (ESI): m/z=} [\text{M+Na}^+] \text{ calculated: 348.2145; detected: 348.2143.} \]

\[ ^{1}H \text{ NMR (300 MHz, CDCl}_3\rangle: \delta \text{ [ppm]} = 4.20 - 4.06 \text{ (m, 1H, H-2), 2.81} \text{ (s, 1H, H-5), 1.95 - 1.60}\text{ (m, 6H, H-3/6/9), 1.43; 1.40 (2}s, 18H, H-12/15), 1.34 - 1.02 \text{ (m, 5H, H-7/8/4).} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3\rangle: \delta \text{ [ppm]} = 172.4 \text{ (C-10), 154.7} \text{ (C-13), 80.7;79.5} \text{ (C-11/14), 64.3 (C-2), 60.7 (C-5), 44.2 (C-4), 34.4 (C-3), 31.6 (C-9), 29.4 (C-6), 28.5 (C-12), 28.1 (C-15), 25.8 (C-7), 24.7 (C-8).} \]

\[ \text{IR (ATR)}: \nu \text{ (cm}^{-1}) = 2976 \text{ (m), 2932 (m), 2857 (w), 1744 (s), 1702} \text{ (vs), 1478} \text{ (w), 1456 (m), 1401 (s), 1364} \text{ (vs), 1296 (s), 1218 (s), 1174 (s), 1151} \text{ (vs), 1123} \text{ (vs), 1093 (s), 1049} \text{ (w), 997 (w), 975} \text{ (m), 962 (m), 875 (w), 840} \text{ (m), 774} \text{ (m), 624 (w).} \]

\[ \text{GC-MS} m/z \text{ (}% = 224 \text{ ([M]+ - CO}_3^1\text{Bu}, 11), 168 \text{ ([M]+ - CO}_3^1\text{Bu/C}_4\text{H}_8, 100), 124 \text{ ([M]+ - 2\times CO}_3^1\text{Bu, 63), 57 (60).} \]
2.8. tert-Butyl-(2S,3aR,7aS)-octahydro-1H-indole-2-carboxylate (2a)

To a solution of 100 mg (0.308 mmol, 1 eq.) octahydroindole 13 in 1.5 ml CH₂Cl₂ was added dropwise 0.056 ml (0.308 mmol, 1 eq.) TMSOTf at 0 °C. After stirring for 5 min, 1.5 ml of a saturated NaHCO₃ solution was added at 0 °C and the reaction mixture was stirred for another 15 min. The solution was extracted five times with DCM. The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness. The Boc-deprotected octahydroindole 2a (56 mg, 0.249 mmol, 98%) was obtained as white crystalline solid.

\[
\text{M(C}_{13}\text{H}_{23}\text{NO}_{2}) = 225.33 \text{ g/mol.}
\]

\[
\text{R}_f = 0.14 \text{ (EtOAc/CyHex, 1:4).}
\]

\[
\text{MP} = 101.7 \degree \text{C.}
\]

\[
\begin{align*}
\text{H NMR} & : \delta [\text{ppm}] = 3.76 (\text{dd, } J = 10.3, 1.6 \text{ Hz}, 1\text{H, H-2}), 2.66 (s, 1\text{H, -NH}), 2.26 (\text{td, } J = 10.6, 3.4 \text{ Hz}, 1\text{H, H-5}), 2.17 - 2.12 (m, 1\text{H, H-4}), 2.01 - 1.96 (m, 1\text{H, H-3}), 1.94 - 1.89 (m, 1\text{H, H-3'}), 1.84 - 1.80 (m, 1\text{H, H-9}), 1.77 - 1.71 (m, 2\text{H, H-6/9'}), 1.47 (s, 9\text{H, H-12}), 1.31 - 1.18 (m, 4\text{H, H-7/8}), 1.06 - 0.99 (m, 1\text{H, H-6'}). \\
\text{C NMR} & : \delta [\text{ppm}] = 174.7 (\text{C-10}), 81.6 (\text{C-11}), 65.4 (\text{C-2}), 58.8 (\text{C-5}), 45.5 (\text{C-4}), 36.9 (\text{C-3}), 31.34 (\text{C-9}), 29.5 (\text{C-6}), 28.2 (\text{C-12}), 26.1 (\text{C-7}), 25.3 (\text{C-8}).
\end{align*}
\]

\[
\begin{align*}
\text{IR (ATR)} & : \nu (\text{cm}^{-1}) = 2978 (\text{w}), 2928 (\text{m}), 2855 (\text{m}), 1723 (\text{s}), 1448 (\text{m}), 1393 (\text{m}), 1368 (\text{m}), 1331 (\text{m}), 1302 (\text{m}), 1241 (\text{s}), 1219 (\text{m}), 1148 (\text{vs}), 1091 (\text{m}),
\end{align*}
\]
1077 (m), 1031 (m), 979 (w), 929 (w), 848 (m), 811 (w), 752 (m), 667 (w), 638 (m).

**GC-MS**

\[ m/z \% = 124 ([M]^+ - \text{CO}_2^\text{Bu}, 100), 81 (12), 56 ([M]^+ - \text{CO}_2^\text{Bu}/\text{C}_4\text{H}_8, 24). \]

**HR-MS**


\[ [\alpha]^{20}_D \]

\( (c = 0.525, \text{CHCl}_3) = -71.9 ^\circ (365 \text{ nm}), -38.9 ^\circ (436 \text{ nm}), -25.0 ^\circ (546 \text{ nm}), -22.9 ^\circ (579 \text{ nm}), -22.9 ^\circ (589 \text{ nm}). \)

2.9. **tert-Butyl-(2S,3aR,7aS)-1-(((S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl)-L-alanyl)octahydro-1H-indole-2-carboxylate (15)**

![Image of chemical structures](image)

To a solution of 40 mg (0.178 mmol, 1.0 eq.) amine 2a and 54 mg (0.195 mmol, 1.1 eq.) carboxylic acid 14 in 0.5 ml dry acetonitrile was first added at 0 \(^\circ\)C 0.094 ml (0.534 mmol, 3.0 eq.) DIPEA and afterwards a solution of 0.12 g (0.231 mmol, 1.3 eq.) PyBOP in 0.4 ml dried acetonitrile. The solution was stirred for 17 h at room temperature and the reaction mixture concentrated in vacuum. The residue was dissolved in MTBE and washed with water. The aqueous layer was extracted three times with MTBE and the combined organic layers dried over Na\(_2\)SO\(_4\), filtered and evaporated to dryness. After chromatographic purification on silica (EtOAc:CyHex = 1:1) trandolapril-\textit{tert-}butylester 15 (0.70 mg, 0.144 mmol, 95%) was obtained as a yellow oil.
M(C$_{28}$H$_{42}$N$_{2}$O$_{5}$)  486.65 g/mol.

R$_f$  0.32 (EtOAc/CyHex, 1:1).


$^1$H NMR  (400 MHz, CDCl$_3$, mixture of rotamers): $\delta$ [ppm] = 7.29 - 7.24 (m, 2H, H-22/22$'$), 7.21 - 7.16 (m, 3H, H-21/21$/'$/23), 4.52 (d, $J$ = 8.7 Hz, 0.55H, H-2$^{\text{rot1}}$), 4.23 – 4.08 (m, 2.45H, H-25$^2$/2$^{\text{rot2}}$), 3.52 (q, $J$ = 6.7 Hz, 0.55H, H-14$^{\text{rot1}}$), 3.31 – 3.28 (m, 0.45H, H-14$^{\text{rot2}}$), 3.16 – 3.13 (m, 1H, H-17), 3.04 – 2.93 (m, 1H, H-5), 2.71 – 2-62 (m, 2H, H-19), 2.40 – 2.28 (m, 2H, H-18), 2.09 – 1.88 (m, 4H, H-3/4/16), 1.77 – 1.55 (m, 4H, H-10/12), 1.46 (s, 9H, H-8), 1.31 – 1.21 (m, 10H, H-11/9/15/26).

$^{13}$C NMR  (100 MHz, CDCl$_3$, mixture of rotamers): 175.7; 174.2 (C-13), 171.5; 171.3 (C-6), 169.6; 167.1 (C-24), 141.7; 141.3; 140.4 (C-20), 128.8; 128.6; 128.5 (C-22), 128.4; 128.4; 128.3 (C-21), 126.5; 126.0; 125.9 (C-23), 82.1; 81.1 (C-7), 65.9; 64.0 (C-5), 61.6; 60.8; 60.5 (C-25), 60.6; 60.2; 59.9(C-2), 59.7; 59.4; 58.6 (C-17), 54.8; 52.9 (C-14), 45.9; 43.4 (C-4), 35.6; 35.5; 35.1 (C-8), 33.9; 33.3 (C-3), 32.6; 32.0; 31.7 (C-9), 30.5 29.8; 29.5 (C-19), 28.1 (C-8), 26.0; 25.5 (C-10), 25.2; 24.9 (C-11), 20.1; 19.5; 19.3 (C-15), 14.5; 14.4; 14.2 (C-26).

IR (ATR)  $\nu$ (cm$^{-1}$) = 3198 (w), 2981 (w), 2871 (w), 2683 (w), 2513 (w), 1737 (w), 1668 (w), 1469 (w), 1450 (w), 1395 (m), 1294 (w), 1241 (w), 1206 (m), 1167 (m), 1132 (m), 1088 (m), 1016 (m), 831 (vs), 782 (m), 767 (m), 749 (m), 580 (m), 557 (s).

GC-MS  m/z (%) = 224 (17), 196 (4), 168 (100), 124 (59), 81 (8), 57 (56).
$[\alpha]^{20}_D (c = 0.565, \text{CHCl}_3) = -60.8 ^\circ \text{ (365 nm)}, -36.9 ^\circ \text{ (436 nm)}, -21.4 ^\circ \text{ (546 nm)}, -18.9 ^\circ \text{ (579 nm)}, -18.4 ^\circ \text{ (589 nm)}.$

2.10. Trandolapril (1)

To a stirred solution of 14 mg (28.8 µmol, 1.0 eq.) of trandolapril-tert-butylester 15 in 0.25 ml dried CH$_2$Cl$_2$ was added at 0 °C 44 µl (0.57 mmol, 20.0 eq.) TFA and the solution stirred for 30 min. The reaction mixture was subsequently concentrated in vacuum. After re-dissolving the residue in CH$_2$Cl$_2$ and evaporation under reduced pressure, trandolapril 1 (12 mg, 27.9 µmol, 97%) was obtained as a white solid.

\[
\text{M(C$_{28}$H$_{34}$N$_2$O$_5$)} = 430.55 \text{ g/mol.}
\]

\[
\text{Rf} = 0.05 \text{ (EtOAc/CyHex, 1:1).}
\]

\[
\text{MP} = 122 \text{ °C.}
\]

\[
\text{HR-MS (ESI): } m/z = [\text{M-H}]^- \text{ calculated: 429.2395; detected: 429.3257.}
\]

\[
\text{H NMR} \text{ (600 MHz, CDCl}_3): \delta \text{ [ppm] = 7.32-7.30 (m, 2H, H-19/19'), 7.23-7.20 (m, 3H, H-20/20'/21), 4.50 (d, J = 7.9 Hz, 1H, H-2), 4.24-4.15 (m, 2H, H-23), 3.65 (q, J = 6.3 Hz, 1H, H-12), 3.15 (t, J = 6.7 Hz, 1H, H-15), 3.05 (td, J = 10.8 Hz, 2.7 Hz, 1H, H-5), 2.70 (t, J = 7.5 Hz, 2H, H-17), 2.51 (dd, J = 12.0 Hz, 1H, H-14), 2.22-2.19 (m, 1H, H-4), 2.07-1.78 (m, 6H, H-3/10/16), 1.49-1.22 (m, 12H, H-7/8/9/13/24).}
\]
**13C NMR**

(150 MHz, CDCl$_3$): $\delta$ [ppm] = 180.6 (C-6), 174.1 (C-11), 171.2 (C-22), 140.9 (C-18), 128.5; 128.4 (C-19/20), 126.1 (C-21), 64.6 (C-2), 62.0 (C-5), 60.9 (C-23), 58.9 (C-15), 52.1 (C-12), 46.2 (C-4), 34.5 (C-3), 33.4 (C-17), 31.8 (C-16), 30.8 (C-7), 29.3 (C-10), 25.0; 24.9 (C-8/9), 19.6 (C-13), 14.4 (C-24).

**IR (ATR)**

$\nu$ (cm$^{-1}$) = 3032 (w), 2931 (m), 2853 (w), 1737 (s), 1656 (s), 1550 (m), 1498 (m), 1448 (m), 1375 (m), 1342 (m), 1309 (m), 1183 (vs), 1172 (vs), 1138 (vs), 1096 (m), 1046 (m), 938 (w), 836 (m), 817 (m), 798 (m), 749 (m), 720 (s), 701 (s), 619 (m), 569 (w), 519 (w), 435 (m).

**Nota bene:** In an initial experiment, the deprotection of 15 to 1 was conducted under harsher conditions (TFA/CH$_2$Cl$_2$ = 2:1; 2 h, r.t.). In this case, the isolated material contained significant amounts of the diketopiperazine 16 as a by-product, the structure of which was proven by X-ray crystal structure analysis.
3. Spectra of Selected Compounds

$^1$H NMR spectrum of 11, measured at 300 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 11, measured at 75 MHz in CDCl$_3$. 
$^1$H NMR spectrum of 9, measured at 300 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 9, measured at 75 MHz in CDCl$_3$.
$^{1}H$ NMR spectrum of cis-9, measured at 300 MHz in CDCl$_3$.

$^{13}C$ NMR spectrum of cis-9, measured at 75 MHz in CDCl$_3$. 
$^{1}$H NMR spectrum of 12, measured at 300 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 12, measured at 75 MHz in CDCl$_3$. 
$^1$H NMR spectrum of 8, measured at 300 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 8, measured at 75 MHz in CDCl$_3$.
$^1$H NMR spectrum of 7, measured at 300 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 7, measured at 75 MHz in CDCl$_3$. 
$^1$H NMR spectrum of 13, measured at 300 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 13, measured at 75 MHz in CDCl$_3$. 
$^1$H NMR spectrum of 2a, measured at 600 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 2a, measured at 150 MHz in CDCl$_3$. 
$^1$H NMR spectrum of 15, measured at 500 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 15, measured at 125 MHz in CDCl$_3$. 

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$^1$H NMR spectrum of 1, measured at 600 MHz in CDCl$_3$.

$^{13}$C NMR spectrum of 1, measured at 150 MHz in CDCl$_3$. 
GC-MS spectrum of 13.
GC-MS spectrum of 2a.
GC-MS spectrum of 15.
4. Structure of compounds 2a, 1 and 16 in the crystalline State (color graphics)

From top to bottom: CCDC 1862524 (for 2a), CCDC 1896252 (for 1), and CCDC 1896253 (for 16) contain the supplementary crystallographic data for this publication. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.