Supporting Information File 1:

Full experimental details and characterization data for all new compounds

Enantioselective synthesis of tricyclic amino acid derivatives based on a rigid 4-azatricyclo[5.2.1.0^2,6]decane skeleton

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Table of Contents

1. General Information ......................................................................................................... S3
2. Synthesis of the racemic ketone \textit{rac}-9 ........................................................................ S4
3. Synthesis of the enantiomerically enriched ketone 9 ..................................................... S5
4. Synthesis of the racemic aldehyde \textit{rac}-15 ................................................................. S7
5. Synthesis of the amino acid 7a\textbullet HCl and of the N-tosyl amide 7b\textbullet HCl .......... S10
6. Synthesis of the amino acid 8a\textbullet HCl and of the N-tosyl amide 8b\textbullet HCl .............. S13
1. **General Information**

All reactions were carried out in flame dried flasks under an argon atmosphere with anhydrous solvents. Anhydrous tetrahydrofuran (THF), dichloromethane (CH₂Cl₂), diethyl ether (Et₂O), methanol (MeOH), dimethyl sulfoxide (DMSO), toluene, and acetone were prepared using standard procedures [1].

All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel (Merck F254); spots were visualized by UV light (254 nm) or by staining with aqueous KMnO₄. For column chromatography, silica gel (Merck, particle size 63–200 μm) was used.

Carbic anhydride ([10]), (R)-MOP [(R)-2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl], [Pd(C₅H₅)Cl]₂, trichlorosilane (HSiCl₃), methyltriphenylphosphonium bromide, pyridinium-chlorochromate (PCC), meta-chloroperbenzoic acid (MCPBA), boron trifluoride diethyl etherate (BF₃•OEt₂), (methoxymethyl)triphenylphosphonium chloride, para-toluene sulfonamide (TsNH₂), n-butyllithium (nBuLi, 1.6 M in hexanes) and ethyl 2-(trimethylsilyl)acetate are commercially available and were used as received.

Melting point ranges (mp) and decomposition points (dp) were measured on a Reichert Kofler-Heiztisch microscope and are uncorrected. Optical rotations ([α]₅) were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on Bruker Avance 400 and Bruker DMX 600 instruments and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ¹H and ¹³C NMR data were made on basis of 2D NMR methods (COSY, HSQC, HMBC, NOESY). The following symbols were used for the description of the multiplicities: s = singulett, d = dublett, t = triplett, m = multiplett, quin = quintett, br = broad. Infrared (IR) spectra were recorded on a Jasco FT-IR-3410 spectrometer, high resolution mass spectra (HRMS) on a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization).

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2. Synthesis of the racemic ketone rac-9

2.1 3,5-Dioxo-endo-4-azatricyclo[5.2.1.0²,6]dec-8-ene (I)

A solution of endo-carbic anhydride (10, 25.2 g, 154 mmol) and NH₄OAc (35.5 g, 461 mmol) in acetic acid (500 mL) was stirred at 140 °C for 4 d. The solvent was evaporated, water (200 mL) was added, and the mixture was extracted with EtOAc (4 × 100 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The imide I (25.1 g, 154 mmol, 100%) was obtained as a white solid and used in the next step without further purification.

The analytical data of I were in accordance with those given in ref. [2].

2.2 endo-4-Azatricyclo[5.2.1.0²,6]dec-8-ene (II)

LiAlH₄ (23.3 g, 614 mmol) was suspended in anhydrous THF (200 mL) and the imide I (25.1 g, 154 mmol), dissolved in THF (300 mL), was added dropwise at 0 °C. After 1 d heating at 90 °C, water (60 mL) was added at 0 °C, and the mixture was filtered through a pad of Celite® and washed with EtOAc (500 mL). The solvent was removed in vacuo to deliver the crude amine II (18.1 g, 134 mmol, white solid, 87%), which was used in the following step without further purification.

The analytical data of II were in accordance with those given in ref. [2].

2.3 4-tert-Butoxycarbonyl-endo-4-azatricyclo[5.2.1.0²,6]dec-8-ene (11)

A solution of the amine II (14.2 g, 105 mmol), Boc₂O (25.1 g, 115 mmol), and DMAP (1.28 mg, 10.5 mmol) in CH₂Cl₂ (500 mL) was stirred for 16 h at rt. Water (200 mL) was added and the mixture was extracted with CH₂Cl₂ (2 × 120 mL). The combined organic layers were washed with brine (200 mL) and dried over MgSO₄. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, n-pentane/Et₂O 1:0 → 4:1) to give 11 as a white solid (21.3 g, 90.5 mmol, 85%).

The analytical data of 11 were in accordance with those given in ref. [2].
[M + Na]: 258.1465; found: 258.1465; Elemental analysis (%) calcd for C\textsubscript{14}H\textsubscript{21}NO\textsubscript{2} (253.32): C 71.46, H 8.99, N 5.95; found: C 71.18, H 8.98, N, 5.88.

### 2.4 4-tert-Butoxycarbonyl-2-endo,6-endo,8-exo-4-azatricyclo[5.2.1.0\textsuperscript{2,6}]decan-8-ol (rac-12)

To a solution of the alkene 11 (4.44 g, 18.9 mmol) in anhydrous THF (80 mL), NaBH\textsubscript{4} (927 mg, 24.5 mmol) was added in one portion at 0 °C. Me\textsubscript{2}SO\textsubscript{4} (4.05 g, 3.04 mL, 32.1 mmol) was introduced dropwise within 15 min and the reaction mixture was stirred for 6 h at rt. Aqueous H\textsubscript{2}O\textsubscript{2} (35%, 44 mL), 1 N NaOH (22 mL), and water (33 mL) were added at 0 °C and the mixture was heated to reflux for 90 min. THF was evaporated and the remaining aqueous phase was extracted at 0 °C with CH\textsubscript{2}Cl\textsubscript{2} (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO\textsubscript{4}, and concentrated under reduced pressure. Purification of the crude material by column chromatography (silica gel, n-pentane/Et\textsubscript{2}O 4:3 → 2:3) gave the racemic alcohol rac-12 (3.59 g, 14.2 mmol, 75%) as a colorless oil.

The spectroscopic data of rac-12 were identical to those of 12 given in section 3.1.

### 2.5 4-tert-Butoxycarbonyl-endo-4-azatricyclo[5.2.1.0\textsuperscript{2,6}]decan-8-one (rac-9)

PCC (6.08 g, 28.2 mmol) and Celite\textsuperscript{®} (26.0 g) were suspended in CH\textsubscript{2}Cl\textsubscript{2} (130 mL). A solution of rac-12 (3.57 g, 14.1 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (130 mL) was added dropwise. The mixture was stirred overnight and then filtered through a pad of Celite\textsuperscript{®}. The filter cake was washed with EtOAc (300 mL) and the combined organic layers were dried over MgSO\textsubscript{4} and evaporated. The residue was purified by column chromatography (silica gel, n-pentane/Et\textsubscript{2}O 1:0 → 0:1) to give the ketone rac-9 (2.78 g, 11.1 mmol, 79%) as a white solid.

The spectroscopic data of rac-9 were identical to those of 9 given in section 3.3.

### 3. Synthesis of the enantiomerically enriched ketone 9

#### 3.1 (1R,2S,6S,7R,8S)-4-tert-Butoxycarbonyl-4-azatricyclo[5.2.1.0\textsuperscript{2,6}]decan-8-ol (12)

The alkene 11 (2.39 g, 10.2 mmol) was dissolved in anhydrous toluene (4.8 mL) under an argon atmosphere and cooled to 0 °C. (R)-MOP (12.0 mg, 25.6 μmol), [Pd(C\textsubscript{3}H\textsubscript{5})Cl]\textsubscript{2} (2.30 mg, 6.29 μmol), and trichlorosilane (4.43 g, 3.31 mL, 32.7 mmol) were added consecutively. The reaction was warmed to rt and stirred for 3 d. After evaporation of the solvent, the residue was re-dissolved in THF (22 mL) and MeOH (22 mL) and poured at 0 °C into a suspension of KF (4.74 g, 81.6 mmol) and KHCO\textsubscript{3} (10.2 g, 102 mmol) in THF (22 mL) and MeOH (22 mL). Aqueous H\textsubscript{2}O\textsubscript{2} (30%, 12.3 mL) was added and the reaction mixture was stirred for 1 d at rt. The suspension was filtered and the filter cake was washed with MeOH (2 × 50 mL). The filtrate was concentrated under reduced pressure and water (50 mL) and Et\textsubscript{2}O (50 mL) were added. The aqueous layer was extracted with Et\textsubscript{2}O (3 × 50 mL), and the combined organic layers were dried over MgSO\textsubscript{4} and evaporated under reduced pressure. The crude
product was purified by column chromatography (silica gel, n-pentane/Et₂O 4:3 → 3:4) to give 12 (2.08 g, 8.21 mmol, 81%) as a colorless oil. \( [\alpha]^{22}_{D} = 12.8 \) (c = 0.46, CH₂Cl₂); \( R_f = 0.25 \) (CH₂Cl₂/MeOH 95:5); \( ^1H \) NMR (600 MHz, CDCl₃, 1:1 mixture of rotamers): \( \delta = 1.18 \) (t, 1 H, \( J = 10.0 \) Hz, 9-H), 1.37 (m, 1 H, 10-H), 1.45 [s, 9 H, C(CH₃)₃], 1.79 (t, 1 H, \( J = 8.7 \) Hz, 10'-H), 1.94 (dd, 0.5 H, \( J = 12.4, 6.5 \) Hz, 9'-H), 2.03 (dd, 0.5 H, \( J = 13.2, 6.0 \) Hz, 9'-H), 2.25 (m, 2 H, 1-H, 7-H), 2.42 (m, 1 H, 2-H), 2.54 (s, 1 H, 6-H), 2.99 (m, 2 H, 3-H, 5-H), 3.44 (d, 0.5 H, \( J = 12.1 \) Hz, 3-H'), 3.52 (d, 0.5 H, \( J = 11.9 \) Hz, 3-H'), 3.59 (d, 0.5 H, \( J = 12.1 \) Hz, 5-H'), 3.69 (d, 0.5 H, \( J = 12.0 \) Hz, 5-H'), 3.90 (br s, 0.5 H, 8-H), 3.91 (br s, 0.5 H, 8-H); \( ^13C \) NMR (150 MHz, CDCl₃, 1:1 mixture of rotamers): \( \delta = 28.5 \) [C(C(CH₃)₃], 35.6 (C-9), 36.0 (C-9), 38.3 (C-10), 40.5 (C-1), 41.2 (C-2), 41.6 (C-6), 42.2 (C-2), 42.6 (C-6), 45.2 (C-5), 45.7 (C-5), 46.1 (C-3), 46.5 (C-3), 49.4 (C-7), 69.1 (C-8), 69.4 (C-8), 79.3 [C(CH₃)], 154.0 (CO₂N); IR (film): \( \tilde{\nu} = 3426, 2957, 2872, 1674, 1420, 1240, 1172, 1116, 874, 454 \) cm⁻¹; HRMS (ESI, pos.): \( m/z \) calcd for C₁₄H₂₃NNaO₃ [M + Na]⁺: 276.1570; found: 276.1572.

3.2 General procedure GP1 (synthesis of the Mosher esters of 12)

(R)-(−)- or (S)-(+)-%-Methoxy-%-trifluoromethyl phenylacetic acid chloride (2.00 equiv) were added at rt to a solution of 12, NEt₃ (2.70 equiv), and a catalytic amount of DMAP in anhydrous CH₂Cl₂ (37 mL/mmol 12). After 18 h, water (187 mL/mmol 12) was added and the solution was extracted with Et₂O (3 × 375 mL/mmol 12). The combined organic layers were dried over MgSO₄ and evaporated under reduced pressure. Purification of the crude product by column chromatography (silica gel, n-pentane/Et₂O 1:0 → 4:1) delivered the Mosher esters (S)-III or (R)-III as colorless liquids.

3.2.1 (S)-Mosher ester of 12

The (S)-Mosher ester (S)-III (20.0 mg, 42.5 µmol, 63%, colorless liquid) was obtained in 85% de (according to line shape analysis) from 12 (17.0 mg, 67.1 µmol) and the (R)-Mosher acid chloride (34.0 mg, 25.1 µL, 134 µmol) according to GP1. \( ^1H \) NMR (400 MHz, CDCl₃): \( \delta = 1.35 \) (m, 1 H), 1.43 (m, 1 H), 1.49 [s, 9 H, C(CH₃)₃], 1.57 (br s, 1 H), 1.68 (br d, 1 H, \( J = 10.2 \) Hz), 2.08 (br s, 1H), 2.47 (m, 2 H), 2.61 (m, 1 H), 3.03 (m, 2 H), 3.42–2.62 (m, 4 H), 3.78 (d, 1 H, \( J = 12.2 \) Hz), 7.39 (m, 3 H, Ph), 7.51 (m, 2 H, Ph).

3.2.2 (R)-Mosher ester of 12

The (S)-Mosher acid chloride (34.0 mg, 25.1 µL, 134 µmol) was treated with 12 (17.0 mg, 67.1 µmol) following GP1 to give (R)-III (20.3 mg, 43.1 µmol, 64%) as a colorless liquid in 85% de (according to line shape analysis). \( ^1H \) NMR (400 MHz, CDCl₃): \( \delta = 1.42 \) (m, 2 H), 1.48 [s, 9 H, C(CH₃)₃], 1.59 (m, 2 H), 2.10 (m, 1 H), 2.30 (br s, 1 H), 2.45 (m, 2 H), 2.60 (m, 1 H), 3.04 (m, 2 H), 3.33–3.65 (m, 4 H), 3.78 (d, 1 H, \( J = 12.2 \) Hz), 7.39 (m, 3 H, Ph), 7.51 (m, 2 H, Ph).
3.3 (1R,2S,6S,7R)-4-tert-Butoxycarbonyl-4-azatricyclo[5.2.1.0\(^2,6\)]decan-8-one (9)

The ketone 9 (849 mg, 3.38 mmol, 86%) was synthesized from 12 (1.00 g, 3.95 mmol), according to the procedure described for rac-9 in section 2.5. Mp = 111–113 °C; \([\alpha]_{D}^{22} = 99.9\) (c = 1.08, CH\(_2\)Cl\(_2\)); \(R_f = 0.45\) (CH\(_2\)Cl\(_2\)/MeOH 95:5); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 1.43\) [s, 9 H, C(CH\(_3\))\(_3\)], 1.74 (dd, 1 H, \(J = 10.3, 3.7\) Hz, 10-H), 1.82 (d, 1 H, \(J = 10.4\) Hz, 10-H'), 1.96 (m, 1 H, 9-H), 2.08 (m, 1 H, 9-H'), 2.58 (m, 1 H, 7-H), 2.68 (br s, 1 H, 1-H), 2.76 (m, 1 H, 2-H), 2.85 (m, 1 H, 6-H), 3.09 (m, 2 H, 3-H, 5-H), 3.44 (m, 1 H, 5-H'), 3.61 (d, 1 H, \(J = 12.0\) Hz, 3-H'); \(^{13}\)C NMR (150 MHz, CDCl\(_3\), mixture of rotamers): \(\delta = 28.4\) [C(CH\(_3\))\(_3\)], 39.0 (C-1), 39.5 (C-9), 39.7 (C-10), 41.2 (C-2), 42.1 (C-2), 43.8 (C-6), 44.9 (C-6), 46.0 (C-3), 46.2 (C-3), 46.5 (C-5), 46.6 (C-5), 55.5 (C-7), 55.7 (C-7), 79.5 [C(CH\(_3\))\(_3\)], 79.8 [C(CH\(_3\))\(_3\)], 153.6 (CO\(_2\)N), 154.0 (CO\(_2\)N), 214.2 (C-8), 214.8 (C-8); IR (KBr): \(\tilde{\nu} = 3464, 2967, 2932, 2888, 1741, 1686, 1422, 1166, 1123, 457\) cm\(^{-1}\); HRMS (ESI, pos.): \(m/z\) calcd for C\(_{14}\)H\(_{21}\)NNaO\(_3\) [M + Na\(^{+}\)]: 274.1414; found: 274.1414; Elemental analysis (%) calcd for C\(_{14}\)H\(_{21}\)NO\(_3\) (251.32): C 66.91, H 8.42, N 5.57; found: C 67.03, H 8.18, N 5.47.

4. Synthesis of the racemic aldehyde rac-15

4.1 4-tert-Butoxycarbonyl-8-methylidene-endo-4-azatricyclo[5.2.1.0\(^2,6\)]decane (rac-13)

4.1.1 Methylenation of rac-9 by Wittig reaction

A suspension of KOtBu (148 mg, 1.29 mmol) and methyltriphenylphosphonium bromide (462 mg, 1.29 mmol) in anhydrous toluene (2 mL) was heated to reflux for 2 h. The racemic ketone rac-9 (250 mg, 995 \(\mu\)mol) was added and heating was continued for 5 h. Water (5 mL) was added and the mixture was extracted with Et\(_2\)O (3 \(\times\) 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO\(_4\), and evaporated under reduced pressure. The crude material was purified by column chromatography (silica gel, \(n\)-pentane/Et\(_2\)O 1:0 → 4:1) to deliver the alkene rac-13 (190 mg, 762 \(\mu\)mol, 77%) as a colorless oil. \(R_f = 0.24\) (\(n\)-pentane/Et\(_2\)O 4:1); \(^1\)H NMR (600 MHz, CDCl\(_3\), 1:1 mixture of rotamers): \(\delta = 1.43\) [m, 9 H, C(CH\(_3\))\(_3\)], 1.54 (br d, 1 H, \(J = 9.5\) Hz, 10-H), 1.60 (br d, 1 H, \(J = 9.3\) Hz, 10-H'), 1.99 (m, 1 H, 9-H), 2.10 (m, 1 H, 9-H'), 2.33 (br s, 1 H, 1-H), 2.51–2.63 (m, 3 H, 2-H, 6-H, 7-H), 3.02 (m, 2 H, 3-H, 5-H), 3.47 (m, 1.5 H, 3-H', 5-H'), 3.58 (br d, 0.5 H, \(J = 12.0\) Hz, 3-H', 5-H'), 4.69 (s, 1 H, C=CH\(_2\)), 4.82 (br s, 1 H, C=CH\(_2\)'); \(^{13}\)C NMR (150 MHz, CDCl\(_3\), 1:1 mixture of rotamers): \(\delta = 28.5\) [C(CH\(_3\))\(_3\)], 31.5 (C-9), 40.8 (C-1), 41.9 (C-10), 42.2 (C-2 or C-6), 43.1 (C-2 or C-6), 44.1 (C-2 or C-6), 45.0 (C-2 or C-6), 45.8 (C-3 or C-5), 46.2 (C-3 or C-5), 46.3 (C-3 or C-5), 46.6 (C-3 or C-5), 50.7 (C-7), 50.8 (C-7), 78.8 [C(CH\(_3\))\(_3\)], 105.0 (C=CH\(_2\)), 105.6 (C=CH\(_2\)), 148.6 (C-8), 149.6 (C-8), 153.6 (CO\(_2\)N), 153.9 (CO\(_2\)N); IR (KBr): \(\tilde{\nu} = 3069, 2955, 2870, 1697, 1416, 1391, 1364, 1240, 1173, 1111, 877\) cm\(^{-1}\); HRMS (ESI, pos.): \(m/z\) calcd for C\(_{15}\)H\(_{23}\)NNaO\(_2\) [M + Na\(^{+}\)]: 272.1621; found: 272.1623.
4.1.2 Methylation of rac-9 with CH₂Cl₂ promoted by Mg/TiCl₄

A solution of the ketone rac-9 (400 mg, 1.59 mmol) in anhydrous THF (3.1 mL) was added dropwise at 0 °C to a suspension of Mg (309 mg, 12.7 mmol) and TiCl₄ (604 mg, 339 µL, 3.18 mmol) in anhydrous CH₂Cl₂ (6.3 mL). The reaction mixture was stirred for 1 h at 0 °C and for 1 h at rt. The suspension was cooled to 0 °C, treated with saturated aqueous K₂CO₃ (20 mL), filtered through a pad of Celite®, and washed with CH₂Cl₂ (100 mL). Saturated aqueous K₂CO₃ (20 mL) was added and the organic layer was extracted with CH₂Cl₂ (2 × 100 mL). The organic layers were combined, washed with brine (100 mL), dried over MgSO₄, and concentrated under reduced pressure. The product rac-13 (220 mg, 882 µmol, 55%) was obtained by column chromatography (silica gel, n-pentane/Et₂O 1:0 → 5:1).

For the spectroscopic data of rac-13, see the preceding procedure.

4.2 4-tert-Butoxycarbonyl-endo-8-(hydroxymethyl)-endo-4-azatricyclo[5.2.1.0²,6]decane (rac-14)

NaBH₄ (37.2 mg, 984 µmol) and Me₂SO₄ (163 mg, 123 µL, 1.29 mmol) were added to a solution of rac-13 (189 mg, 758 µmol) in anhydrous THF (6 mL) at 0 °C. After 18 h at rt, the reaction mixture was cooled to 0 °C and water (1.35 mL), NaOH (1 N, 900 µL), and aqueous H₂O₂ (30%, 1.74 mL) were added. The reaction mixture was stirred for 3 h at rt. Water (20 mL) was added and the mixture was extracted with Et₂O (3 × 60 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, and evaporated. Purification by column chromatography (silica gel, n-pentane/Et₂O 1:0 → 0:1) gave the racemic alcohol rac-14 (68.4 mg, 256 µmol, 34%) as a colorless oil. Rf = 0.10 (n-pentane/Et₂O 1:1); ¹H NMR (600 MHz, CDCl₃): δ = 1.10 (m, 1 H, 9-H), 1.46 [s, 9 H, C(CH₃)₃], 1.50 (m, 1 H, 10-H), 1.54 (d, 1 H, J = 9.5 Hz, 10-H'), 1.67 (m, 1 H, 9-H'), 1.75 (br s, 1 H, OH), 2.16 (br s, 1 H, 8-H), 2.28 (br s, 1 H, 1-H), 2.40 (br d, 1 H, J = 9.3 Hz, 7-H), 2.59 (m, 2 H, 2-H, 6-H), 3.05 (dd, 1 H, J = 12.4, 8.6 Hz, 3-H or 5-H), 3.12 (m, 1 H, 3-H or 5-H), 3.46–3.61 (m, 2 H, 3-H', 5-H'), 3.68 (m, 2 H, CH₂OH); ¹³C NMR (150 MHz, CDCl₃, mixture of rotamers): δ = 25.1 (C-9), 25.3 (C-9), 28.5 [C(CH₃)₃], 41.3 (C-1), 43.0 (C-2 or C-6), 43.06 (C-2 or C-6), 43.15 (C-7), 44.0 (C-10), 44.1 (C-2 or C-6), 44.2 (C-8), 44.8 (C-8), 45.7 (C-3 or C-5), 46.0 (C-3 or C-5), 46.5 (C-3 or C-5), 47.0 (C-3 or C-5), 64.2 (CH₂OH), 64.4 (CH₂OH), 79.3 [C(CH₃)₃], 154.39 (CO₂N), 154.45 (CO₂N); IR (KBr): ν = 3417, 2945, 2875, 1691, 1674, 1394, 1365, 1169, 1138, 1105, 1012, 874, 777 cm⁻¹; HRMS (ESI, pos.): m/z calcd for C₁₅H₂₃NNaO₃ [M + Na]⁺: 290.1727; found: 290.1727.
4.3 4-tert-Butoxycarbonyl-spiro[endo-4-azatricyclo[5.2.1.02,6]decane-8,1'-exo-2'-oxacyclop propane] (rac-16)

MCPBA (70%, 212 mg, 860 µmol) and NaHCO₃ (515 mg, 6.14 mmol) were added at 0 °C to a solution of the alkene rac-13 (153 mg, 610 µmol) in CH₂Cl₂ (7 mL). The reaction mixture was stirred for 3 h at rt. Excess MCPBA was decomposed by treatment with aqueous Na₂SO₃ (0.5 M, 10 mL). After extraction of the crude reaction mixture with CH₂Cl₂ (3 × 10 mL), the combined organic layers were washed with saturated aqueous NaHCO₃ (10 mL), dried with MgSO₄, and evaporated. The crude product was purified by column chromatography (silica gel, n-pentane/Et₂O 1:0 → 2:1) to afford rac-16 (97.7 mg, 368 µmol, 60%) as a white powder. Mp = 60–62 °C; Rf = 0.33 (n-pentane/Et₂O 1:1); ¹H NMR (600 MHz, CDCl₃, 1:1 mixture of rotamers): δ = 1.45 [s, 9 H, C(CH₃)₃], 1.52 (quin, 0.5 H, J = 1.4 Hz, 10-H), 1.53 (quin, 0.5 H, J = 1.4 Hz, 10-H), 1.55 (m, 0.5 H, 9-H), 1.57 (m, 0.5 H, 9-H), 1.76 (br d, 0.5 H, J = 14.3 Hz, 9-H'), 1.82 (br d, 0.5 H, J = 14.0 Hz, 9-H'), 1.85 (m, 1 H, 7-H), 1.89 (t, 0.5 H, J = 1.5 Hz, 10-H'), 1.90 (t, 0.5 H, J = 1.5 Hz, 10-H'), 2.42 (br s, 1 H, 1-H), 2.54 (m, 1 H, 2-H), 2.62 (m, 1 H, 6-H), 2.83 (d, 0.5 H, J = 3.4 Hz, CH/HO), 2.86 (d, 0.5 H, J = 3.9 Hz, CH/HO), 2.95 (d, 0.5 H, J = 3.9 Hz, CH/HO), 3.02 (m, 2.5 H, 3-H, 5-H, CH/HO), 3.55 (d, 0.5 H, J = 12.2 Hz, 3-H'), 3.61 (d, 0.5 H, J = 11.9 Hz, 3-H'), 3.65 (d, 0.5 H, J = 12.0 Hz, 5-H'), 3.78 (d, 0.5 H, J = 12.1 Hz, 5-H'); ¹³C NMR (150 MHz, CDCl₃, 1:1 mixture of rotamers): δ = 28.50 [C(CH₃)₃], 28.54 [C(CH₃)₃], 32.08 (C-9), 32.14 (C-9), 40.9 (C-10), 41.1 (C-1), 41.2 (C-11), 41.5 (C-2), 42.4 (C-6), 42.6 (C-2), 43.3 (C-6), 45.3 (C-5), 45.9 (C-5), 46.0 (C-3), 46.5 (C-3), 47.9 (C-7), 51.2 (CH₂O), 51.5 (CH₂O), 63.1 (C-8), 63.3 (C-8), 79.2 [C(CH₃)₃], 79.3 [C(CH₃)₃], 153.6 (CO₂N), 153.7 (CO₂N); IR (ATR): ν ~ = 2956, 2868, 1686, 1481, 1426, 1364, 1242, 1164, 1133, 874, 762 cm⁻¹; HRMS (ESI, pos.): m/z calcd for C₁₅H₂₄NO₃ [M + H]⁺: 266.1751; found: 266.1751.

4.4 4-tert-Butoxycarbonyl-2-endo,6-endo,8-endo-4-azatricyclo[5.2.1.0²⁶]decane-8-carbaldehyde (rac-15)

4.4.1 Oxidation of the alcohol rac-14

A solution of rac-14 (35.4 mg, 132 µmol) in CH₂Cl₂ (1.50 mL) was added dropwise at rt to a suspension of PCC (57.0 mg, 264 µmol) and Celite® (251 mg) in CH₂Cl₂ (1.50 mL). The mixture was stirred for 6 h at rt, filtered through a pad of Celite®, and washed with EtOAc (150 mL). The organic layer was dried over MgSO₄ and evaporated. The residue was purified by column chromatography (silica gel, n-pentane/EtOAc 1:0 → 2:1) to give the aldehyde rac-15 (18.0 mg, 67.8 µmol, 51%) as a colorless oil.

The spectroscopic data of rac-15 were identical to those of 15 given in section 5.2.
4.4.2 4-tert-Butoxycarbonyl-2-endo,8-endo,12-endo-4-aza-6-oxatetracyclo[6,2,1,1^{2,5},0^{9,12}]undecane (rac-17) and rac-15 via Lewis acid-catalyzed rearrangement of rac-16

The epoxide rac-16 (31.2 mg, 118 µmol) was dissolved in anhydrous toluene (11 mL) and BF$_3$•OEt$_2$ (4.14 mg, 3.70 µL, 29.3 µmol) was added at 0 °C. After stirring at 0 °C for 5 min, water (10 mL) was added and the mixture was extracted with Et$_2$O (3 × 10 mL). The combined organic layers were dried over K$_2$CO$_3$ and evaporated under reduced pressure. Column chromatographic separation (silica gel, n-pentane/Et$_2$O 1:0 → 2:1) delivered rac-17 (11.0 mg, 41.5 µmol, 35%) as a white solid and rac-15 (8.00 mg, 30.1 µmol, 26%) as a colorless oil. Rac-17: Mp = 65–67 °C; $R_f$ = 0.40 (n-pentane/Et$_2$O 1:1); $^1$H NMR (600 MHz, CDCl$_3$, 1:1 mixture of rotamers): $\delta$ = 1.45 [s, 9 H, C(CH$_3$)$_3$], 1.56 (m, 1 H, 11-H), 1.62 (s, 2 H, 10-H, 10-H'), 1.71 (br dd, 1 H, $J$ = 13.0, 4.0 Hz, 11-H'), 1.92 (m, 1 H, 8-H), 2.14 (br s, 1 H, 1-H), 2.19 (br s, 1 H, 9-H), 2.43 (br s, 1 H, 12-H), 2.62 (br s, 1 H, 2-H), 3.30 (dd, 1 H, $J$ = 11.3, 6.2 Hz, 3-H), 3.38–3.60 (m, 2 H, 3-H, 7-H), 3.66 (br d, 1 H, $J$ = 11.2 Hz, 7-H'), 5.20 (br s, 0.5 H, 5-H), 5.33 (br s, 0.5 H, 5-H); $^{13}$C NMR (150 MHz, CDCl$_3$, 1:1 mixture of rotamers): $\delta$ = 25.6 (C-11), 28.4 [C(CH$_3$)$_3$], 33.6 (C-9), 37.9 (C-9), 40.1 (C-1), 41.9 (C-12), 43.0 (C-12), 43.5 (C-3), 44.1 (C-3), 44.6 (C-10), 45.1 (C-2), 63.4 (C-7), 79.7 [C(CH$_3$)$_3$], 80.7 (C-5), 80.9 (C-5), 154.1 (CO$_2$N), 154.5 (CO$_2$N); IR (ATR): $\tilde{\nu}$ = 2947, 1697, 1389, 1364, 1344, 1330, 1169, 1151, 1103, 808, 1008, 893 cm$^{-1}$; HRMS (ESI, pos.): m/z calcd for C$_{15}$H$_{23}$NNaO$_3$ [M + Na]$^+$: 288.1570; found: 288.1563.

The spectroscopic data of rac-15 were identical to those of 15 given in section 5.2.

5. Synthesis of the amino acid 7a•HCl and of the N-tosyl amide 7b•HCl

5.1 (1R,2S,6R,7R)-4-tert-Butoxycarbonyl-8-methoxymethylidene-4-azatricyclo[5.2.1.0$^{2,6}$]-decane (18)

A suspension of (methoxymethyl)triphenylphosphonium chloride (15.9 g, 46.4 mmol) and KO$_t$Bu (6.25 g, 55.7 mmol) in anhydrous toluene (375 mL) was stirred at rt for 5 h. A solution of the ketone 9 (1.61 g, 6.41 mmol) in anhydrous THF (90 mL) was added slowly via a syringe and stirring was continued for 1 d at rt. EtOAc (400 mL) was added and the mixture was washed with water (3 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over K$_2$CO$_3$ and concentrated under reduced pressure. Purification by column chromatography (silica gel, n-pentane/Et$_2$O 10:1) gave 18 (1.51 g, 5.41 mmol, 84%, 1:1 mixture of E/Z-isomers) as a colorless oil. $[\alpha]_D^{20}$ = 23.5 (c = 0.56, CHCl$_3$); $R_f$ = 0.26 (n-pentane/Et$_2$O 4:1); $^1$H NMR (600 MHz, CDCl$_3$, 1:1:1 mixture of rotamers and E/Z-isomers): $\delta$ = 1.45 [m, 9 H, C(CH$_3$)$_3$], 1.53 (m, 1.5 H, 10-H), 1.58 (m, 0.5 H, 10-H), 1.99 (m, 1.5 H, 9-H), 1.99 (m, 0.5 H, 9-H), 2.30 (m, 0.5 H, 1-H), 2.30 (m, 0.5 H, 1-H), 2.47 (m, 0.5 H, 7-H), 2.50–2.67 (m, 2 H, 2-H, 6-H), 2.97–3.10 (m, 2.5 H, 3-H, 5-H, 7-H), 3.35 (m, 0.5, 3-H, 5-H), 3.47 (m, 1 H, 3-H, 5-H), 3.54 (m, 3.5 H, 3-H, 5-H, OCH$_3$), 5.78 (br s, 0.2 H, C=CH), 5.83 (br s, 0.8 H, C=CH); $^{13}$C NMR (150 MHz, CDCl$_3$, 1:1:1 mixture of rotamers and E/Z-conformers): $\delta$ = 26.8 (C-9), 27.2 (C-9), 27.5 (C-9), 27.7 (C-9), 28.47 [C(CH$_3$)$_3$], 28.51 [C(CH$_3$)$_3$], 28.55 [C(CH$_3$)$_3$], 28.6
5.2 (1R,2S,6R,7R,8R)-4-tert-Butoxycarbonyl-4-azatricyclo[5.2.1.0^2,6]decane-8-carbaldehyde (15)

Trichloroacetic acid (8.48 g, 51.9 mmol) and water (one drop) were added to a solution of 18 (1.45 g, 5.19 mmol) in CH₂Cl₂ (610 mL). After stirring for 1.5 h at rt, the reaction was treated with saturated aqueous NaHCO₃ (570 mL) and extracted with CH₂Cl₂ (3 × 380 mL). The combined organic layers were dried over K₂CO₃ and evaporated under reduced pressure. Column chromatographic purification (silica gel, n-pentane/Et₂O 2:1 → 1:2) delivered 15 (1.05 g, 3.96 mmol, 76%) as a colorless oil. [α]_D^20 = 46.3 (c = 0.63, CHCl₃); R_f = 0.12 (n-pentane/Et₂O 1:1); ¹H NMR (400 MHz, CDCl₃): δ = 1.42 [s, 9 H, C(CH₃)₃], 1.55 (m, 2 H, 10-H, 10-H'), 1.60 (br td, 1 H, J = 12.9, 4.6 Hz, 9-H), 1.92 (br dd, 1 H, J = 13.3, 5.8 Hz, 9-H'), 2.32 (m, 1 H, 1-H), 2.53 (m, 3 H, 2- H, 6- H, 8- H), 2.78 (br s, 1 H, 7-H), 2.93 (br dd, 1 H, J = 12.5, 7.3 Hz, 5-H), 3.00 (dd, 1 H, J = 11.9, 8.0 Hz, 3-H), 3.23 (d, 1 H, J = 12.3 Hz, 5-H'), 3.53 (br d, 1 H, J = 11.6 Hz, 3-H'), 9.79 (s, 1 H, CHO); ¹³C NMR (100 MHz, CDCl₃): δ = 22.4 (C-9), 28.3 [C(CH₃)₃], 41.0 (C-1), 42.7 (C-2 or C-6), 43.3 (C-10), 43.6 (C-2 or C-6), 43.9 (C-7), 45.8 (C-3), 46.6 (C-5), 53.3 (C-8), 79.4 [C(CH₃)₃], 154.4 (CO₂N), 203.1 (CHO); IR (ATR): ν = 2944, 2866, 1689, 1412, 1363, 1239, 1217, 1170, 1120, 877 cm⁻¹; HRMS (ESI, pos.): m/z calcd for C₁₆H₂₅NNaO₃ [M + Na]^+: 302.1727; found: 302.1727.

5.3 (1R,2S,6R,7R,8R)-4-tert-Butoxycarbonyl-4-azatricyclo[5.2.1.0^2,6]decane-8-carboxylic acid (19)

The aldehyde 15 (856 mg, 3.23 mmol) was dissolved in MeCN (24 mL). KH₂PO₄ (pH = 4, 2.78 mL) and a solution of H₂O₂ (30%, 1.15 mL, 11.3 mmol) and NaClO₂ (642 mg, 7.10 mmol) in water (34 mL) were added. After stirring for 6 h at rt, Na₂SO₃ (350 mg) was added and stirring was continued for 30 min. The solution was acidified to pH = 3 by careful addition of HCl (1 N) and extracted with Et₂O (4 × 100 mL). The combined organic layers were dried over MgSO₄ and evaporated under reduced pressure to give the acid 19 (679 mg, 2.41 mmol, 75%) as a white solid after column chromatography (silica gel, CH₂Cl₂/MeOH 99:1 → 95:1). Mp = 64–66 °C; [α]_D^20 = 4.0 (c = 0.28, CHCl₃); R_f = 0.17 (CH₂Cl₂/MeOH 95:5); ¹H NMR (600 MHz, CD₃OD, 1:1 mixture of rotamers): δ = 1.47 [s, 9 H, C(CH₃)₃], 1.53 (m, 3 H, 9-H, 10-H, 10-H'), 1.85 (m, 1 H, 9-H'), 2.29 (br s, 1 H, 1-H), 2.61–2.71 (m,
3 H, 2-H, 6-H, 7-H), 2.79 (m, 1 H, 8-H), 2.97 (m, 1 H, 5-H), 3.06 (m, 1 H, 3-H), 3.50 (br t, 1 H, $J = 11.4$ Hz, 3′-H), 3.72 (d, 0.5 H, $J = 12.2$ Hz, 5′-H), 3.76 (d, 0.5 H, $J = 12.5$ Hz, 5′-H); $^{13}$C NMR (150 MHz, CD$_3$OD, 1:1 mixture of rotamers): δ = 24.1 (C-9), 24.4 (C-9), 28.7 [C(CH$_3$)$_3$], 29.0 [C(CH$_3$)$_3$], 42.69 (C-1), 42.73 (C-1), 44.4 (C-2 or C-6), 44.6 (C-2 or C-6), 44.67 (C-10), 44.74 (C-7), 44.78 (C-10), 44.84 (C-7), 45.2 (C-2 or C-6), 45.4 (C-2 or C-6), 45.7 (C-8), 45.9 (C-8), 46.4 (C-5), 46.8 (C-3), 46.9 (C-5), 47.2 (C-3), 80.7 [C(CH$_3$)$_3$], 80.9 [C(CH$_3$)$_3$], 155.9 (CO$_2$N), 156.4 (CO$_2$N), 177.4 (CO$_2$H), 177.2 (CO$_2$H); IR (ATR): ~ν = 2969, 2867, 1726, 1643, 1420, 1365, 1286, 1236, 1194, 1155, 1120, 1095 cm$^{-1}$; HRMS (ESI, pos.): m/z calcd for C$_{15}$H$_{23}$NNaO$_4$ [M + Na]$^+$: 304.1519; found: 304.1519.

5.4 (1R,2S,6R,7R,8R)-4-Azatricyclo[5.2.1.0$^{2,6}$]decane-8-carboxylic acid hydrochloride (7a•HCl)

A suspension of the acid 19 (178 mg, 633 μmol) in aqueous HCl (4.8 M, 9.00 mL) was refluxed for 1 d. The solvent was evaporated under reduced pressure, and the crude product was filtered through a pad of silica gel (CH$_2$Cl$_2$/MeOH 1:0 → 9:1) affording the amino acid 7a•HCl (114 mg, 524 μmol, 79%) as a white solid. Mp = 173–175 °C; [α]$_{D}^22$ = –14.5 (c = 0.29, MeOH); R$_f$ = 0.06 (MeOH); 1H NMR (600 MHz, CD$_3$OD): δ = 1.68 (s, 2 H, 10-H, 10-H′), 1.74 (m, 2 H, 9-H, 9-H′), 2.38 (br s, 1 H, 1-H), 2.64 (br s, 1 H, 7-H), 2.78 (m 1 H, 8-H), 2.91 (m, 2 H, 2-H, 6-H), 3.00 (m, 1 H, 5-H), 3.10 (m, 1 H, 3-H), 3.32 (d, 1 H, $J = 12.6$ Hz, 5-H′), 3.52 (d, 1 H, $J = 12.6$ Hz, 3-H′); $^{13}$C NMR (150 MHz, CD$_3$OD): δ = 26.3 (C-9), 42.3 (C-1), 45.14 (C-2 or C-6), 45.15 (C-2 or C-6), 45.4 (C-7), 45.5 (C-10), 45.8 (C-3), 46.7 (C-3), 47.0 (C-5), 48.2 (C-8), 183.8 (CO$_2$H); IR (ATR): ~ν = 2950, 2768, 1697, 1558, 1393, 1288, 1206, 1165, 1019, 886 cm$^{-1}$; HRMS (ESI, pos.): m/z calcd for C$_{10}$H$_{16}$NO$_2$ [M + H]$^+$: 182.1176; found: 182.1176.

5.5 N-[(4-Methylphenyl)sulfonyl] (1R,2S,6R,7R,8R)-4-tert-butoxycarbonyl-4-azatricyclo[5.2.1.0$^{2,6}$]decane-8-carboxamide (IV)

A mixture of acid 19 (177 mg, 629 μmol), DCC (132 mg, 629 μmol) and DMAP (7.00 mg, 62.9 μmol) in anhydrous CH$_2$Cl$_2$ (3.0 mL) was stirred at rt for 1 h. TsNH$_2$ (108 mg, 629 μmol) was added and stirring was continued for 1 d. The suspension was filtered through a frit and washed with CH$_2$Cl$_2$ (2 × 10 mL). The crude product mixture was filtered through a pad of silica gel (CH$_2$Cl$_2$/MeOH 1:0 → 50:1) to give IV (175 mg, 403 μmol, 64%) as white solid. Mp = 116–118 °C; [α]$_{D}^22$ = –26.3 (c = 0.07, MeOH); R$_f$ = 0.32 (n-pentane/EtOAc 1:2); $^1$H NMR (600 MHz, CD$_3$OD): δ = 1.38 (m, 1 H, 9-H), 1.52 [m, 9 H, C(CH$_3$)$_3$], 1.64 (m, 2 H, 10-H, 10-H′), 1.90 (dd, 1 H, $J = 13.5$, 6.6 Hz, 9-H′), 2.24 (m, 1 H, 7-H), 2.42 (s, 3 H, ArCH$_3$), 2.56 (m, 1 H, 8-H), 2.61–2.78 (m, 3 H, 1-H, 2-H, 6-H), 3.02–3.13 (m, 2 H, 3-H, 5-H), 3.38–3.48 (m, 2 H, 3-H′, 5-H′), 7.34 (br d, 2 H, $J = 8.1$ Hz, Ar), 7.86 (br d, 2 H, $J = 8.2$ Hz, Ar); $^{13}$C NMR (150 MHz, CD$_3$OD, mixture of rotamers): δ = 21.6 (ArCH$_3$), 22.3 (C-9), 28.7 [C(CH$_3$)$_3$], 42.2 (C-7), 44.9 (CH), 45.1 (CH), 45.7 (C-10), 45.8 (CH), 46.7 (C-3 or C-5), 46.9 (C-3 or C-5), 48.4 (C-8), 81.1 [C(CH$_3$)$_3$], 129.2 (Ar), 130.4 (Ar), 138.5 (Ar), 145.7 (Ar), 156.6 (CO$_2$N), 158.6 (CO$_2$N).
173.3 (CONH); IR (ATR): \( \tilde{\nu} = 2946, 2879, 1691, 1652, 1405, 1363, 1234, 1170, 1120, 1089 \text{ cm}^{-1} \); HRMS (ESI, pos.): \( m/z \) calcd for \( \text{C}_{22}\text{H}_{30}\text{N}_{2}\text{NaO}_{5}\text{S} [\text{M} + \text{Na}]^+: 457.1768 \); found: 457.1768.

5.6 \( N\)-(4-Methylphenyl)sulfonyl \( (1R,2S,6R,7R,8R)-4\)-azatricyclo[5.2.1.0\( ^2,6 \)]decane-8-carboxamide hydrochloride (7b•HCl)

A solution of the amide IV (163 mg, 375 \( \mu \text{mol} \)) in ethereal HCl (1.0 M, 16.7 mL, 16.7 mmol) and anhydrous MeOH (1.00 mL) was stirred for 3 h at rt. The precipitate formed was dried in vacuo to yield 7b•HCl (52.7 mg, 142 \( \mu \text{mol}, 38\% \)) as a colorless solid. Dp = >210 °C; \([\alpha]_{D}^{22} = –48.1 \) (\( c = 0.05, \text{MeOH} \)); \( R_f = 0.47 \) (MeOH); \( \text{1H NMR (600 MHz, CD}_{3}\text{OD)}: \delta = 1.66 \) (m, 1 H, 9-H), 1.76 (m, 3 H, 9-H', 10-H, 10-H'), 2.38 (br s, 1 H, 1-H), 2.45 (s, 3 H, CH\(_3\)), 2.59 (d, 1 H, \( J = 12.1 \) Hz, 5-H), 2.67 (br s, 1 H, 7-H), 2.83–2.94 (m, 4 H, 2-H, 5-H', 6-H, 8-H), 3.12 (m, 1 H, 3-H), 3.49 (d, 1 H, \( J = 12.1 \) Hz, 3-H'), 7.42 (dd, 2 H, \( J = 8.6, 0.7 \) Hz, Ar), 7.92 (dt, 2 H, \( J = 8.5, 1.9 \) Hz, Ar); \( \text{13C NMR (150 MHz, CD}_{3}\text{OD)}: \delta = 21.6 \) (CH\(_3\)), 23.4 (C-9), 41.5 (C-1), 44.9 (C-8), 45.5 (C-6), 45.8 (C-7), 46.1 (C-10), 46.3 (C-5), 47.0 (C-3), 47.1 (C-2), 129.6 (Ar), 130.7 (Ar), 137.6 (Ar), 146.6 (Ar), 177.9 (CONH); IR (ATR): \( \tilde{\nu} = 2974, 2822, 2710, 2624, 2589, 1671, 1598, 1455, 1335, 1148, 1089, 877, 809 \text{ cm}^{-1} \); HRMS (ESI, pos.): \( m/z \) calcd for \( \text{C}_{17}\text{H}_{23}\text{N}_{2}\text{O}_{3}\text{S} [\text{M} + \text{H}]^+ \): 335.1424; found: 335.1423.

6. Synthesis of the amino acid 8a•HCl and the \( N\)-tosyl amide 8b•HCl

6.1 \( (1R,2S,6R,7R)-4\)-tert-Butoxycarbonyl-8-(ethoxycarbonylmethylidene)-4-azatricyclo[5.2.1.0\( ^2,6 \)]decane (20)

LDA was prepared by adding \( n\)BuLi (1.6 M in hexanes, 14.4 mL, 23.1 mmol) to a solution of freshly destilled iPr\(_2\)NH (2.34 g, 3.24 mL, 23.1 mmol) in anhydrous THF (116 mL) at –78 °C. After 30 min, ethyl 2-(trimethylsilyl)acetate (3.70 g, 4.22 mL, 23.1 mmol) was added dropwise at –78 °C and stirring was continued for 30 min. The ketone 9 (2.90 g, 11.5 mmol), dissolved in anhydrous THF (24 mL), was added slowly to the red reaction mixture at –78 °C and stirring was continued for 1 h. After 18 h at rt, saturated aqueous NH\(_4\)Cl (100 mL) was added, and the mixture was extracted with Et\(_2\)O (3 × 100 mL). The combined organic layers were dried over MgSO\(_4\) and evaporated under reduced pressure. Column chromatographic purification (silica gel, \( n\)-pentane/Et\(_2\)O 4:1 \( \rightarrow 3:2 \)) gave 20 (1.87 g, 5.81 mmol, 50\%) as a colorless oil. \([\alpha]_{D}^{20} = 232.5 \) (\( c = 0.36, \text{CHCl}_{3} \)); \( R_f = 0.33 \) (\( n\)-pentane/Et\(_2\)O 1:2); \( \text{1H NMR (400 MHz, CDCl}_{3}, 77:23 \text{ mixture of } E/Z-\text{isomers): } \delta = 1.27 \) (t, 3 H, \( J = 7.1 \) Hz, OCH\(_2\)CH\(_3\)), 1.38 [s, 7 H, C(CH\(_3\))\(_3\)], 1.42 [s, 2 H, C(CH\(_3\))\(_3\)], 1.53 (br d, 1 H, \( J = 9.9 \) Hz, 10-H), 1.60 (br dt, 1 H, \( J = 10.0, 1.6 \) Hz, 10-H'), 2.11 (m, 1 H, 9-H), 2.23 (m, 1 H, 9-H'), 2.35 (m, 1 H, 1-H), 2.57 (m, 1 H, 2-H), 2.76 (m, 1 H, 6-H), 2.90 (dd, 1 H, \( J = 11.9, 7.7 \) Hz, 5-H), 2.97 (dd, 1 H, \( J = 12.2, 8.1 \) Hz, 3-H), 3.42 (d, 1.2 H, \( J = 12.0 \) Hz, 5-H'), 3.59 (d, 0.8 H, \( J = 12.3 \) Hz, 3-H'), 3.98 (d, 1 H, \( J = 4.8 \) Hz, 7-H), 4.07–4.22 (m, 2 H, OCH\(_2\)CH\(_3\)), 5.62 (br s, 0.2 H, C=CH), 5.65 (br s, 0.8 H, C=CH); \( \text{13C NMR (100 MHz, CDCl}_{3}, 77:23 \text{ mixture of } E/Z-\text{isomers): } \delta = 14.25 \) (OCH\(_2\)CH\(_3\)), 14.32 (OCH\(_2\)CH\(_3\)), 28.3 [C(CH\(_3\))\(_3\)], 28.5 [C(CH\(_3\))\(_3\)], 33.9 (C-9), 34.4 (C-9), 39.3 (C-1), 41.5 (C-10), 54.2 (OCH\(_2\)CH\(_3\)), 54.7 (OCH\(_2\)CH\(_3\)), 60.8 (C=CH), 102.2 (C=CH), 126.4 (Ar), 131.8 (Ar), 141.5 (Ar), 177.9 (CONH); IR (ATR): \( \tilde{\nu} = 2974, 2822, 2710, 2624, 2589, 1671, 1598, 1455, 1335, 1148, 1089, 877, 809 \text{ cm}^{-1} \); HRMS (ESI, pos.): \( m/z \) calcd for \( \text{C}_{17}\text{H}_{23}\text{N}_{2}\text{O}_{3}\text{S} [\text{M} + \text{Na}]^+ \): 357.1608; found: 357.1608.
6.2 Methyl (1S,2S,6R,7S,8S)-4-tert-butoxycarbonyl-4-azatricyclo[5.2.1.0^2,6]decan-8-acetate (V)

Powdered Mg (251 mg, 10.3 mmol) was added at rt to a solution of the \(\alpha,\beta\)-unsaturated ester 20 (1.66 g, 5.16 mmol) in anhydrous MeOH (52 mL). After the gas evolution had ceased, this procedure was repeated several times until all starting material was consumed. The reaction was treated with saturated aqueous NH₄Cl (40 mL) and the aqueous layer was extracted with CH₂Cl₂ (6 \(\times\) 40 mL). The organic layers were combined, dried over MgSO₄, and evaporated under reduced pressure. The methyl ester V (1.21 g, 3.91 mmol, 76%) was isolated as a colorless oil after column chromatography (silica gel, n-pentane/Et₂O 3:1 \(\rightarrow\) 3:2). \([\alpha]^{20}_D = 14.9\) (c = 0.50, CHCl₃); \(R_f = 0.37\) (n-pentane/Et₂O 2:1); \(^1\)H NMR (600 MHz, CDCl₃, 3:2 mixture of rotamers): \(\delta = 1.06\) (m, 1 H, 9-H), 1.46 [m, 10 H, C(CH₃)₃, 10-H], 1.56 (d, 1 H, \(J = 9.6\) Hz, 10-H′), 1.74 (m, 1 H, 9-H′), 2.25 (m, 2 H, 1-H, 7-H), 2.32 (m, 1 H, 8-H), 2.38–2.48 (m, 1 H, C/HCO₂), 2.56 (m, 3 H, 2-H, 6-H, CH₂HCO₂), 3.01 (dd, 1 H, \(J = 12.3\), 8.2 Hz, 3-H), 3.08 (m, 1 H, 5-H), 3.50 (br d, 0.4 H, \(J = 11.4\) Hz, 5-H′), 3.55 (br d, 0.6 H, \(J = 11.9\) Hz, 5-H′), 3.64 (m, 3.6 H, 3-H′, COT₂CH₃), 3.72 (br d, 0.4 H, \(J = 11.7\) Hz, 3-H′); \(^{13}\)C NMR (150 MHz, CDCl₃, 3:2 mixture of rotamers): \(\delta = 27.4\) (C-9), 28.4 [C(CH₂)₃], 28.5 [C(CH₂)₃], 35.9 (CH₂CO₂), 36.0 (CH₂CO₂), 37.2 (C-8), 37.7 (C-8), 41.4 (C-1 or C-7), 43.0 (C-2 or C-6), 44.0 (C-10), 44.2 (C-2 or C-6), 44.6 (C-1 or C-7), 45.6 (C-5), 45.9 (C-5), 46.1 (C-3), 46.6 (C-3), 51.3 (CO₂CH₃), 79.3 [C(CH₂)₃], 79.4 [C(CH₂)₃], 154.2 (CO₂N), 174.2 (CO₂CH₃), 174.5 (CO₂CH₃); IR (ATR): \(\tilde{\nu} = 2947, 2876, 1735, 1692, 1392, 1365, 1236, 1164, 1125, 1097, 875\) cm⁻¹; HRMS (ESI, pos.): \(m/z \) calcd for C₁₇H₂₇NNaO₄ [M + Na]⁺: 332.1832; found: 332.1832.

6.3 (1S,2S,6R,7S,8S)-4-tert-Butoxycarbonyl-4-azatricyclo[5.2.1.0^2,6]decan-8-acetic acid (21)

A solution of V (1.12 g, 3.91 mmol) and KOH (4.06 g, 72.4 mmol) in aqueous EtOH (50%, 24 mL) was refluxed for 1 d. Water (30 mL) was added at rt and the mixture was extracted with Et₂O (2 \(\times\) 30 mL). The pH of the aqueous layer was adjusted to 4 by addition of HCl (1 N). The white suspension was extracted with EtoAc (2 \(\times\) 100 mL) and the combined organic layers were dried over MgSO₄ and evaporated under reduced pressure to provide the acid 21 (959 mg, 3.25 mmol, 90%) as a colorless solid. Dp = 160 °C; \([\alpha]^{20}_D = 14.2\) (c = 0.41, CHCl₃); \(R_f = 0.24\) (n-pentane/Et₂O 1:1); \(^1\)H NMR (600 MHz, CDCl₃): \(\delta = 1.05\) (m, 1 H, 9-H), 1.49 [s, 9 H, C(CH₃)₃], 1.53 (dd, 1 H, \(J = 9.8\), 1.3 Hz, 10-H), 1.59 (d, 1 H, \(J = 9.5\) Hz, 10-H′), 1.78 (m, 1 H, 9-H′), 2.29 (m, 3 H, 1-H, 7-H, 8-H), 2.40 (m, 1 H, C/HCO₂), 2.53 (m, 1 H, CH₂HCO₂), 2.57–2.69 (m, 2 H, 2-H, 6-H), 2.98–3.14 (m, 2 H, 3-
H, 5-H), 3.53 (m, 1 H, 3-H'), 3.74 (m, 1 H, 5-H'); \(^{13}\)C NMR (150 MHz, CDCl\(_3\), mixture of rotamers): \(\delta = 28.6\) (C-9), 28.7 [C(CH\(_3\)\(_3\)], 28.9 [C(CH\(_3\)\(_3\)], 37.1 (C\(_2\)CO\(_2\)), 37.2 (C\(_2\)CO\(_2\)), 38.8 (C-8), 39.1 (C-8), 42.8 (C-1), 44.4 (C-2), 44.5 (C-2), 45.0 (C-10), 45.4 (C-6), 45.7 (C-7), 46.1 (C-7), 47.2 (C-3), 47.2 (C-3), 47.7 (C-5), 81.0 [C(CH\(_3\)\(_3\)], 81.3 [C(CH\(_3\)\(_3\)], 156.0 (CO\(_2\)N), 177.2 (CO\(_2\)H), 177.4 (CO\(_2\)H); IR (ATR): \(\tilde{\nu} = 3219, 2939, 2880, 1733, 1658, 1421, 1241, 1168, 1160, 1143, 1132 \text{ cm}^{-1}\); HRMS (ESI, pos.): \(m/z\) calcd for C\(_{16}\)H\(_{25}\)NNaO\(_4\) [M + Na\(^+\)]: 318.1676; found: 318.1676.

6.4 (1S,2S,6R,7S,8S)-4-Azatricyclo[5.2.1.0\(^2\)\(^6\)]decane-8-acetic acid hydrochloride (8a•HCl)

A suspension of the acid 21 (154 mg, 521 \(\mu\)mol) in aqueous HCl (4.8 M, 6.40 mL) was refluxed for 1d. The solution was concentrated under reduced pressure and the crude product was filtered through a pad of silica gel (CH\(_2\)Cl\(_2\)/MeOH 1:0 \(\rightarrow\) 9:1). The amino acid 8a•HCl (86.0 mg, 371 \(\mu\)mol, 71%) was obtained as a white solid. Crystallization from MeOH/Et\(_2\)O gave colorless cubic crystals. Mp = 156–158 °C; \([\alpha]\)\(_{D}\) = 7.5 (c = 1.0, CHCl\(_3\)); \(R_t = 0.08\) (MeOH); \(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta = 1.19\) (ddd, 1 H, J = 13.9, 7.0, 1.7 Hz, 9-H), 1.76 (m, 2 H, 10-H, 10-H'), 1.96 (m, 1 H, 9-H'), 2.36 (m, 2 H, 1-H, 7-H), 2.51 (m, 1 H, 8-H), 2.60 (m, 2 H, CH\(_2\)CO\(_2\)), 2.92 (m, 2 H, 2-H, 6-H), 3.25 (m, 3 H, 3-H, 5-H, 5-H'), 3.49 (m, 1 H, 3-H'); \(^{13}\)C NMR (150 MHz, CD\(_3\)OD): \(\delta = 28.4\) (C-9), 37.9 (C\(_2\)CO\(_2\)), 39.0 (C-8), 41.3 (C-1), 44.7 (C-7), 45.7 (C-6), 46.1 (C-5), 46.8 (C-2), 47.0 (C-3), 47.1 (C-10), 174.9 (CO\(_2\)H); IR (ATR): \(\tilde{\nu} = 2883, 2736, 1733, 1429, 1320, 1196, 1175, 1149, 989, 879 \text{ cm}^{-1}\); HRMS (ESI, pos.): \(m/z\) calcd for C\(_{11}\)H\(_{18}\)NO\(_2\) [M + H\(^+\)]: 196.1332; found: 196.1336.

6.5 \(N\)-[(4-Methylphenyl)sulfonyl] (1S,2S,6R,7S,8S)-4-tert-butoxycarbonyl-4-azatricyclo-
[5.2.1.0\(^2\)\(^6\)]decane-8-acetamide (VI)

A mixture of the acid 21 (355 mg, 1.20 mmol), DCC (252 mg, 1.20 mmol), and DMAP (13.5 mg, 120 \(\mu\)mol) in anhydrous CH\(_2\)Cl\(_2\) (6.0 mL) was stirred at rt for 1 h. TsNH\(_2\) (206 mg, 1.20 mmol) was added and stirring was continued for 4 d. The suspension was filtered through a frit and washed with CH\(_2\)Cl\(_2\) (2 × 10 mL). The crude product mixture was filtered through a pad of silica gel (CH\(_2\)Cl\(_2\)/MeOH 1:0 \(\rightarrow\) 50:1) to yield VI (390 mg, 870 \(\mu\)mol, 72%) as a white solid. Mp = 84–86 °C; \([\alpha]\)\(_{D}\) = 15.7 (c = 0.1, CHCl\(_3\)); \(R_t = 0.24\) (n-pentane/Et\(_2\)O 1:1); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 0.88\) (br s, 1 H, 9-H), 1.41 (br d, 1 H, J = 9.5 Hz, 10-H'), 1.96 (m, 1 H, 9-H'), 2.36 (m, 2 H, CH\(_2\)CONH), 2.42 (s, 3 H, ArCH\(_3\)), 2.46 (m, 1 H, 6-H), 2.56 (m, 1 H, 2-H), 2.98 (dd, 1 H, J = 12.6, 8.9 Hz, 5-H), 3.07 (t, 1 H, J = 10.2 Hz, 3-H), 3.48 (d, 1 H, J = 12.1 Hz, 3-H'), 3.54 (d, 1 H, J = 12.6 Hz, 5-H'), 7.30 (d, 2 H, J = 8.1 Hz, Ar), 7.93 (d, 2 H, J = 8.3 Hz, Ar); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta = 21.7\) (ArCH\(_3\)), 27.8 (C-9), 28.6 [C(CH\(_3\)\(_3\)], 35.6 (C-8), 37.9 (CH\(_2\)CONH), 41.3 (C-1), 42.8 (C-6), 43.8 (C-10), 44.0 (C-2), 44.1 (C-7), 45.9 (C-3), 46.2 (C-5), 80.1 [C(CH\(_3\)\(_3\)], 128.4 (Ar), 129.4 (Ar), 136.0 (Ar), 144.6 (Ar), 154.8 (CO\(_2\)N), 170.7 (CONH); IR
(ATR): $\tilde{\nu}$ = 2946, 2875, 1657, 1412, 1343, 1240, 1169, 1130, 1087, 866 cm\(^{-1}\); HRMS (ESI, neg.): \textit{m/z} caleed for C\(_{23}\)H\(_{31}\)N\(_{2}\)O\(_{5}\)S [M – H\(^-\)]: 447.1959; found: 447.1960.

6.6 \textit{N}-(4-Methylphenyl)sulfonyl] (1S,2S,6R,7S,8S)-4-azatricyclo[5.2.1.0\(^2\),6]decane-8-acetamide hydrochloride (8b•HCl)

The amide \textit{VI} (100 mg, 223 μmol) was dissolved in an ethereal solution of HCl (1.0 M, 8.50 mL, 8.50 mmol) and stirred for 20 h at rt. The precipitate formed was collected and dried to give 8b•HCl (36.3 mg, 94.3 μmol, 42%) as a colorless solid. \textit{M}p = 135–137 °C; $\lbrack \alpha \rbrack_{D}^{22}$ = −18.9 (\textit{c} = 0.05, MeOH); $R_f$ = 0.56 (MeOH); \(^1\)H NMR (600 MHz, CD\(_3\)OD): $\delta$ = 1.12 (ddd, 1 H, $J$ = 13.9, 7.1, 2.1 Hz, 9-H), 1.68 (dt, 1 H, $J$ = 9.8, 2.3 Hz, 10-H), 1.71 (dd, 1 H, $J$ = 9.9, 1.7 Hz, 10-H'), 1.83 (m, 1 H, 9-H'), 2.18 (br s, 1 H, 7-H), 2.32 (br t, 1 H, $J$ = 4.4 Hz, 1-H), 2.36 (m, 1 H, 8-H), 2.44 (m, 4 H, CH\(_2\)CONH, CH\(_3\)), 2.48 (dd, 1 H, $J$ = 14.8, 9.5 Hz, CH\(_2\)CONH), 2.81–2.92 (m, 2 H, 2-H, 6-H), 3.21 (m, 2 H, 3-H, 5-H), 3.26 (dd, 1 H, $J$ = 12.5, 8.6 Hz, 3-H'), 3.46 (dd, 1 H, $J$ = 12.9, 6.3 Hz, 5-H'), 7.41 (dd, 2 H, $J$ = 8.6, 0.7 Hz, Ar), 7.89 (dd, 2 H, $J$ = 8.5, 1.9 Hz, Ar); \(^1\)C NMR (150 MHz, CD\(_3\)OD): $\delta$ = 21.6 (CH\(_3\)), 28.2 (C-9), 38.9 (C-8), 39.9 (CH\(_2\)CONH), 41.2 (C-1), 44.6 (C-7), 45.5 (C-6), 46.0 (C-3), 46.7 (C-2), 46.95 (C-5), 46.97 (C-10), 129.3 (Ar), 130.6 (Ar), 137.9 (Ar), 146.3 (Ar), 172.7 (CONH); IR (ATR): $\tilde{\nu}$ = 2950, 1714, 1595, 1439, 1338, 1167, 1085, 855, 815, 660 cm\(^{-1}\); HRMS (ESI, pos.): \textit{m/z} caleed for C\(_{18}\)H\(_{23}\)N\(_{2}\)O\(_{3}\)S [M + H\(^+\)]: 349.15804; found: 349.15804.