Supporting Information
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Supporting Information

Synthesis of Novel Amino Acids Containing Cubane
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General Analytical Information

Nuclear Magnetic Resonance spectra were recorded on a Bruker 700 MHz, 500 MHz or 400 MHz instrument at ambient temperature. All $^1$H NMR spectra were measured in parts per million (ppm) relative to the signals for residual chloroform (CHCl$_3$) in deuterated CDCl$_3$ (7.26 ppm), or the signals for tetramethylsilane (TMS) added into the deuterated chloroform (0 ppm). Data for $^1$H NMR were reported as: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad), coupling constants, and integration. All $^{13}$C NMR spectra were reported in ppm relative to CDCl$_3$ (77.16 ppm) or MeOD (49.00 ppm) unless otherwise stated, and were obtained with complete $^1$H decoupling. IR spectra were reported on an Avatar 370 FT-IR Thermo Nicolet Spectrometer. High resolution mass spectra were obtained on a Thermo LTQ-FT/Accela/CTC/PDA instrument. Melting points were obtained on a Buchi B-545 capillary melting point apparatus.

General Reagent Information

Unless otherwise noted, all chemicals were commercially available and were used as received without further purification. Dry solvents were used directly from Sigma-Aldrich Sure-Seal bottles. Cubane-1,4-dimethylester was purchased from Prof Philip Eaton, cubane and its derivatives can also be purchased from http://www.boronmolecular.com/Products/Cubanes. 2,2-Dibromo-1-(cuban-1-yl)ethanone,$^1$ 2-(Cuban-1-yl)-2-hydroxyacetic acid,$^9$ cuban-1-ylmethanol$^1$ (18) and cubane-1-carbaldehyde$^2$ (14) were prepared according to the previously reported procedures.$^{1,2}$
Experimental procedures and physical data

Methyl 2-(cuban-1-yl)-2-hydroxyacetate (10)

To a suspension of 2-(cuban-1-yl)-2-hydroxyacetic acid 9 (0.300 g, 1.68 mmol) and potassium carbonate (0.279 g, 2.02 mmol) in DMF (8.31 mL) was slowly added methyl iodide (0.105 mL, 0.240 g, 1.68 mmol). The resulting solution was stirred at room temperature for 2 h, when water was added and the reaction mixture was extracted with Et₂O (3 x 10 mL). The organic phase was dried (MgSO₄), filtered and evaporated to afford a yellow residue. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in heptane. Pure fractions were evaporated to dryness to afford methyl 2-(cuban-1-yl)-2-hydroxyacetate 10 (0.310 g, 96 %) as a white solid.

m.p.: 140.5-144.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.61 (d, J = 6.6 Hz, 1H), 3.79 (s, 3H), 3.87 – 3.94 (m, 3H), 3.95 – 4.00 (m, 3H), 4.00 – 4.04 (m, 1H), 4.32 (d, J = 6.6 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 44.5, 47.1, 48.7, 52.5, 58.3, 71.3, 173.9; HRMS (EI+) Calcd for C₁₁H₁₂O₃ [M]+ 192.0781, Found 192.0792; IR (neat cm⁻¹): 3467, 2980, 1736.

Methyl 2-azido-2-(cuban-1-yl)acetate (11)

To a solution of triphenylphosphine (1.890 g, 7.21 mmol) in THF (15 mL) cooled to 0 °C, diisopropyl azodicarboxylate (1.420 mL, 1.985 g, 7.21 mmol) was added dropwise over a period of 5 minutes. The resulting slurry was stirred at 0 °C for 15 minutes before a solution of methyl 2-(cuban-1-yl)-2-hydroxyacetate 10 (0.66 g, 3.43 mmol) in THF (15 mL) was added followed by diphenylphosphoryl azide (1.550 mL, 1.984 g, 7.21 mmol). The resulting solution was warmed up to room temperature and stirred over night. The reaction mixture was evaporated to dryness (water bath at 20°C) and the crude product was purified by flash silica chromatography, elution gradient 10 to 20% EtOAc in heptane. Pure fractions were evaporated to dryness to afford methyl 2-azido-2-(cuban-1-yl)acetate 11 (0.450 g, 61 %) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 3.79 (s, 3H), 3.93 - 3.99 (m, 3H), 4.01 (obsured s, 1H CHN₃), 4.01 – 4.04 (m, 1H), 4.04 – 4.08 (m, 3H); ¹³C NMR (101 MHz, CDCl₃, 27 °C) δ 44.6, 48.1, 48.3, 52.4, 57.8, 62.9, 169.1; HRMS (EI+) Calcd for C₁₁H₁₁N₃O₂ [M-N₂]+ 189.0784, Found 189.0796; IR (neat cm⁻¹): 3467, 2980, 1736.
Methyl 2-amino-2-(cuban-1-yl)acetate (12)

To a solution of triphenylphosphine polymer bound (3 mmol/1g of resin, 0.640 g, 1.93 mmol) in THF (6 mL) was added methyl 2-azido-2-(cuban-1-yl)acetate 11 (0.280 g, 1.29 mmol), and the reaction was stirred at room temperature for 2 h. To the resulting solution water (0.23 mL, 12.89 mmol) was added and the reaction was heated under reflux for 5 h. The reaction mixture was then filtered, the resin was washed with 10% MeOH in DCM (100 mL), the filtrate was evaporated to dryness to afford racemic methyl 2-amino-2-(cuban-1-yl)acetate 12 (0.227 g, 92%) as a colourless oil.

\( ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 3.64 (s, 1H), 3.71 (s, 3H), 3.85 - 3.9 (m, 3H), 3.91 - 3.95 (m, 3H), 3.97 - 4.05 (m, 1H);

\( ^{13}C \text{ NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 44.2, 47.1, 48.7, 51.8, 56.0, 59.2, 174.2;

\( \text{HRMS (ESI)} \) Calcd for C\(_{11}\)H\(_{14}\)NO\(_2\) [M+H]\(^+\) 192.1019, Found 192.1025;

\( \text{IR (neat cm}\(^{-1}\)) 3583, 3184, 2978, 1738, 1660.\)

\( R \)-Methyl 2-((\text{tert}-butoxycarbonyl)amino)-2-(cuban-1-yl)acetate (13)

To a solution of methyl 2-amino-2-(cuban-1-yl)acetate 12 (0.550 g, 2.88 mmol) in DCM (5 mL) was added Boc\(_2\)O (0.67 mL, 0.628 g, 2.88 mmol) in DCM (5 mL) and the reaction was stirred at room temperature for 5 h. The reaction mixture was diluted with DCM (10 mL) and 1 M citric acid (5 mL) was added. The aqueous layer was separated and washed with DCM (10 mL). The combined organic extracts were dried (Na\(_2\)SO\(_4\)), filtered and evaporated to afford a white solid. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in heptane. Pure fractions were evaporated to dryness to afford racemic methyl 2-((\text{tert}-butoxycarbonyl)amino)-2-(cuban-1-yl)acetate 13 (0.710 g, 85%) as a white solid.

\( \text{m.p.} 90.0-91.0^\circ \text{C}; ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\), 27^\circ \text{C}) \( \delta \) 1.43 (s, 9H), 3.71 (s, 3H), 3.85 - 3.89 (m, 3H), 3.89 - 3.93 (m, 3H), 3.95 - 4.02 (m, 1H), 4.49 (d, \( J = 8.1 \text{ Hz}, 1H \)), 4.97 (d, \( J = 5.6 \text{ Hz}, 1H \));

\( ^{13}C \text{ NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 28.4, 44.2, 47.3, 48.7, 52.1, 55.2, 57.7, 78.0, 155.8, 171.3;

\( \text{HRMS (ESI)} \) Calcd for C\(_{16}\)H\(_{22}\)NO\(_4\) 292.1543, Found 292.1542;

\( \text{IR (neat cm}\(^{-1}\)) 3442, 3358, 2980, 1741, 1713.\)

The enantiomers were separated on chiral HPLC IC (ID-5) 4.6 x 250 mm 5 \( \mu \)m column with heptanes/IPA (80/20), 2 mL/min (1 x 10 \( \mu \)L injection); 1\(^{st}\) enantiomer ret. time 2.87 min, 2\(^{nd}\) enantiomer ret. time 4.46 min.

\( \text{VCD}: \)
VCD analysis performed by Marie Rydén Landergren, AZ Mölndal, Sweden

\[ \alpha^D_{22} -44.3 \ (c\ 2.03, \text{EtOH}) \] for N-Boc-\((R)\)-cubane glycine methyl ester 13; \[ \alpha^D_{22} +45.9 \ (c\ 2.18, \text{EtOH}) \] for N-Boc-\((S)\)-cubane glycine methyl ester 13.

\((R)\)-Methyl 2-amino-2-(cuban-1-yl)acetate (12)
\((S)\)-Methyl 2-amino-2-(cuban-1-yl)acetate (12)

A solution of TFA (10% in DCM) (1.7 mL) was added to separate samples of \((R)\)-methyl 2-((tert-butoxycarbonyl)amino)-2-(cuban-1-yl)acetate 13 (0.05 g, 0.17 mmol) and \((S)\)-methyl 2-((tert-butoxycarbonyl)amino)-2-(cuban-1-yl)acetate 13 (0.05 g, 0.17 mmol) at room temperature. The resulting solutions were stirred at room temperature for 2 h. The reaction mixtures were separately concentrated and diluted with DCM (5 mL), washed sequentially with saturated NaHCO\(_3\) (5 mL), and saturated brine (5 mL). The organic layer was dried over MgSO\(_4\), filtered and evaporated to afford pure products \((R)\)-enantiomer 12 (30.0 mg, 91%) and \((S)\)-enantiomer 12 (28.0 mg, 86%) as a colourless oil.

\[ \alpha^D_{22} -41.2 \ (c\ 1.7, \text{EtOH}) \] for \(N-(R)\)-cubane glycine methyl ester 12; \[ \alpha^D_{22} +42.8 \ (c\ 2.8, \text{EtOH}) \] for \(N-(S)\)-cubane glycine methyl ester 12.

\((R)\)-2-Amino-2-(cuban-1-yl)acetic acid (5)
\((S)\)-2-Amino-2-(cuban-1-yl)acetic acid (5)

To two separate solutions of lithium hydroxide monohydrate (0.044 g, 1.05 mmol) in water (0.2 mL) at 0 °C was added dropwise a solution of \((R)\)-methyl 2-amino-2-(cuban-1-yl)acetate 12 (0.017 g, 0.09 mmol) in THF (0.87 mL) and \((S)\)-methyl 2-amino-2-(cuban-1-yl)acetate 12 (0.030 g, 0.16 mmol) in THF (0.870 mL). The resulting mixtures were stirred at room temperature over night. The reaction mixtures were evaporated to dryness, then redissolved in water (3 mL) and extracted with DCM (3 x 5 mL). The aqueous layer from the extraction was carefully acidified with 1 M HCl to pH ~4, and the samples were evaporated to dryness. The crude products were redissolved in DCM/MeOH. The white precipitate formed was filtered off and the filtrates were
concentrated under reduced pressure to afford pure (R)-2-amino-2-(cuban-1-yl)acetic acid 5 (0.016 g, 99 %) and (S)-2-amino-2-(cuban-1-yl)acetic acid 5 (0.028 g, 99 %) as white powders.

**m.p.: 185 °C (browned without melting);** [α]$_D^{24}$ +27.2 (c 1.84, MeOH) for (R)-cubane glycine 5; [α]$_D^{24}$ +35.2 (c 2.13, EtOH) for (S)-cubane glycine 5; $^1$H NMR (400 MHz, $d_6$-DMSO + TFA drop, 27 °C) δ 3.85 – 3.92 (m, 3H), 3.94 – 4.00 (m, 1H), 4.02 – 4.09 (m, 3H), 4.13 - 4.2 (m, 1H), 8.27 (s, 3H); $^{13}$C NMR (101 MHz, $d_6$-DMSO + TFA drop) δ 43.3, 46.9, 47.1, 51.3, 52.4, 169.0; HRMS (ESI+) Calcd for C$_{10}$H$_{12}$NO$_2$ [M+H]$^+$ 178.0863, Found 178.0865; IR (neat cm$^{-1}$): 3421, 3151, 2987, 1732.

**To a stirred solution of methyl 2-((tert-butoxycarbonyl)amino)-2-(dimethoxyphosphoryl)acetate 15 (1.98 g, 6.66 mmol) and DBU (0.96 mL, 0.96 g, 6.36 mmol) in DCM (11.0 mL) was added a solution of cubane-1-carbaldehyde 14 (0.800 g, 6.05 mmol) in DCM (3.0 mL) at 0 °C. The resulting solution was stirred at room temperature for 12 h. The reaction mixture was quenched with water (20 mL), extracted with Et$_2$O (3 x 20 mL), the organic layer was dried (MgSO$_4$), filtered and evaporated to afford yellow residue. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in heptane. Pure fractions were evaporated to dryness to afford (Z)-methyl 2-((tert-butoxycarbonyl)amino)-3-(cuban-1-yl)acrylate 16 (0.610 g, 34 %) as a colourless solid (alkene stereochemistry was assigned as Z based on the similar literature example).**

**m.p.: 116.0-117.6 °C $^1$H NMR (400 MHz, CDCl$_3$) 1.46 (s, 9H), 3.76 (s, 3H), 3.91 – 3.98 (m, 4H), 4.17 (dt, $J$ = 3.6, 6.2 Hz, 3H), 5.92 (br s, 1H), 6.72 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) 28.3, 45.3, 47.8, 51.5, 52.3, 57.1, 80.3, 123.5, 134.5, 153.9, 165.7; HRMS (ESI+) Calcd for C$_{17}$H$_{22}$NO$_4$ [M+H]$^+$ 304.1543, Found 304.1541; IR (neat cm$^{-1}$): 3410, 3360, 2980, 1709, 1643.

**To a solution of (Z)-methyl 2-((tert-butoxycarbonyl)amino)-3-(cuban-1-yl)acrylate 16 (0.100 g, 0.33 mmol) in 1 M NH$_3$ in methanol (6.0 mL) was added diisopropylethylamine (57.0 µL, 0.043 g, 0.33 mmol) and the reaction mixture was hydrogenated in the H-Cube hydrogenation cell at room temperature, using a 30 mm RaNi cartridge and a flow rate of 0.3 mL/minute under 40 bar H$_2$, (pressure regulator to 30), several cycles were performed over 24 hours. The solution was concentrated, to provide crude product, which was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in heptane to afford racemic methyl 2-((tert-butoxycarbonyl)amino)-3-(cuban-1-yl)propanoate 17 (0.080 g, 79 %) as a white solid.**

**m.p.: 92.6-94.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) 1.43 (s, 9H), 1.96 (dd, $J$ = 7.9, 14.4 Hz, 1H), 2.05 (dd, $J$ = 6.2, 14.4 Hz, 1H), 3.72 (s, 3H), 3.77 (dt, $J$ = 2.2, 5.5 Hz, 3H), 3.86 (q, $J$ = 5.0 Hz, 3H), 3.98 (tt, $J$ = 2.4, 4.9 Hz, 1H),
4.39 (q, $J = 8.1$ Hz, 1H), 4.98 (d, $J = 8.6$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 28.5, 36.4, 44.6, 48.2, 49.0, 51.2, 52.4, 56.5, 79.9, 155.0, 174.0; HRMS (ESI$^+$) Calcd for C$_{17}$H$_{24}$NO$_4$ [M+H]$^+$ 306.1700, Found 306.1700; IR (neat cm$^{-1}$): 3369, 2968, 2920, 1749, 1686.

The enantiomers were separated on chiral HPLC IC (ID-5) 4.6 x 250 mm 5 µm column, with heptanes/EtOH (98/02), 2 mL/min (1 x 10 µL injection), 1$^\text{st}$ enantiomer ret. time 2.86 min, 2$^\text{nd}$ enantiomer ret. time 4.46 min.

**VCD:**

Figure 4. Experimental spectra of isomer 1 (blue) and isomer 2 (purple) of EN07716-33-1 and simulated spectra of the two isomers R (red) and S (green).

VCD analysis performed by Marie Rydén Landergren, AZ Mölndal, Sweden

$[\alpha]_D^{22}$ -14.3 (c 2.1, CHCl$_3$) for $N$-Boc-(R)-cubane alanine methyl ester 17; $[\alpha]_D^{22}$ +21.7 (c 0.46, CHCl$_3$) for $N$-Boc-(S)-cubane alanine methyl ester 17.

**Methyl 2-amino-3-(cuban-1-yl)propanoate**

A solution of TFA (10% in DCM) (3.90 mL) was added to methyl 2-((tert-butoxycarbonyl)amino)-3-(cuban-1-yl)propanoate 17 (0.120 g, 0.39 mmol) at room temperature. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and diluted with DCM (5.0 mL), washed sequentially with saturated NaHCO$_3$ (5.0 mL), and saturated brine (5.0 mL). The organic layer was dried (MgSO$_4$), filtered and evaporated to afford racemic product methyl 2-amino-3-(cuban-1-yl)propanoate (0.080 g, 99 %) as a white solid.

m.p.: 111.0-113.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.56 (s, 2H), 1.93 (dd, $J = 7.0, 14.3$ Hz, 1H), 2.00 (dd, $J = 6.9, 14.3$ Hz, 1H), 3.55 (t, $J = 7.0$ Hz, 1H), 3.70 (s, 3H), 3.74 – 3.79 (m, 3H), 3.84 – 3.9 (m, 3H), 3.97 – 4.04 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 39.0, 44.6, 48.3, 49.2, 51.9, 52.5, 57.1, 177.1; HRMS (ESI$^+$) Calcd for C$_{12}$H$_{16}$NO$_2$ [M+H]$^+$ 206.1176, Found 206.1174; IR (neat cm$^{-1}$): 3377, 2974, 2848, 1738.
2-Amino-3-(cuban-1-yl)propanoic acid (6)

To a solution of methyl 2-amino-3-(cuban-1-yl)propanoate (0.068 g, 0.33 mmol) in THF (1.5 mL) at 0 °C was added dropwise a solution of sodium hydroxide (2.0 M in MeOH, 0.18 mL, 0.36 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and redissolved in water (5.0 mL), and extracted with DCM (5.0 mL). The aqueous layer from the extraction was carefully acidified with 1M HCl to pH ~4, the solvent was evaporated to dryness and the crude product was redissolved in DCM/MeOH. The filtrate was concentrated under reduced pressure to give racemic 2-amino-3-(cuban-1-yl)propanoic acid 6 (0.060 g, 95 %) as a white powder.

m.p.: 160 °C browned, >200 °C decomposed; \( ^1H \) NMR (400 MHz, MeOD) \( \delta \) 2.09 (dd, \( J = 14.5, 8.1 \) Hz, 1H), 2.13 (dd, \( J = 14.5, 6.2 \) Hz, 1H), 3.86 – 3.94 (m, 6H), 3.93 – 3.98 (m, 1H), 3.99 – 4.07 (m, 1H); \( ^13C \) NMR (101 MHz, D\(_2\)O, 30 °C) \( \delta \) 33.9, 44.1, 47.9, 48.5, 51.0, 54.9, 172.9; HRMS (ESI\(^+\)) Calcd for C\(_{11}\)H\(_{13}\)NO\(_2\) [M+H]\(^+\) 192.1019, Found 192.10195; IR (neat cm\(^{-1}\)): 3410, 2974, 2908, 1740.

Ethyl 3-(cuban-1-yl)-2-cyanopropanoate (19)

To a solution of tributylphosphine (2.05 mL, 1.66 g, 8.20 mmol) in THF (10.0 mL) was added diisopropyl azodicarboxylate (1.61 mL, 1.66 g, 8.20 mmol) cooled to 0 °C over a period of 5 minutes under nitrogen. The resulting slurry was stirred at 0 °C for 30 minutes before a solution of ethyl 2-cyanoacetate (0.92 mL, 0.97 g, 8.61 mmol) in THF (6.0 mL) was added with further stirring for 20 min. Cuban-1-ylmethanol 18 (0.550 g, 4.10 mmol) was then added. The resulting solution was warmed up to room temperature and stirred overnight. The reaction mixture was evaporated to dryness and the crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in heptane. Pure fractions were evaporated to dryness to afford ethyl 3-(cuban-1-yl)-2-cyanopropanoate 19 (0.450 g, 48 %) as a colorless liquid.

\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.33 (t, \( J = 7.2 \) Hz, 3H), 2.28 (d, \( J = 7.1 \) Hz, 2H), 3.49 (t, \( J = 7.1 \) Hz, 1H), 3.86 - 3.96 (m, 6H), 4.01-4.06 (m, 1H), 4.20-4.31 (m, 2H); \( ^13C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 14.1, 33.3, 33.9, 44.5, 48.4, 48.6, 56.7, 62.9, 116.9, 166.6; HRMS (EI\(^+\)) Calcd for C\(_{14}\)H\(_{15}\)NO\(_2\) [M]\(^+\) 229.1097, Found 229.1097; IR (neat cm\(^{-1}\)): 2982, 2251, 1745.

Ethyl 3-amino-2-(cuban-1-ylmethyl)propanoate (20)

![Diagrams of compounds 18, 19, and 20]
A solution of ethyl 3-(cuban-1-yl)-2-cyanopropanoate 19 (0.150 g, 0.65 mmol) in 1 M NH₃ in EtOH (65.0 mL) at room temperature was hydrogenated in the H-Cube hydrogenation cell using a 30 mm RanI cartridge, a flow rate of 0.2 mL/min, under pressure regulator set to 20 with the effective H₂ pressure of 30 bar. Two cycles were performed. The solution was then concentrated to provide the crude product, which was purified by flash silica chromatography, elution gradient 0 to 10% 1 M NH₃ in MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 3-amino-2-(cuban-1-ylmethyl)propanoate 20 (80.0 mg, 53%) as a colourless oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta 1.26 (t, J = 7.1 Hz, 3H), 1.75 (dd, J = 5.6, 14.3 Hz, 1H), 1.94 (dd, J = 8.8, 14.3 Hz, 1H), 2.48 – 2.57 (m, 1H), 2.79 (dd, J = 4.7, 12.8 Hz, 1H), 2.91 (dd, J = 8.5, 12.8 Hz, 1H), 3.68 – 3.75 (m, 3H), 3.81 – 3.88 (m, 3H), 3.99-4.04 (m, 1H), 4.10 (dq, J = 10.8, 7.1 Hz, 1H), 4.16 (dq, J = 10.8, 7.1 Hz, 1H); \]

\[ \text{13C NMR (101 MHz, CDCl}_3\text{)} \delta 14.3, 33.7, 44.3, 44.6, 45.8, 48.4, 48.9, 57.9, 60.5, 175.9; \]

\[ \text{HRMS (ESI\textsuperscript{+}) Calcd for C}_{14}\text{H}_{20}\text{NO}_2 [M+H\textsuperscript{+}] 234.1489, Found 234.1490; \]

\[ \text{IR (neat cm}^{-1}\text{): 3367, 3292, 2974, 1728.} \]

3-Amino-2-(cuban-1-ylmethyl)propanoic acid (7)

To a solution of lithium hydroxide monohydrate (45.0 mg, 1.07 mmol) in water (0.20 mL) at 0 °C was added dropwise a solution of ethyl 3-amino-2-(cuban-1-ylmethyl)propanoate 20 (50.0 mg, 0.21 mmol) in THF (1.0 mL). The resulting mixture was stirred at room temperature over night. The reaction mixture was evaporated to dryness and redissolved in water (5 mL), and extracted with DCM (3 x 10 mL). The aqueous layer from the extraction was carefully acidified with 1M HCl to pH ~4, and then evaporated to dryness. The crude product was redissolved in DCM/MeOH, the solids were filtered off and the solution was concentrated under reduced pressure to give crude racemic 3-amino-2-(cuban-1-ylmethyl)propanoic acid 7 (43.0 mg, 98%) as a white powder.

\[ \text{m.p.: 121.0-130.0 °C (browned without melting)}; \]

\[ \text{1H NMR (500 MHz, MeOD) } \delta 1.92 (dd, J = 6.1, 14.5 Hz, 1H), 2.03 (dd, J = 7.9, 14.5 Hz, 1H), 2.79 – 2.87 (m, 1H), 3.02 (dd, J = 4.4, 12.9 Hz, 1H), 3.18 (dd, J = 9.4, 12.9 Hz, 1H), 3.8 – 3.86 (m, 3H), 3.88 – 3.93 (m, 3H), 4.02 – 4.07 (m, 1H); \]

\[ \text{13C NMR (126 MHz, MeOD) } \delta 34.5, 41.4, 42.0, 45.3, 49.4 (obscured by MeOD, taken from HSQC spectrum in MeOD), 50.1, 58.7, 176.8; \]

\[ \text{HRMS (ESI\textsuperscript{+}) Calcd for C}_{12}\text{H}_{17}\text{NO}_2 [M+H\textsuperscript{+}] 206.1176, Found 206.1177; \]

\[ \text{IR (neat cm}^{-1}\text{): 3427, 2970, 2893, 1714.} \]

(E)-tert-Butyl 3-(cuban-1-yl)acrylate (22)

To a stirred solution of tert-butyl 2-(diethoxyphosphoryl)acetate 21 (0.960 mL, 1.031 g, 4.09 mmol), lithium chloride (0.577 g, 13.62 mmol) and diisopropylethyl amine (0.593 mL, 3.40 mmol) in acetonitrile (2.0 mL) was
added cubane-1-carbaldehyde 14 (0.450 g, 3.40 mmol) in acetonitrile (2.0 mL) at room temperature over a period of 10 minutes. The resulting solution was stirred at room temperature for 5 h. The reaction mixture was quenched with water (20 mL), extracted with Et₂O (3 x 20 mL), the organic layer was dried (MgSO₄), filtered and evaporated to afford yellow residue. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in heptane. Pure fractions were evaporated to dryness to afford (E)-tert-butyl 3-(cuban-1-yl)acrylate 22 (0.620 g, 79 %) as a white solid.

m.p.: 121.0-122.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.49 (s, 9H), 3.91 – 3.97 (m, 3H), 4.02 – 4.08 (m, 4H), 5.60 (d,  J = 15.5 Hz, 1H), 7.06 (d,  J = 15.5 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 28.3, 44.5, 48.6, 50.2, 58.5, 80.1, 120.1, 146.3, 166.6; HRMS (ESI⁺) Calcd for C₁₁H₁₀O₂ [M-C₄H₈]+ 174.0675, Found 174.0685; IR (neat cm⁻¹): 2978, 1711, 1637.

(R)-tert-Butyl 3-(cuban-1-yl)-3-(dibenzylamino)propanoate (23)

To a solution of dibenzylamine (0.281 mL, 0.288 g, 1.46 mmol) in THF (8.0 mL) cooled to -78 °C was added n-butyllithium (0.883 mL, 1.41 mmol, 1.6 M) over a period of 5 minutes under nitrogen, (E)-tert-butyl 3-(cuban-1-yl)acrylate 22 (0.210 g, 0.91 mmol) was added after 30 min in THF (8.0 mL). The resulting solution was stirred at -78 °C for 4 h. The reaction mixture was poured onto saturated NH₄Cl (50 mL), extracted with EtOAc (3 x 50 mL), the organic layer was dried (MgSO₄), filtered and evaporated to afford a yellow residue. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in heptane. Pure fractions were evaporated to dryness to afford tert-butyl 3-(cuban-1-yl)-3-(dibenzylamino)propanoate 23 (0.270 g, 69 %) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) 1.45 (s, 9H), 2.25 (dd,  J = 7.0, 13.9 Hz, 1H), 2.60 (dd,  J = 6.0, 13.9 Hz, 1H), 3.33 (t,  J = 6.5 Hz, 1H), 3.54 (d,  J = 13.7 Hz, 2H), 3.69 (d,  J = 13.6 Hz, 2H), 3.85 - 3.93 (m, 3H), 3.94 - 4.02 (m, 4H), 7.20 (dd,  J = 5.9, 8.5 Hz, 2H), 7.24 - 7.3 (m, 4H), 7.33 (d,  J = 7.0 Hz, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 28.3, 32.2, 44.5, 47.6, 48.4, 52.0, 55.5, 61.8, 80.4, 126.9, 128.2, 129.1, 140.4, 172.6; HRMS (ESI⁺) Calcd for C₂₉H₃₄N₂O₂ [M+H]⁺ 428.2584, Found 428.2587; IR (neat cm⁻¹): 2976, 1726, 1151.

References

$^1$H and $^{13}$C NMR Spectra

1H NMR (400 MHz, CDCl$_3$)

13C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
**1H NMR (400 MHz, CDCl₃)**

![1H NMR Spectrum](image)

**13C NMR (101 MHz, CDCl₃)**

![13C NMR Spectrum](image)
[1H NMR (400 MHz, CDCl₃)  

[13C NMR (101 MHz, CDCl₃)  

[Chemical Structure 8]