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Synthesis of Novel Amino Acids Containing Cubane

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Contents

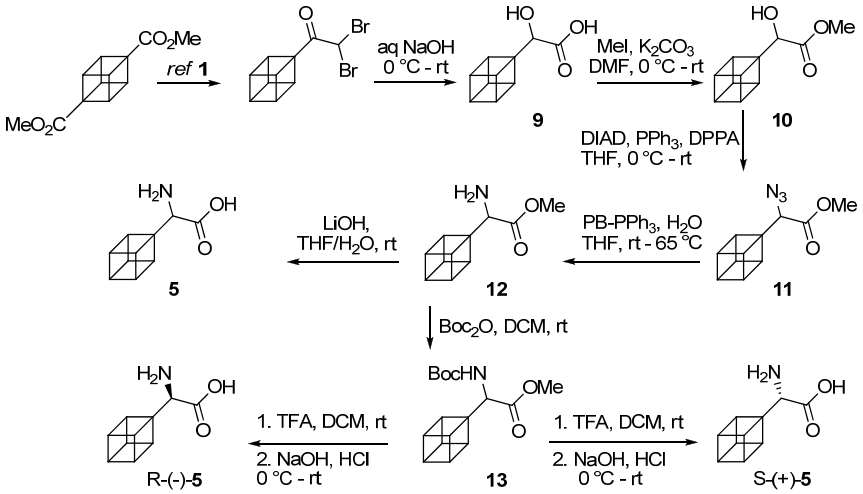
General Analytical Information

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.

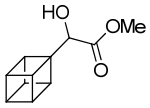
General Reagent Information

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[1] (**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

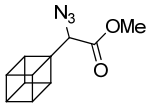


Methyl 2-(cuban-1-yl)-2-hydroxyacetate (10)



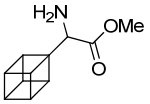
To a suspension of 2-(cuban-1-yl)-2-hydroxyacetic acid **9** (0.300 g, 1.68 mmol) and potassium carbonate (0.279 g, 2.02 mmol) in DMF (8.31 mL) was slowly added methyl iodide (0.105 mL, 0.240 g, 1.68 mmol). The resulting solution was stirred at room temperature for 2 h, when water was added and the reaction mixture was extracted with Et_2O (3 x 10 mL). The organic phase was dried ($MgSO_4$), 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; **^{1}H NMR** (400 MHz, $CDCl_3$) 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); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 44.5, 47.1, 48.7, 52.5, 58.3, 71.3, 173.9; **HRMS** (EI^+) Calcd for $C_{11}H_{12}O_3^+$ $[M]^+$ 192.0781, Found 192.0792; **IR** (neat cm^{-1}): 3467, 2980, 1736.

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



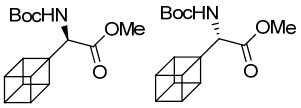
To a solution of triphenylphosphine (1.890 g, 7.21 mmol) in THF (15 mL) cooled to 0 °C, diisopropyl azodicarboxylate (1.420 mL, 1.985 g, 7.21 mmol) was added dropwise over a period of 5 minutes. The resulting slurry was stirred at 0 °C for 15 minutes before a solution of methyl 2-(cuban-1-yl)-2-hydroxyacetate **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.
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.93 - 3.99 (m, 3H), 4.01 (obscured s, 1H C*H*N_3), 4.01 – 4.04 (m, 1H), 4.04 – 4.08 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, 27 °C) δ 44.6, 48.1, 48.3, 52.4, 57.8, 62.9, 169.1; **HRMS** (EI^+) Calcd for $C_{11}H_{11}N_3O_2$ $[M\text{-}N_2]^+$ 189.0784, Found 189.0796; **IR** (neat cm^{-1}): 2985, 2102, 1743.

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.
^{1}H NMR (400 MHz, $CDCl_3$) δ 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 NMR** (101 MHz, $CDCl_3$) δ 44.2, 47.1, 48.7, 51.8, 56.0, 59.2, 174.2; **HRMS** (ESI^+) Calcd for $C_{11}H_{14}NO_2$ $[M+H]^+$ 192.1019, Found 192.1025; **IR** (neat cm^{-1}): 3583, 3184, 2978, 1738, 1660.

(*R*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(cuban-1-yl)acetate (13)
(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(cuban-1-yl)acetate (13)

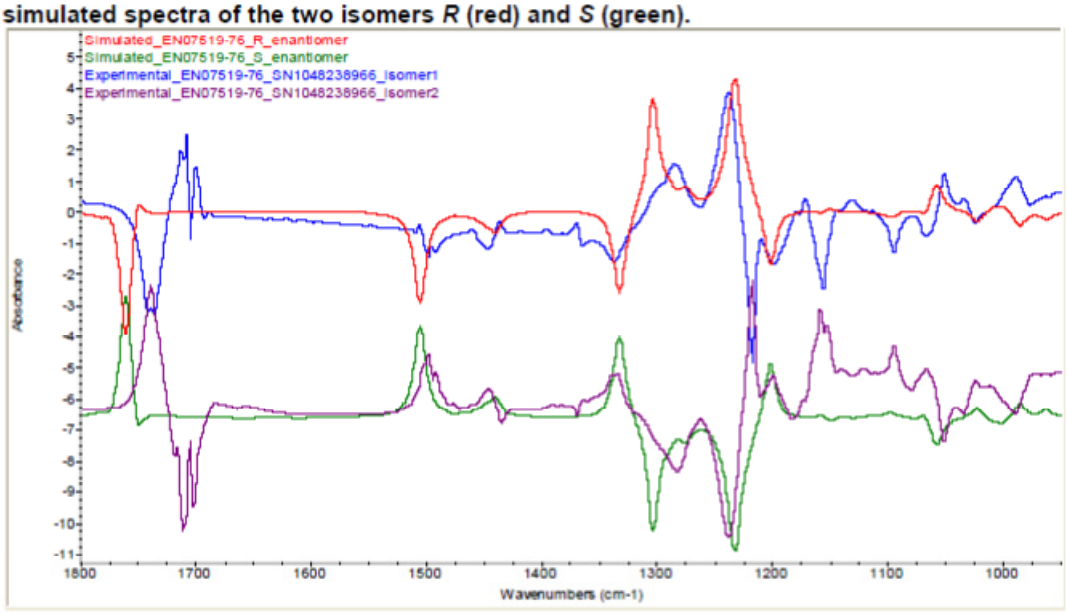


To a solution of methyl 2-amino-2-(cuban-1-yl)acetate **12** (0.550 g, 2.88 mmol) in DCM (5 mL) was added Boc_2O (0.67 mL, 0.628 g, 2.88 mmol) in DCM (5 mL) and the reaction was stirred at room temperature for 5 h. The reaction mixture was diluted with DCM (10 mL) and 1 M citric acid (5 mL) was added. The aqueous layer was separated and washed with DCM (10 mL). The combined organic extracts were dried (Na_2SO_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-((*tert*-butoxycarbonyl)amino)-2-(cuban-1-yl)acetate **13** (0.710 g, 85 %) as a white solid.
m.p.: 90.0-91.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, 27°C) δ 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 Hz, 1H), 4.97 (d, J = 5.6 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.4, 44.2, 47.3, 48.7, 52.1, 55.2, 57.7, 78.0, 155.8, 171.3; **HRMS** (ESI^+) Calcd for $C_{16}H_{22}NO_4$ 292.1543, Found 292.1542; **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 µm column with heptanes/IPA (80/20), 2 mL/min (1 x 10 µL injection); 1st enantiomer ret. time 2.87 min, 2nd enantiomer ret. time 4.46 min.

VCD:

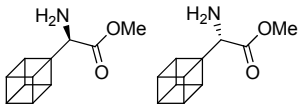
Figure 4. Experimental spectra of isomer 1 (blue) and isomer 2 (purple) of EN07519-76-1 and simulated spectra of the two isomers *R* (red) and *S* (green).



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

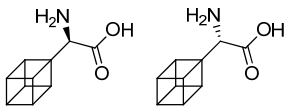
$[\alpha]_D^{22}$ -44.3 (*c* 2.03, EtOH) for *N*-Boc-(*R*)-cubane glycine methyl ester **13**; $[\alpha]_D^{22}$ +45.9 (*c* 2.18, EtOH) for *N*-Boc-(*S*)-cubane glycine methyl ester **13**.

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



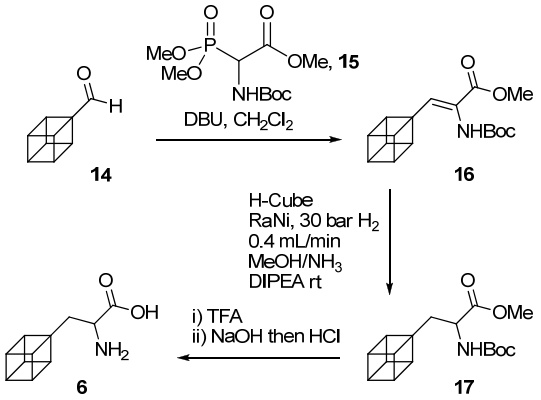
A solution of TFA (10% in DCM) (1.7 mL) was added to separate samples of (*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)-2-(cuban-1-yl)acetate **13** (0.05 g, 0.17 mmol) and (*S*)-methyl 2-((*tert*-butoxycarbonyl)-amino)-2-(cuban-1-yl)acetate **13** (0.05 g, 0.17 mmol) at room temperature. The resulting 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.
$[\alpha]_D^{23}$ -41.2 (*c* 1.7, EtOH) for *N*-(*R*)-cubane glycine methyl ester **12**; $[\alpha]_D^{23}$ +42.8 (*c* 2.8, 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)

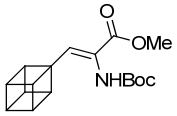


To two separate solutions of lithium hydroxide monohydrate (0.044 g, 1.05 mmol) in water (0.2 mL) at 0 °C was added dropwise a solution of (*R*)-methyl 2-amino-2-(cuban-1-yl)acetate **12** (0.017 g, 0.09 mmol) in THF (0.87 mL) and (*S*)-methyl 2-amino-2-(cuban-1-yl)acetate **12** (0.030 g, 0.16 mmol) 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 withouth melting); $[\alpha]_D^{24}$ -27.2 (*c* 1.84, MeOH) for (*R*)-cubane glycine **5**; $[\alpha]_D^{24}$ +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, 53.2, 54.9, 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.

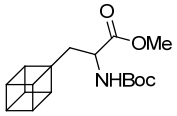


(*Z*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(cuban-1-yl)acrylate (16)



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_2O (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).[3]
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, CDCl3) 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.

(*R*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(cuban-1-yl)propanoate (17)
(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(cuban-1-yl)propanoate (17)



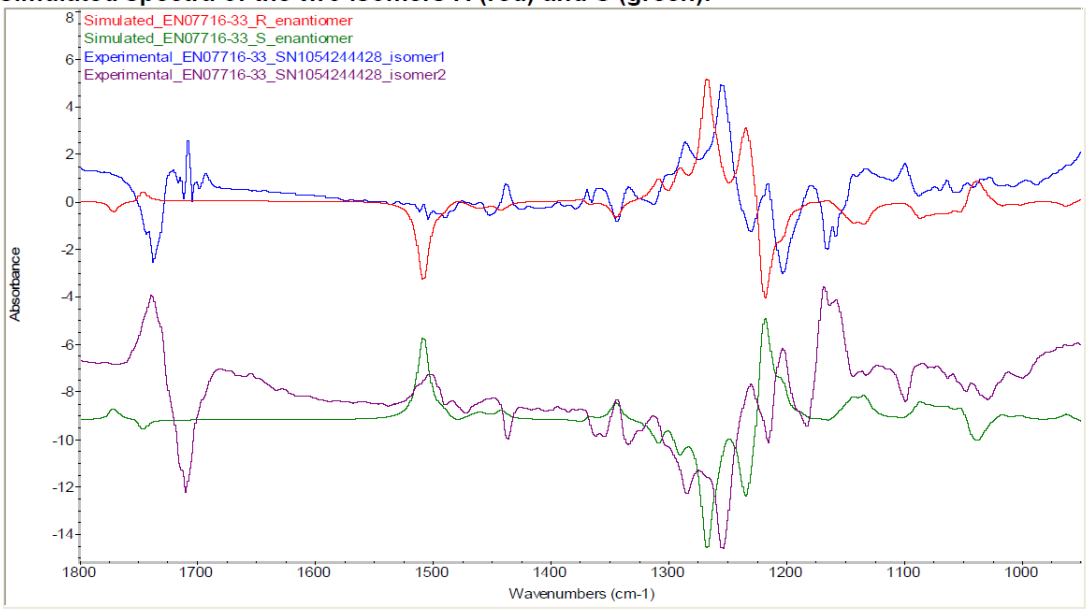
To a solution of (*Z*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(cuban-1-yl)acrylate **16** (0.100 g, 0.33 mmol) in 1 M NH_3 in methanol (6.0 mL) was added diisopropylethylamine (57.0 µL, 0.043 g, 0.33 mmol) and the reaction mixture was hydrogenated in the H-Cube hydrogenation cell at room temperature, 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), 1st enantiomer ret. time 2.86 min, 2nd enantiomer ret. time 4.46 min.

VCD:

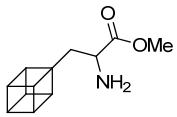
Figure 4. Experimental spectra of isomer 1 (blue) and isomer 2 (purple) of EN07716-33-1 and simulated spectra of the two isomers *R* (red) and *S* (green).



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**.

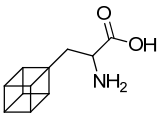
Methyl 2-amino-3-(cuban-1-yl)propanoate



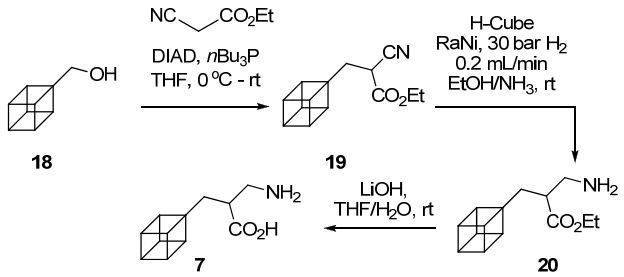
A solution of TFA (10% in DCM) (3.90 mL) was added to methyl 2-((*tert*-butoxycarbonyl)amino)-3-(cuban-1-yl)propanoate **17** (0.120 g, 0.39 mmol) at room temperature. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and diluted with DCM (5.0 mL), 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.

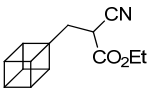
2-Amino-3-(cuban-1-yl)propanoic acid (6)



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 over night. 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; **^{1}H NMR** (400 MHz, MeOD) δ 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); **^{13}C NMR** (101 MHz, D_2O, 30 °C) δ 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.

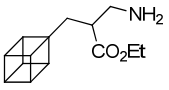


Ethyl 3-(cuban-1-yl)-2-cyanopropanoate (19)



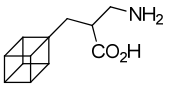
To a solution of tributylphosphine (2.05 mL, 1.66 g, 8.20 mmol) in THF (10.0 mL) was added diisopropyl azodicarboxylate (1.61 mL, 1.66 g, 8.20 mmol) cooled to 0 °C over a period of 5 minutes under nitrogen. The resulting slurry was stirred at 0 °C for 30 minutes before a solution of ethyl 2-cyanoacetate (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 over night. 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.
^{1}H NMR (400 MHz, $CDCl_3$) δ 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); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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)

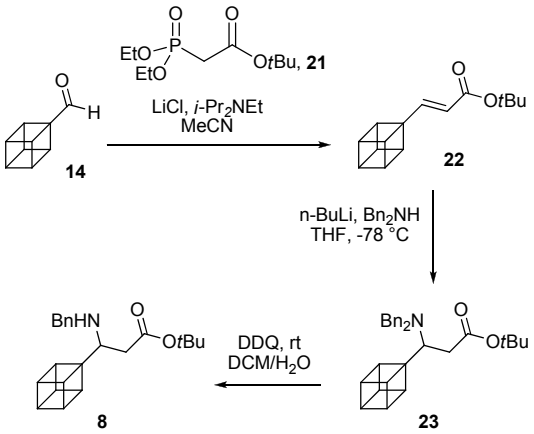


A solution of ethyl 3-(cuban-1-yl)-2-cyanopropanoate **19** (0.150 g, 0.65 mmol) in 1 M NH_3 in EtOH (65.0 mL) at room temperature was hydrogenated in the H-Cube hydrogenation cell using a 30 mm RaNi cartridge, a flow rate of 0.2 mL/min, under pressure regulator set to 20 with the effective H_2 pressure 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 NH_3 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.
^{1}H NMR (400 MHz, $CDCl_3$) δ 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* = 8.7, 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); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.3, 33.7, 44.3, 44.6, 45.8, 48.4, 48.9, 57.9, 60.5, 175.9; **HRMS** (ESI^+) Calcd for $C_{14}H_{20}NO_2$ $[M+H]^+$ 234.1489, Found 234.1490; **IR** (neat cm^{-1}): 3367, 3292, 2974,1728.

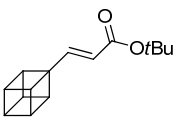
3-Amino-2-(cuban-1-ylmethyl)propanoic acid (7)



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.
m.p.: 121.0-130.0 °C (browned withouth melting); **^{1}H NMR** (500 MHz, MeOD) δ 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); **^{13}C NMR** (126 MHz, MeOD) δ 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; **HRMS** (ESI^+) Calcd for $C_{12}H_{17}NO_2$ $[M+H]^+$ 206.1176, Found 206.1177; **IR** (neat cm^{-1}): 3427, 2970, 2893, 1714.



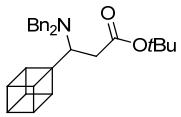
(*E*)-*tert*-Butyl 3-(cuban-1-yl)acrylate (22)



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

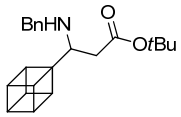
added cubane-1-carbaldehyde **14** (0.450 g, 3.40 mmol) in acetonitrile (2.0 mL) at room temperature over a period of 10 minutes. The resulting solution was stirred at room temperature for 5 h. The reaction mixture was quenched with water (20 mL), extracted with Et_2O (3 x 20 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated to afford yellow residue. The crude product was purified by flash silica chromatography, elution gradient 0 to 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; **^{1}H NMR** (400 MHz, $CDCl_3$) 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); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.3, 44.5, 48.6, 50.2, 58.5, 80.1, 120.1, 146.3, 166.6; **HRMS** (EI^+) Calcd for $C_{11}H_{10}O_2$ $[M\text{-}C_4H_8]^+$ 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 NH_4Cl (50 mL), extracted with EtOAc (3 x 50 mL), the organic layer was dried ($MgSO_4$), 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.
^{1}H NMR (400 MHz, $CDCl_3$) 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); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.3, 32.2, 44.5, 48.0, 48.8, 55.1, 57.1, 62.5, 80.4, 126.9, 128.2, 129.1, 140.4, 172.6; **HRMS** (ESI^+) Calcd for $C_{29}H_{34}NO_2$ $[M+H]^+$ 428.2584, Found 428.2587; **IR** (neat cm^{-1}): 2976, 1724, 1365, 1153.

***tert*-Butyl 3-(benzylamino)-3-(cuban-1-yl)propanoate (8)**



To a solution of *tert*-butyl 3-(cuban-1-yl)-3-(dibenzylamino)propanoate **23** (0.100 g, 0.23 mmol) in DCM/water (4.4 mL 10:1) at room temperature was added DDQ (0.064 g, 0.28 mmol) portionwise. The resulting solution was stirred at room temperature until consumption of starting material (TLC). The reaction mixture was poured onto saturated $NaHCO_3$ (10 mL), extracted with DCM (3 x 10 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated to afford a deep red 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 *tert*-butyl 3-(benzylamino)-3-(cuban-1-yl)propanoate **8** (0.065 g, 82 %) as a light pink oil.
^{1}H NMR (400 MHz, $CDCl_3$) 1.46 (s, 9H), 2.29 (dd, *J* = 7.6, 14.8 Hz, 1H), 2.36 (dd, *J* = 5.0, 14.8 Hz, 1H), 3.28 (dd, *J* = 5.0, 7.6 Hz, 1H), 3.81 (s, 2H), 3.86 – 3.96 (m, 6H), 3.97 – 4.05 (m, 1H), 7.2 – 7.26 (m, 1H), 7.28 – 7.36 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.3, 36.4, 44.4, 47.6, 48.4, 52.0, 55.5, 61.8, 80.5, 126.9, 128.2, 128.4, 141.1, 172.4; **HRMS** (ESI^+) Calcd for $C_{22}H_{28}NO_2$ $[M+H]^+$ 338.2115, Found 338.2117; **IR** (neat cm^{-1}): 3333, 2976, 1726, 1151.

References

[1] J. Wlochal, R. D. Davies and J. Burton, *Org Lett*, 2014, **16**, 4094-4097
[2] R. B. Silverman, J. P. Zhou and P. E. Eaton, *J. Am. Chem. Soc.*, 1993, **115**, 8841-8842
[3] Q. I. Churches, R. J. Mulder, J. M. White, J. Tsanaktsidis and P. J. Duggan, *Aust. J. Chem.*, 2012, **65**, 690-693

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

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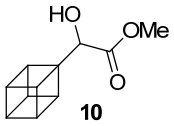

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^{1}H NMR (400 MHz, $CDCl_3$)

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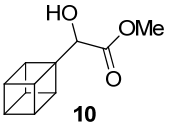

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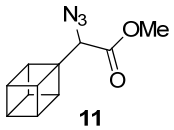

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^{1}H NMR (400 MHz, $CDCl_3$)

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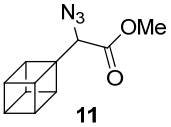

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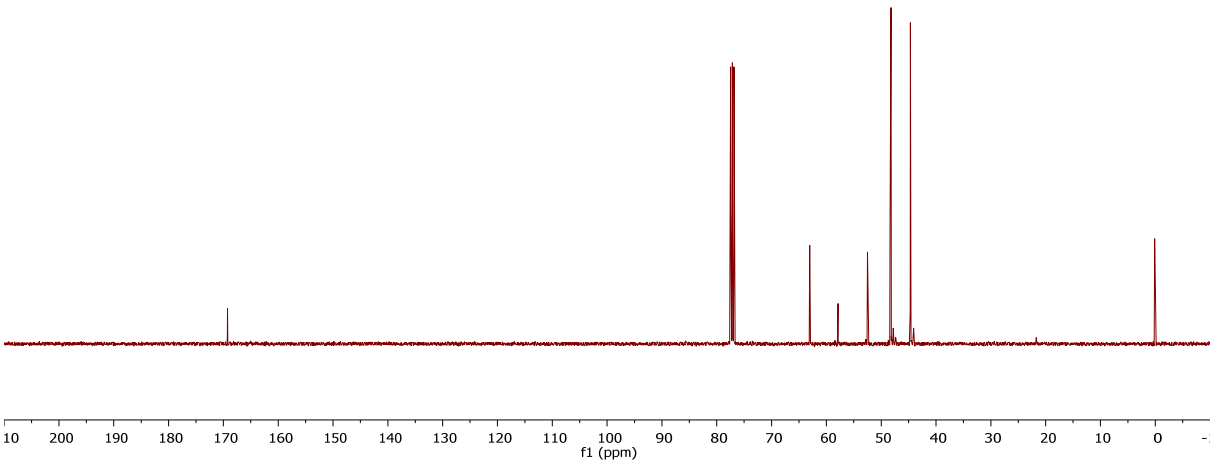

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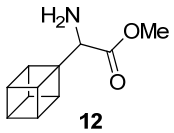
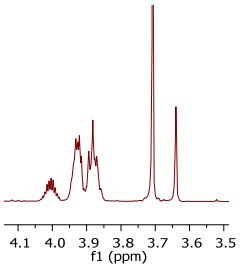
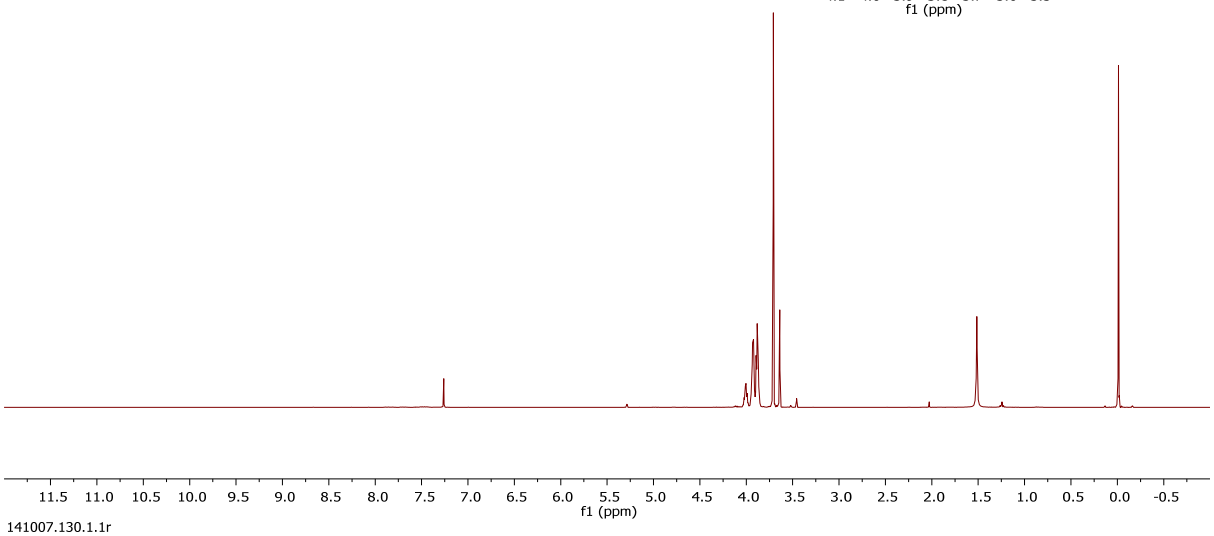


12

^{1}H NMR (400 MHz, $CDCl_3$)





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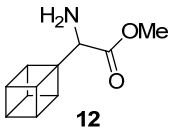

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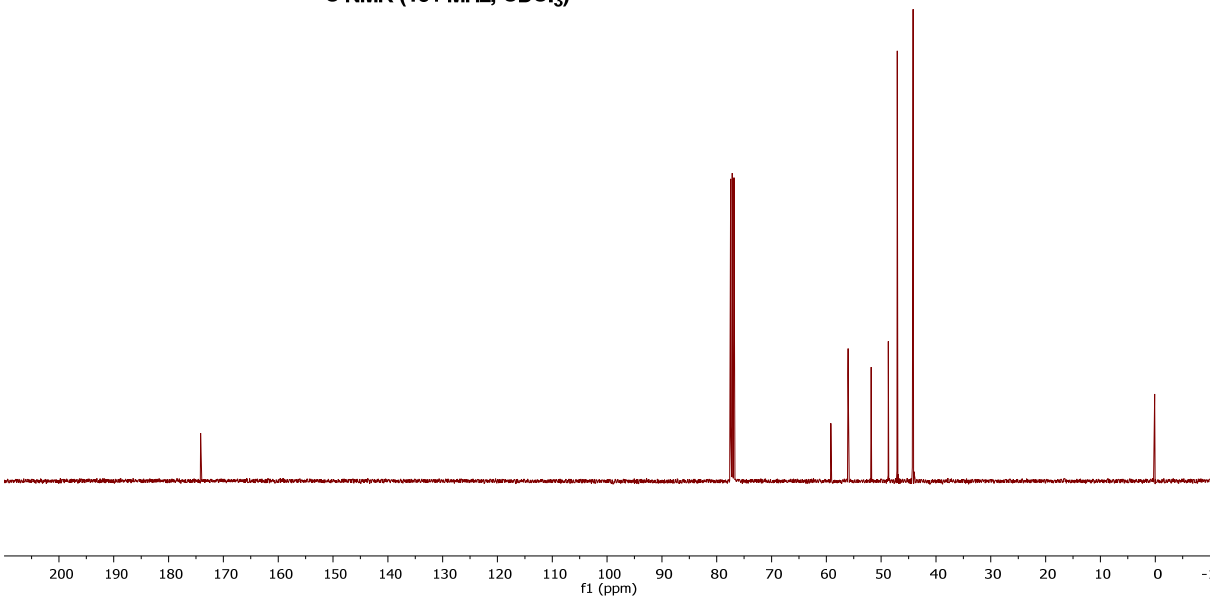
^{13}C NMR (101 MHz, $CDCl_3$)



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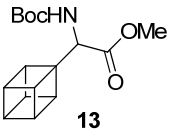

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^{1}H NMR (400 MHz, $CDCl_3$)

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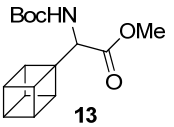

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^{13}C NMR (101 MHz, $CDCl_3$)

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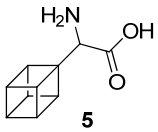
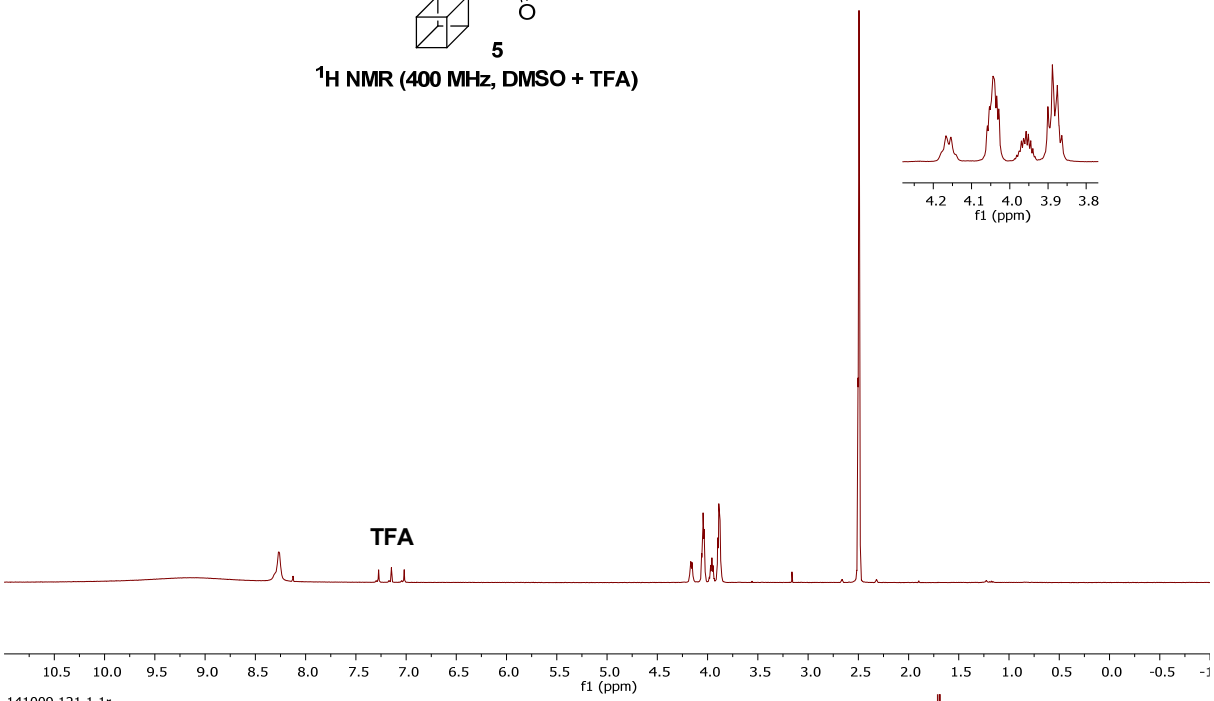


5

^{1}H NMR (400 MHz, DMSO + TFA)



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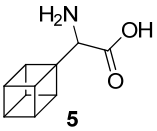

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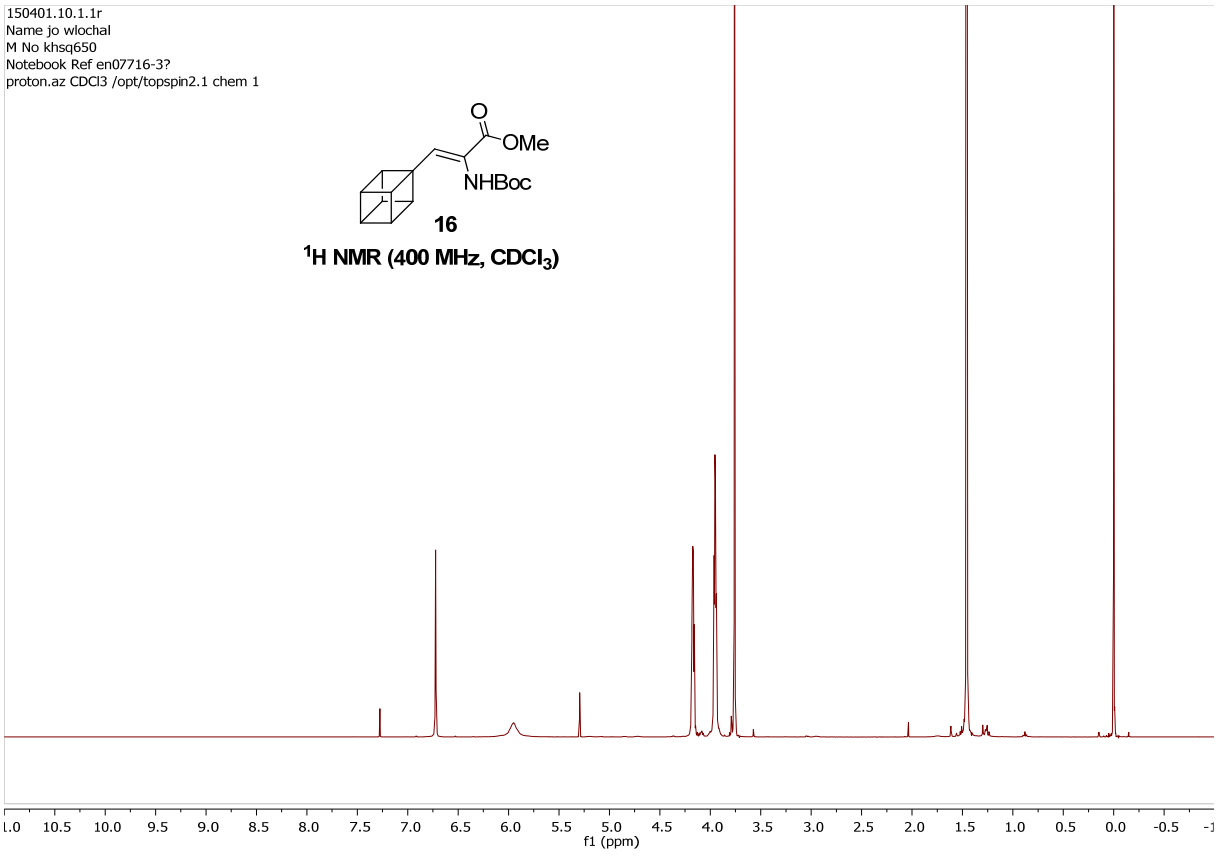
^{13}C NMR (101 MHz, DMSO + TFA)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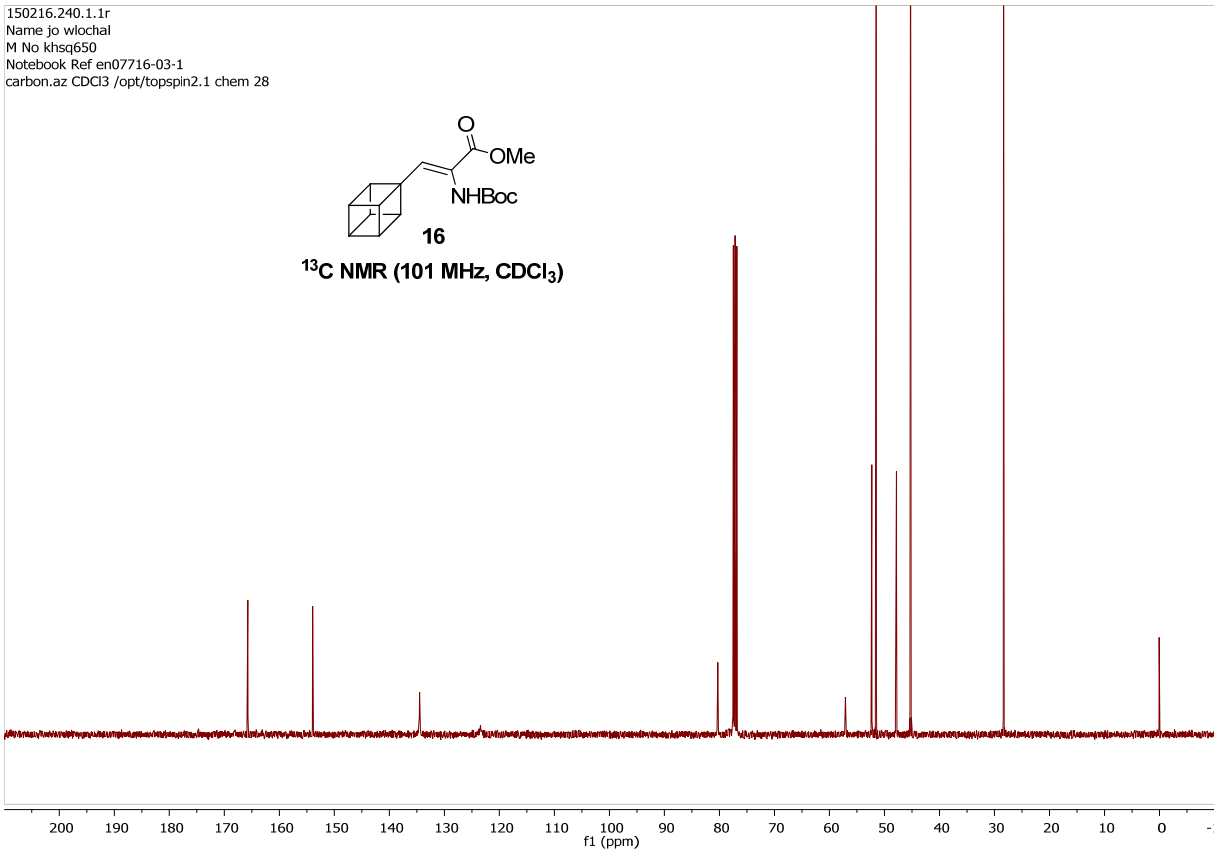
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f1 (ppm)

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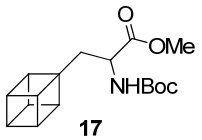

17

^{1}H NMR (700 MHz, $CDCl_3$)

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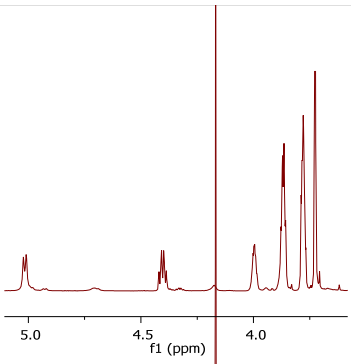
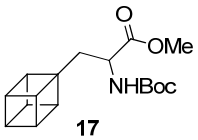


EN07716-33.4.1.1r
Name J Wlochal
M No
Notebook Ref EN07716-33-1st eluted
Experiment proton.c
Solvent CDCl3@285K
AV700
08/05/15

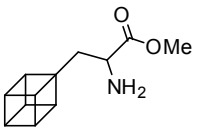


17

^{13}C NMR (176 MHz, $CDCl_3$)

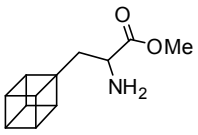
1st eluted

150506.230.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07716-39-1
proton.az CDCl3 /opt/topspin2.1 chem 56

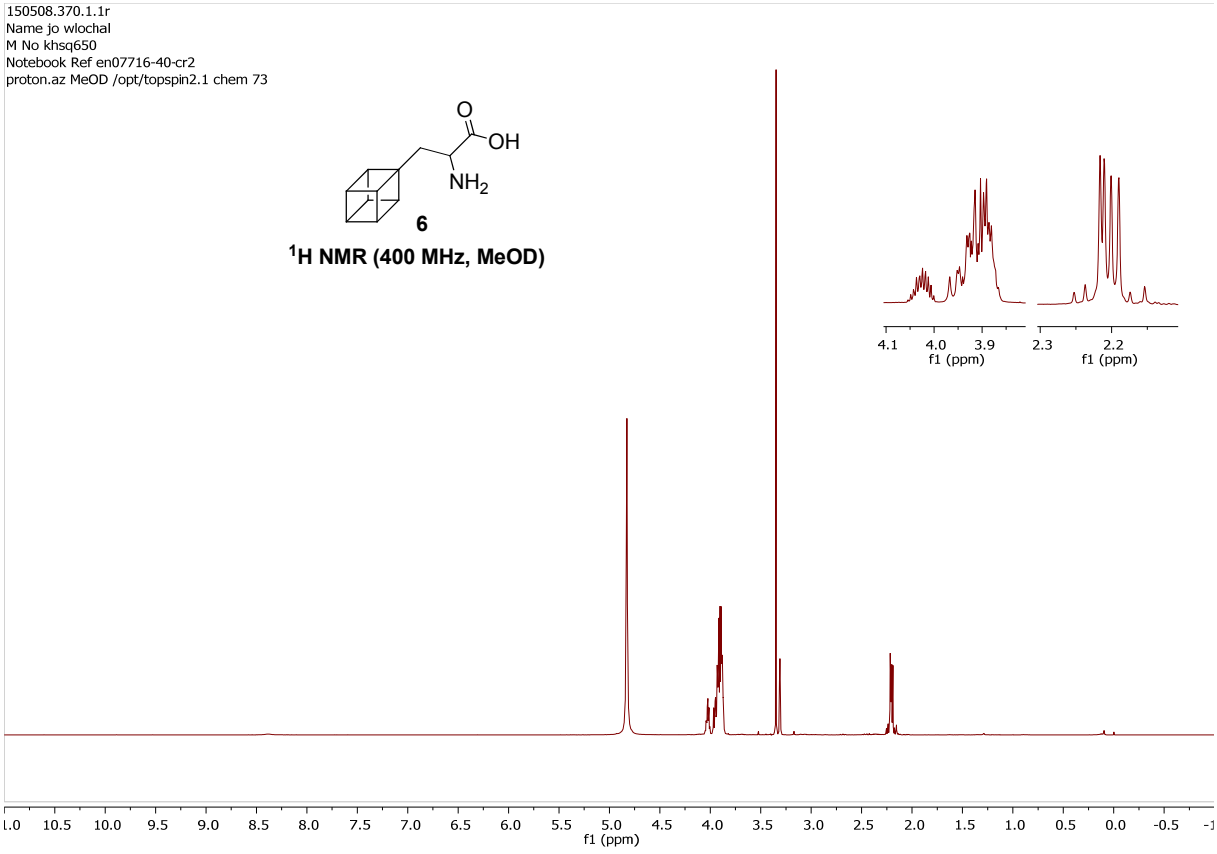


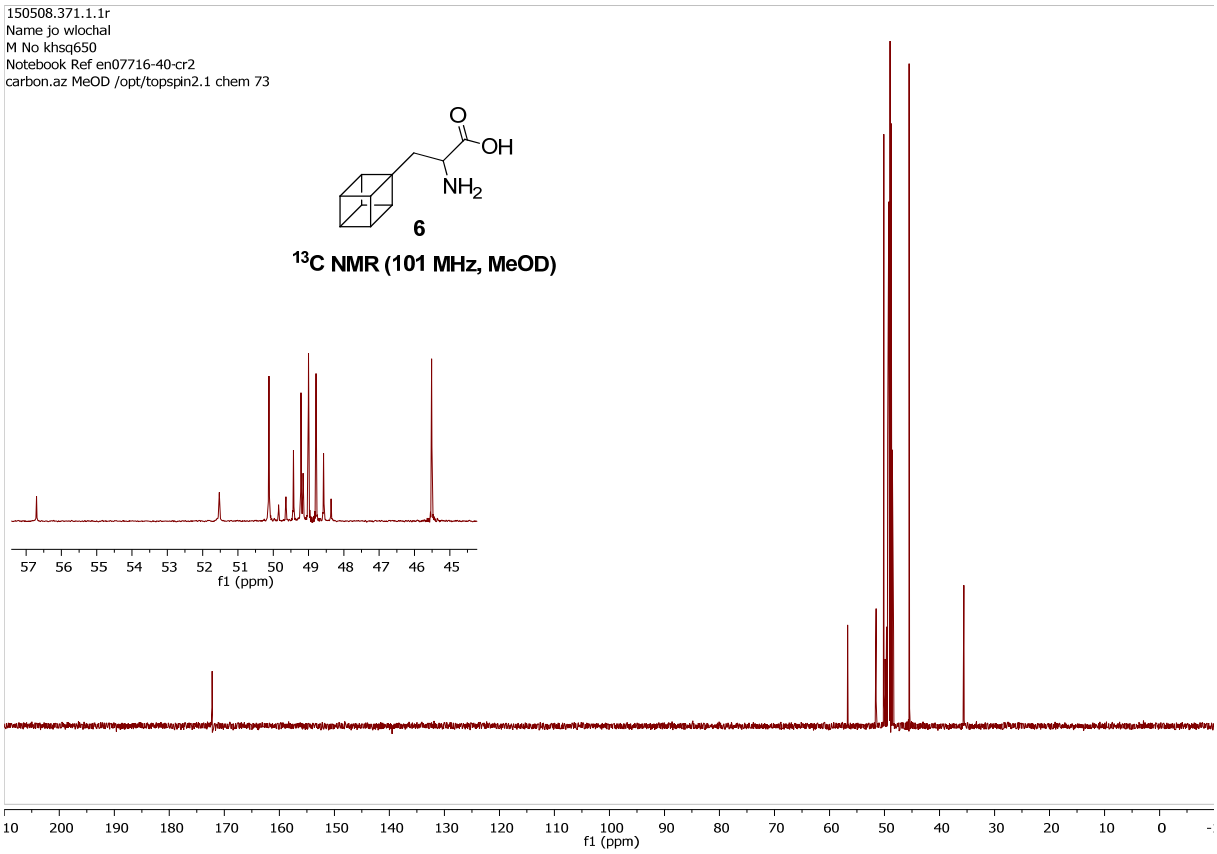
^{1}H NMR (400 MHz, $CDCl_3$)

150506.231.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07716-39-1
carbon.az CDCl3 /opt/topspin2.1 chem 56

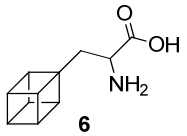


^{13}C NMR (101 MHz, $CDCl_3$)


150508.370.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07716-40-cr2
proton.az MeOD /opt/topspin2.1 chem 73
O
OH
NH2
6
1H NMR (400 MHz, MeOD)
4.1 4.0 3.9
f1 (ppm)
2.3 2.2
f1 (ppm)
f1 (ppm)


150508.371.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07716-40-cr2
carbon.az MeOD /opt/topspin2.1 chem 73
O
OH
NH2
6
13C NMR (101 MHz, MeOD)
57 56 55 54 53 52 51 50 49 48 47 46 45
f1 (ppm)
f1 (ppm)

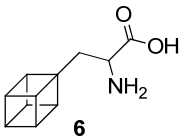
150511.260.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07716-40-1
proton.az D2O /opt/topspin2.1 chem 48



6

^{1}H NMR (400 MHz, D_2O)

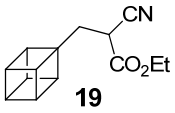
150511.261.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07716-40-1
carbon.az D2O /opt/topspin2.1 chem 48



6

^{13}C NMR (101 MHz, D_2O)

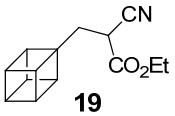
141009.230.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-19-1
proton.az CDCl3 /opt/topspin2.1 chem 38



19

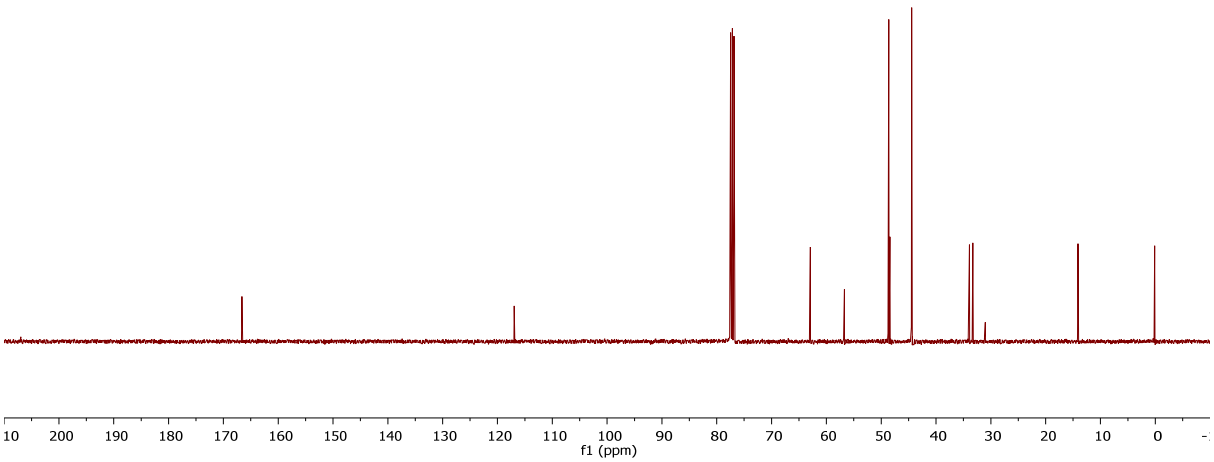
^{1}H NMR (400 MHz, $CDCl_3$)

141009.231.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-19-1
carbon.az CDCl3 /opt/topspin2.1 chem 38

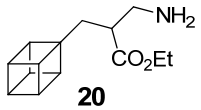


19

^{13}C NMR (101 MHz, $CDCl_3$)

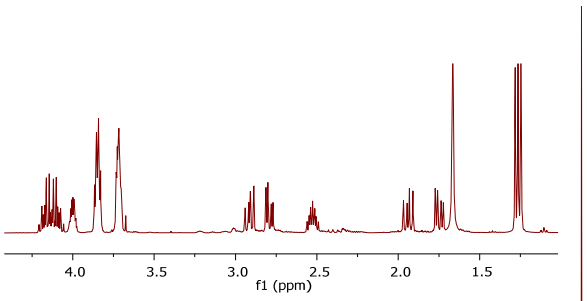


141016.20.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-42-1
proton.az CDCl3 /opt/topspin2.1 chem 5

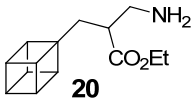


20

^{1}H NMR (400 MHz, $CDCl_3$)

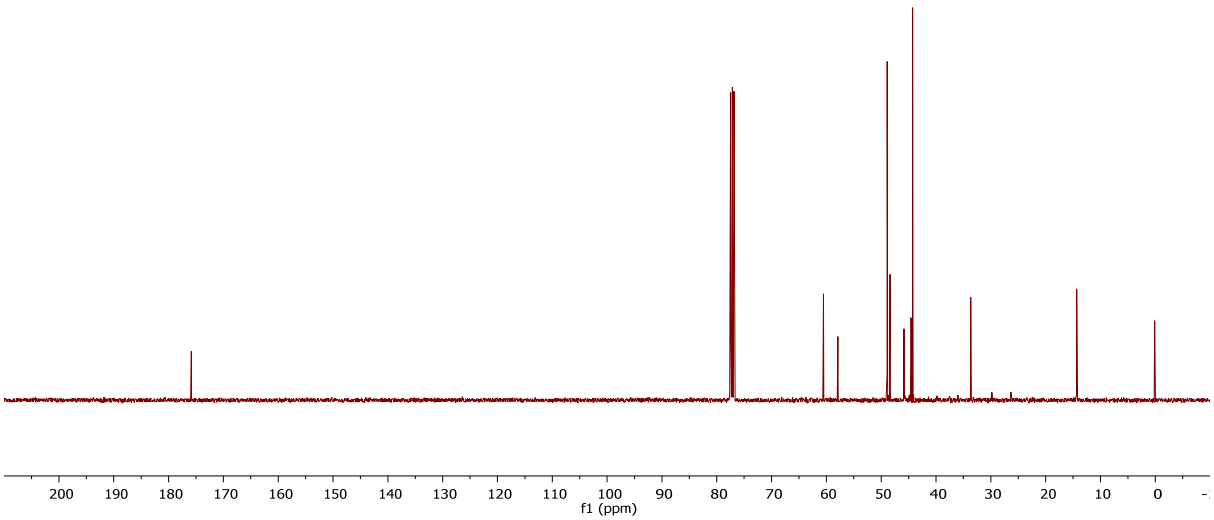


141016.100.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-42-1
carbon.az CDCl3 /opt/topspin2.1 chem 15

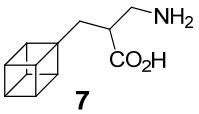


20

^{13}C NMR (101 MHz, $CDCl_3$)

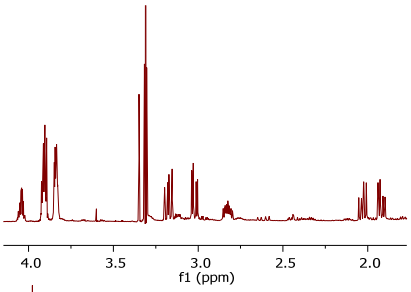


Jul07-2015.160.1.1r
Name jo wlochal
M/PRID No khsq650
Notebook Ref en07716-43-1
proton128p.q MeOD /opt/topspin routine2015 35

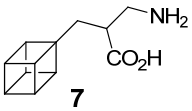


7

^{1}H NMR (500 MHz, MeOD)

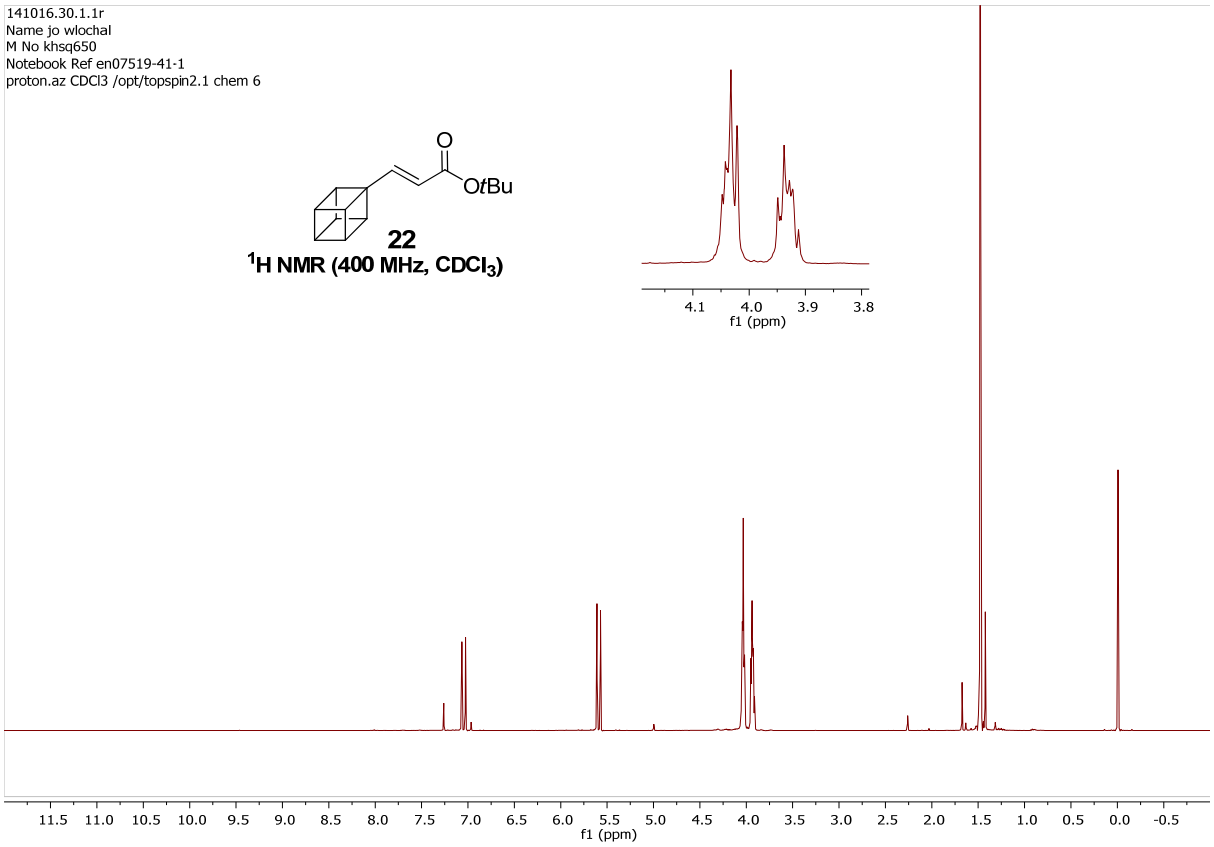


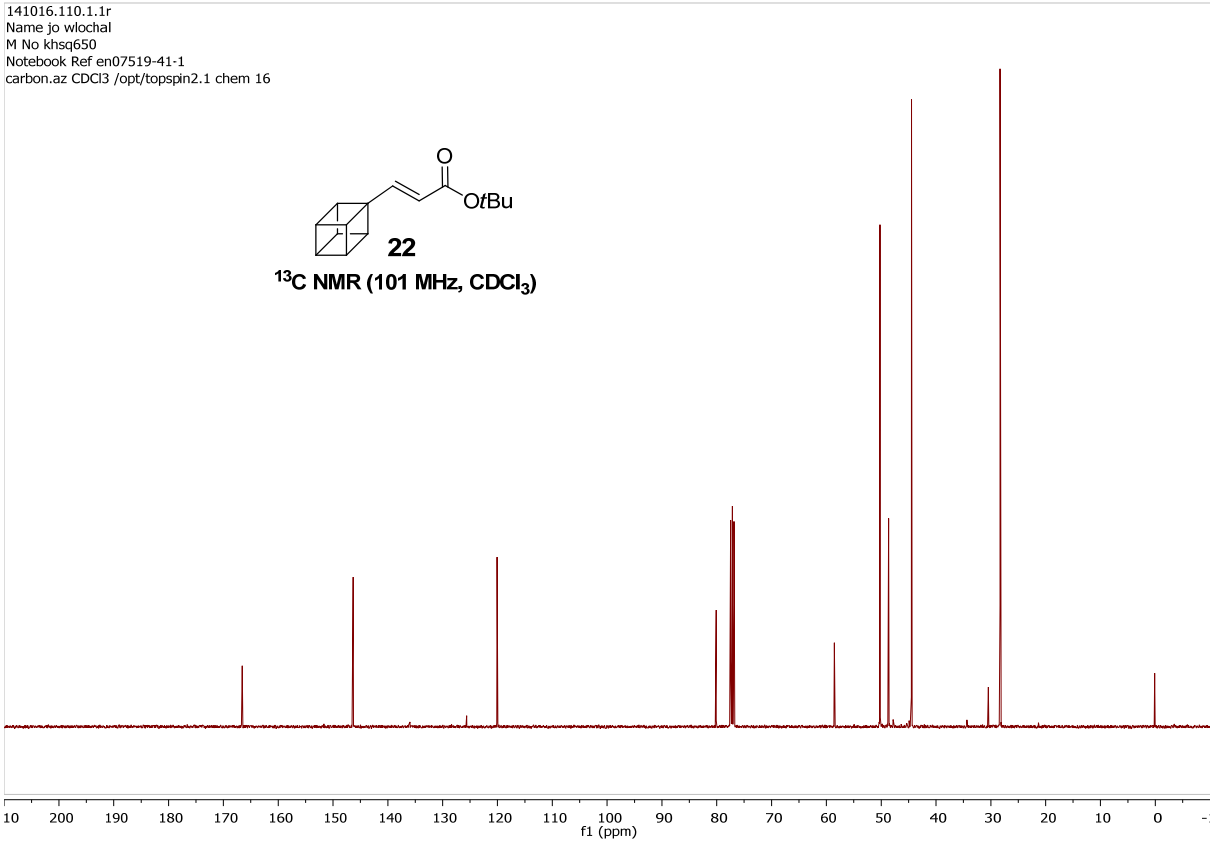
Jul07-2015.161.1.1r
Name jo wlochal
M/PRID No khsq650
Notebook Ref en07716-43-1
c13cpd.q MeOD /opt/topspin routine2015 35

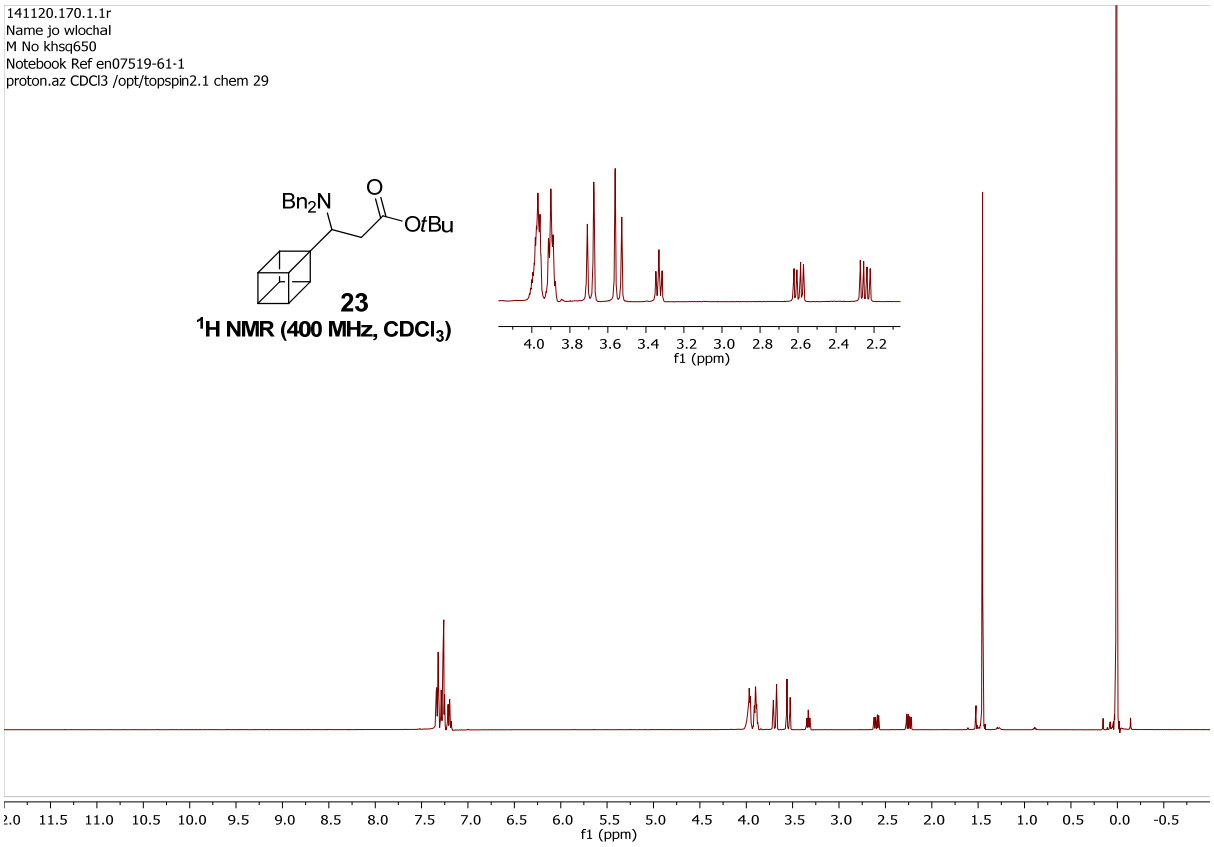


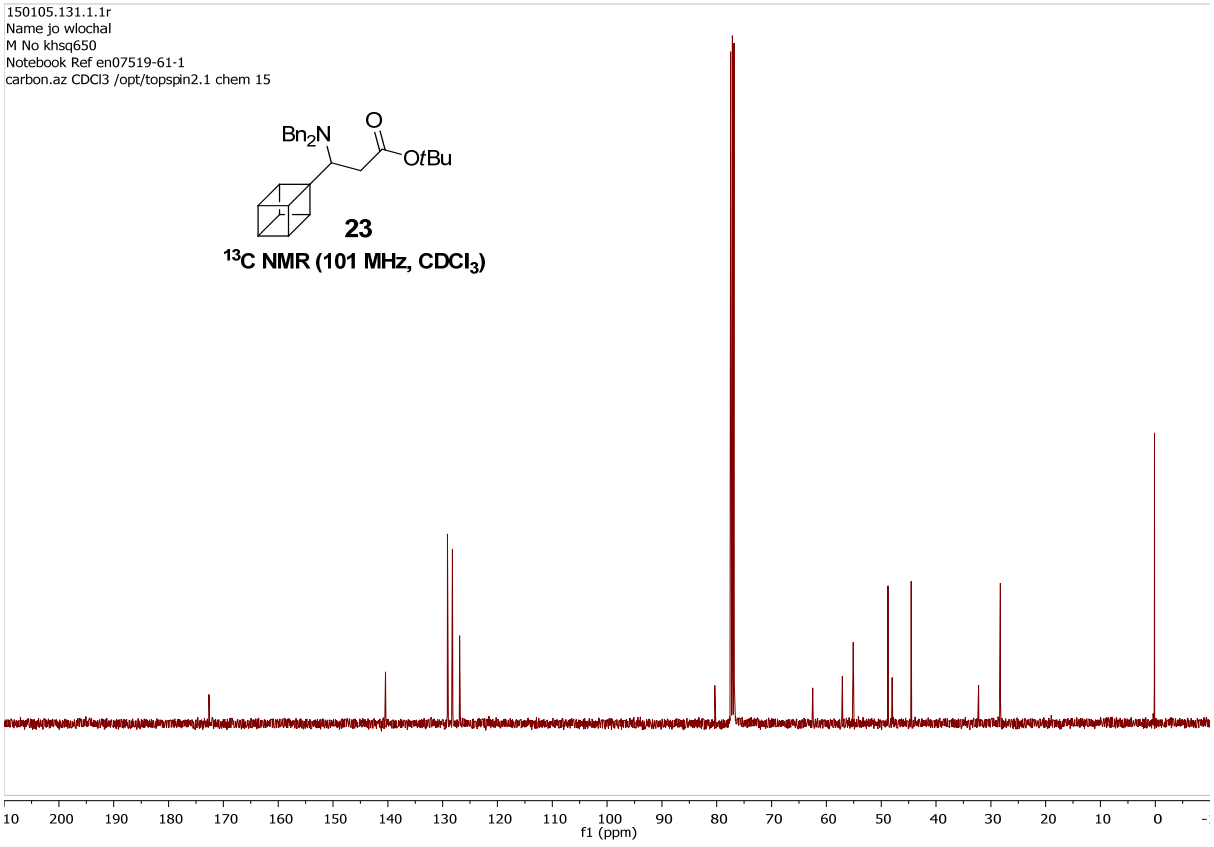
7

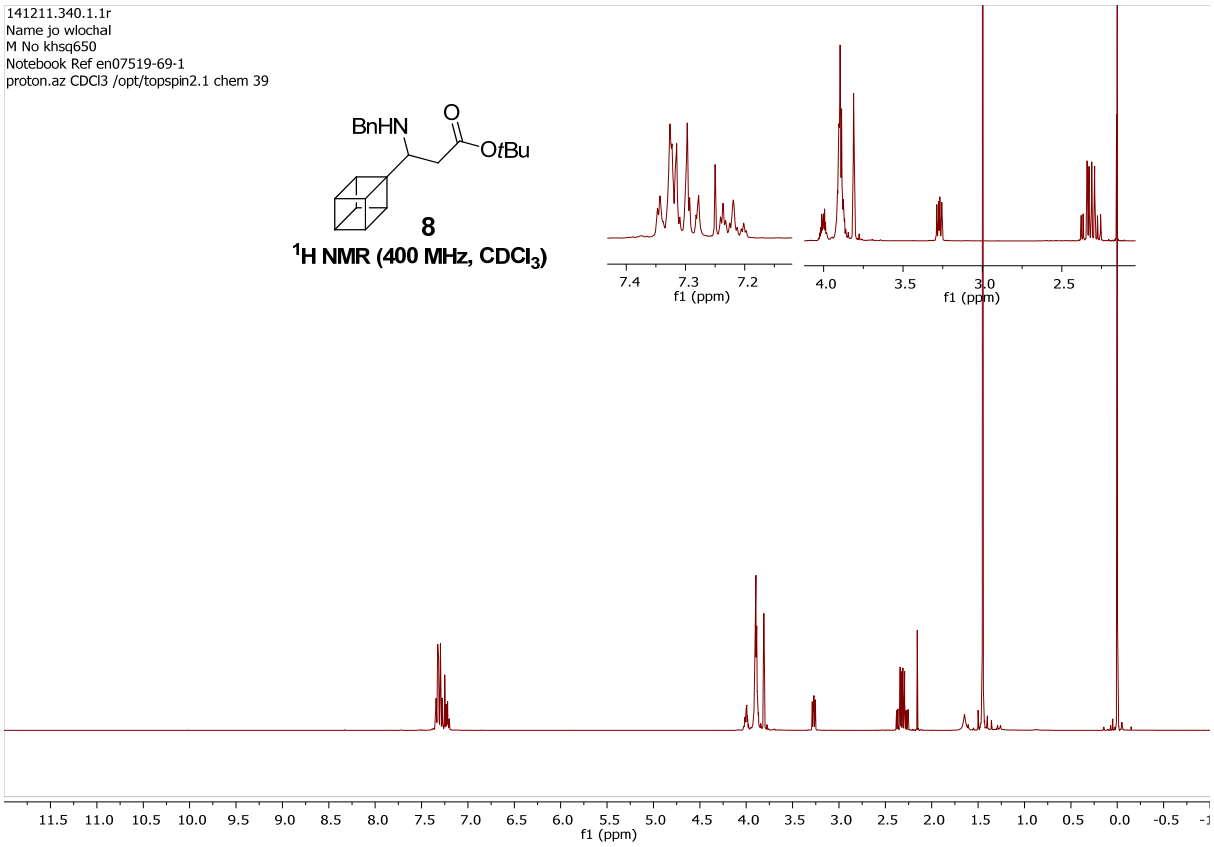
^{13}C NMR (126 MHz, MeOD)

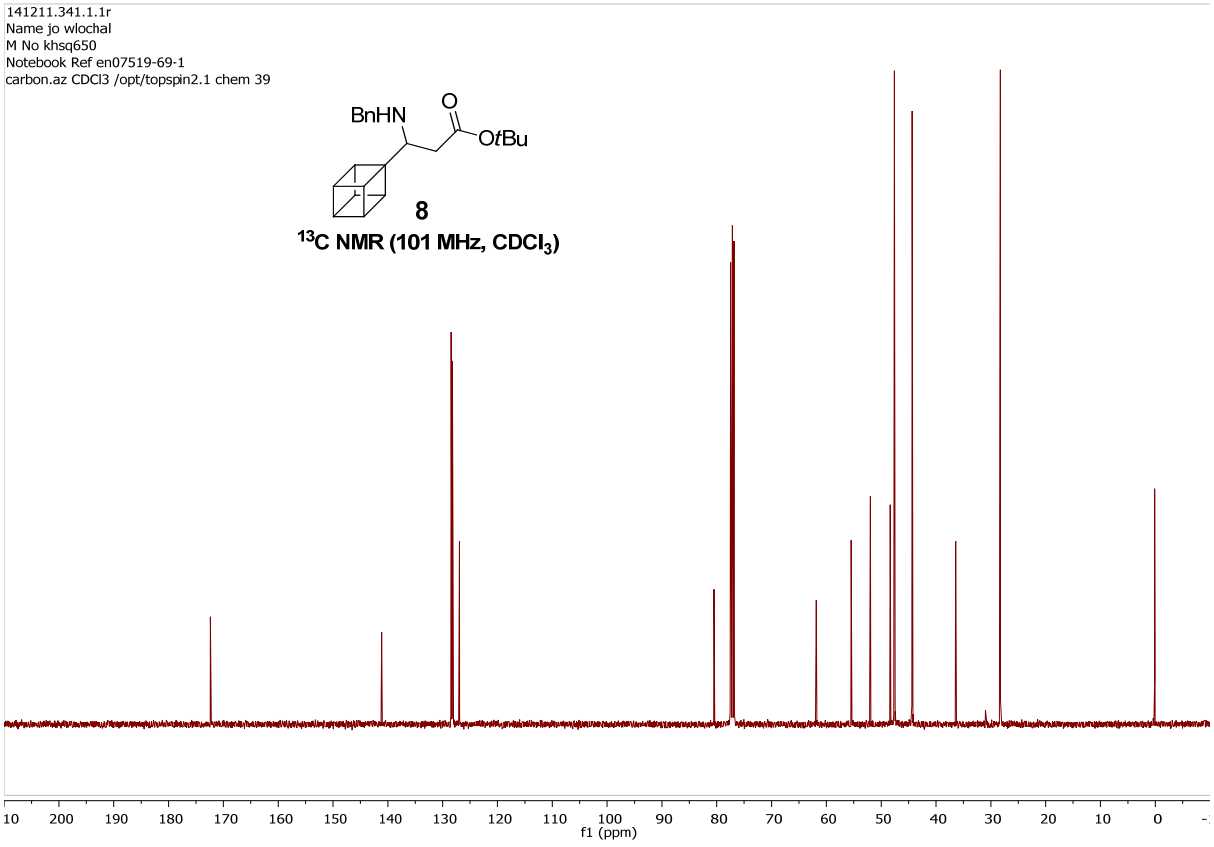

141016.30.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-41-1
proton.az CDCl3 /opt/topspin2.1 chem 6
OtBu
22
1H NMR (400 MHz, CDCl3)
4.1
4.0
3.9
3.8
f1 (ppm)
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


141016.110.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-41-1
carbon.az CDCl3 /opt/topspin2.1 chem 16
OtBu
22
13C NMR (101 MHz, CDCl3)
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


141120.170.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-61-1
proton.az CDCl3 /opt/topspin2.1 chem 29
Bn2N
O
OtBu
23
1H NMR (400 MHz, CDCl3)
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2
f1 (ppm)
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


150105.131.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-61-1
carbon.az CDCl3 /opt/topspin2.1 chem 15
Bn2N
O
OtBu
23
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


141211.340.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-69-1
proton.az CDCl3 /opt/topspin2.1 chem 39
BnHN
O
OtBu
8
1H NMR (400 MHz, CDCl3)
f1 (ppm)


141211.341.1.1r
Name jo wlochal
M No khsq650
Notebook Ref en07519-69-1
carbon.az CDCl3 /opt/topspin2.1 chem 39
BnHN
O
OtBu
8
13C NMR (101 MHz, CDCl3)
f1 (ppm)