Supporting Information

Scalable Synthesis of 1-Bicyclo[1.1.1]pentylamine via a Hydrohydrazination Reaction

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General Methods

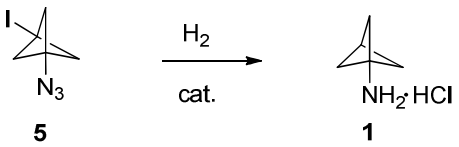
All commercial reagents were purchased from chemical suppliers and used as is. Tris(2,2,6,6-tetramethyl-3,5-heptanedionato) manganese (III) [$Mn(dpm)_3$] was purchased from Strem, methyllithium lithium bromide complex solution in ether (1.5 M) and 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane, technical grade, 90% (by GC) were purchased from Aldrich.

IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer, HATR Trough ZnSe 45. ^{1}H NMR spectra were recorded on a Bruker Ultrashield™ 600 MHz spectrometer and Bruker Ultrashield™ 400 MHz spectrometer. The samples were referenced to residual solvent signal, $CDCl_3$ (7.27 ppm), DMSO-d_6 (2.50 ppm), D_2O (4.75 ppm). ^{13}C NMR spectra were recorded on a Bruker Ultrashield™ 151 MHz spectrometer and Bruker Ultrashield™ 101 MHz spectrometer. The spectra were referenced to residual solvent signals, $CDCl_3$ (77.00 ppm), DMSO-d_6 (39.51 ppm), D_2O (internal standard 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt (TSP)[1] at -0.18 ppm). NMR measurements of **7** were done at 80 °C to minimize signal broadening due to rotamers. Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia, USA.

LC/MS: All data were gathered on an Agilent 1100 LC with MSD (Agilent model G1946B upgraded to D model) single-quadrupole mass spec detectors running with electrospray spray ionization source. The LC instrument includes a binary pump (Agilent model G1312A) with upper pressure limit of 400 bar attached to auto sampler (Agilent model G1313A) which uses external tray for sample submission. The column compartment (Agilent model G1316A) which is attached to diode array (Agilent model G1315A). The instrument acquisition and data handling was done with ChemStation rev. B.02.01. *Elution conditions*: Column: Waters Xbridge C18, 2.1x30 mm, 2.5 µm particle size; Column Temperature 80 °C. Solvent A: Water (0.1% formic acid and 0.05% ammonium formate). Solvent B: Methanol (0.1% formic acid and 0.05% ammonium formate). Gradient for 3 min Method: 5-95 %B in 2.5 min, 95%B 2.5-3.0 min; Flow rate 1.2 mL/min. Gradient for 2 min Method: 5-95 %B in 2 min, Flow rate 1.2 mL/min

Experimental Procedures

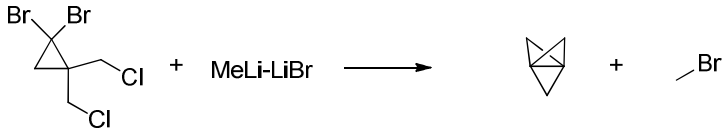
General procedure for the palladium-mediated reduction of 3-iodobicyclo[1.1.1]pentyl azide (5)



5 **1**

A screen of hydrogenation catalysts was conducted to enable this hydrogenation. The use of Johnson Matthey Heterogeneous Catalyst Screening Kit was employed along with additional cherry picked catalysts. The list of catalysts screened include several 5% Pd/C catalysts (with varying characteristics and metal distributions), 5% Pd/Al_2O_3, 5% $Pd/CaCO_3$, $Pd(Pb)/CaCO_3$, $Pd/BaSO_4$, 10% Pd/C, 5% Rh/C, 5% Rh/Al_2O_3, several 5% Pt/C catalysts with varying characteristics and metal distributions, 5% Pt(Bi)/C, 5% Pd(S)/C, 5% Pt/Al_2O_3, 5% Ru/C, 5% Ru/Al_2O_3, mixed metal 4% Pd and 1% Pt on carbon, 4.5% Pd and 0.5 % Rh on carbon, 5% Ru and 0.25% Pd on carbon, 5% Au/C, 5% Au/TiO_2, 5% Au/SiO_2, 5% Au/Al_2O_3, 5% Au/ZrO_2, 20% $Pd(OH)_2/C$, PtO_2, and Raney Nickel.

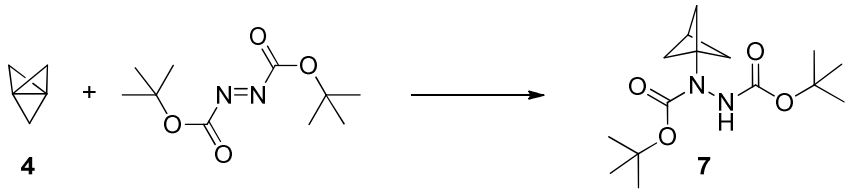
The following is a general method for the hydrogenation screen. The catalysts were pre-dispensed into a vial with stir bar and a 0.045M stock solution of azido iodide (**5**) in an appropriate solvent (AcOH, EtOAc, or MeOH) was added. To selected vials additives were added (AcOH, 3M HCl in MeOH, and benzoyl chloride). The vials were placed in HEL Cat96 pressure reactor and subjected to a nitrogen purge followed by a charge of hydrogen (4 bar) and stirred 15 h at rt. The vials were then analyzed by LC/MS and then re-subjected to hydrogenation conditions at 65 °C and stirred 15 h. The vials were then again analyzed by LC/MS. From this study 20% $Pd(OH)_2/C$ emerged as the leading catalyst with HCl as the additive in methanol to give 1-bicyclo[1.1.1]pentyl amine (**1**). Based on a reference sample of known concentration of **1**, the reaction screen suggested a yield of around 25% with some starting material remaining. These conditions were scaled with 0.229 g (0.976 mmol) of **1** in methanolic HCl (0.5 N, 4 mL) and 20% $Pd(OH)_2/C$ (10 mol%) and subjecting the material to 8 bar of hydrogen at rt for 36 h. The material was filtered through a celite plug and concentrated. The crude residue was purified by SFC purification to give 13.6 mg (16%) of **1**.



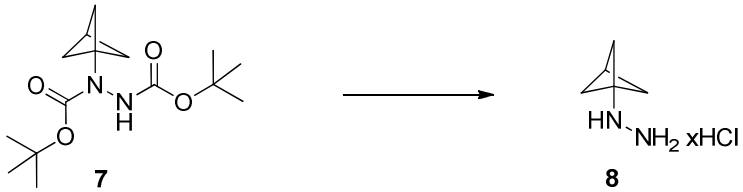
2 **4**

[1.1.1]Propellane (4) solution in pentane/ether.[2] To a stirred and cooled mixture (-50 °C, *iso*-propanol/dry ice bath) of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (**2**; 90% purity, 19.5 g, 59.1 mmol) in pentane (15.6 mL) and diethyl ether (2.34 mL) in a 500 mL 3-neck RBF (attached with nitrogen line, thermometer, and addition funnel) was added an ether solution of methyllithium-lithium bromide complex (94.6 mL, 142 mmol, 1.5 M, 2.4 eq; commercial bottle from Aldrich with Sure/Seal™) slowly in order to keep the temperature between -40 to -50 °C (60 min total addition time). After the addition was complete, the *iso*-propanol/dry ice bath was replaced with an ice bath and the mixture was allowed to warm to 0 °C. After 2 h, the addition funnel was swapped out for a distillation head with attached 200 mL RBF in a -78 °C bath (dry ice/acetone). A vacuum was slowly applied to the system and the distillate collected, while maintaining the reaction/distillation flask below 0 °C. Approximately 95 mL of distillate was collected with an estimated concentration from ^{1}H NMR spectrum analysis of 0.485 M giving 3.043 g (78%) of [1.1.1]propellane. ^{1}H NMR spectrum analysis was done by adding a 0.02 mL aliquot of the distillate by syringe to a NMR tube, followed by a 0.002 mL addition of dichloromethane (internal standard) and then chloroform-*d*.[2] A ^{1}H NMR spectrum indicates a molar ratio of [1.1.1]propellane:dichloromethane to be 1**:**3.215, which would correspond to a 0.485 M or 3.043 g of [1.1.1]propellane (**4**, 78% yield). The distillate was stored in a -70 °C freezer until use. ^{1}H NMR (600 MHz, $CDCl_3$, δ) 2.05 (s, 6H, CH_2).

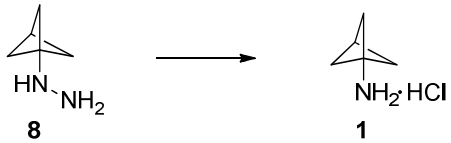
Hydrohydrazination.[3]



Di-*tert*-butyl 1-(bicyclo[1.1.1]pentan-1-yl)hydrazine-1,2-dicarboxylate (7). Under a nitrogen atmosphere, $Mn(dpm)_3$ (533 mg, 0.873 mmol, 0.02 eq) was dissolved in *iso*-propanol (218 mL) at rt and then cooled to 0 °C. Phenylsilane (4.87 g, 5.55 mL, 43.6 mmol, 1 eq) and di-*tert*-butyl azodicarboxylate (15.40 g, 65.5 mmol, 1.5 eq) dissolved in dichloromethane (218 mL) were added (*Note:* on larger scale an exotherm was observed upon addition of the dichloromethane solution, requiring a slow addition over 10 min to maintain the temperature at 0 °C), followed by a [1.1.1]propellane (**4**) solution (90.0 mL, 0.485 M, 43.6 mmol) in ether/pentane. The resulting mixture was stirred at 0 °C for 21 h. The reaction was quenched by adding water (20 mL) and brine (50 mL). The mixture was stirred 5 min and then extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure. The crude residue was then subjected to flash chromatography (silica gel, 0-25% EtOAc/heptane; ninhydrin stain, LC/MS detection) to give 12.87 g (99%) of **7** as a white solid. Differential scanning calorimetry (DSC) of **7** noted two exotherms, the first with a low thermal potential of -27 J/g with an onset temperature of 154 °C and the second with medium thermal potential of -492 J/g with an onset temperature of 230 °C.[4] mp 135 °C dec. ^{1}H NMR (600 MHz, $CDCl_3$, δ) 1.48 (s, 18H, CH_3) 2.05 (br. s., 6H, CH_2) 2.40 (s, 1H, CH) 5.88 - 6.45 (m, 1H, NH). ^{1}H NMR (400 MHz, DMSO-d_6, δ) 1.40 (s, 18H, CH_3) 1.83 - 2.01 (m, 6H, CH_2) 2.30 - 2.43 (m, 1H, CH) 8.39 - 9.17 (m, 1H, NH). Spectrum acquired at 80 °C: ^{1}H NMR (400 MHz, DMSO-d_6, δ) 1.41 (s, 9H, CH_3) 1.42 (s, 9H, CH_3) 1.96 (s, 6H, CH_2) 2.37 (s, 1H, CH) 8.55 (br. s., 1H, NH). Spectrum acquired at 80 °C: ^{13}C NMR (101 MHz, DMSO-d_6, δ) 21.85 (s, 1C, *C*H) 26.91 - 28.14 (m, 6C, *C*H_3) 51.61 (s, 3C, *C*H_2) 54.05 (s, 1C, *C*-N) 78.65 (s, 1C, *C*-O) 79.40 (s, 1C, *C*-O) 153.41 (s, 1C. *C*=O) 154.67 (s, 1C, *C*=O). IR: 3322 (w), 2976 (m), 2917 (w), 2881 (w), 1709 (vs), 1481 (m), 1457 (w), 1366 (s), 1251 (s), 1149 (s), 1060 (m), 1019 (m), 931 (w), 897 (w), 856 (w), 800 (w), 779 (w), 758 (m) cm^{-1}. Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78, N, 9.39; O, 21.45. Found: C, 60.37; H, 8.65, N, 9.47; O, 21.29.

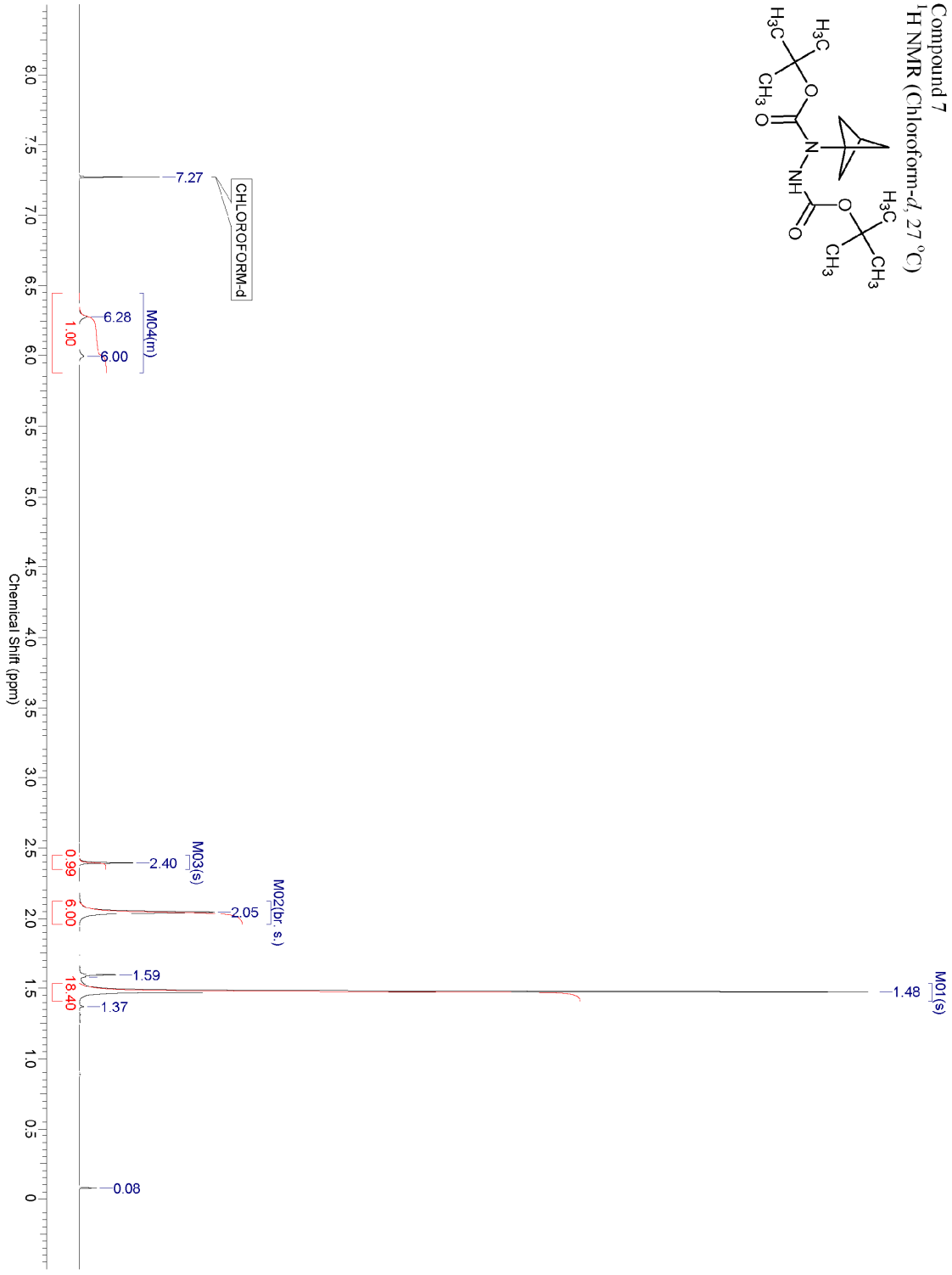


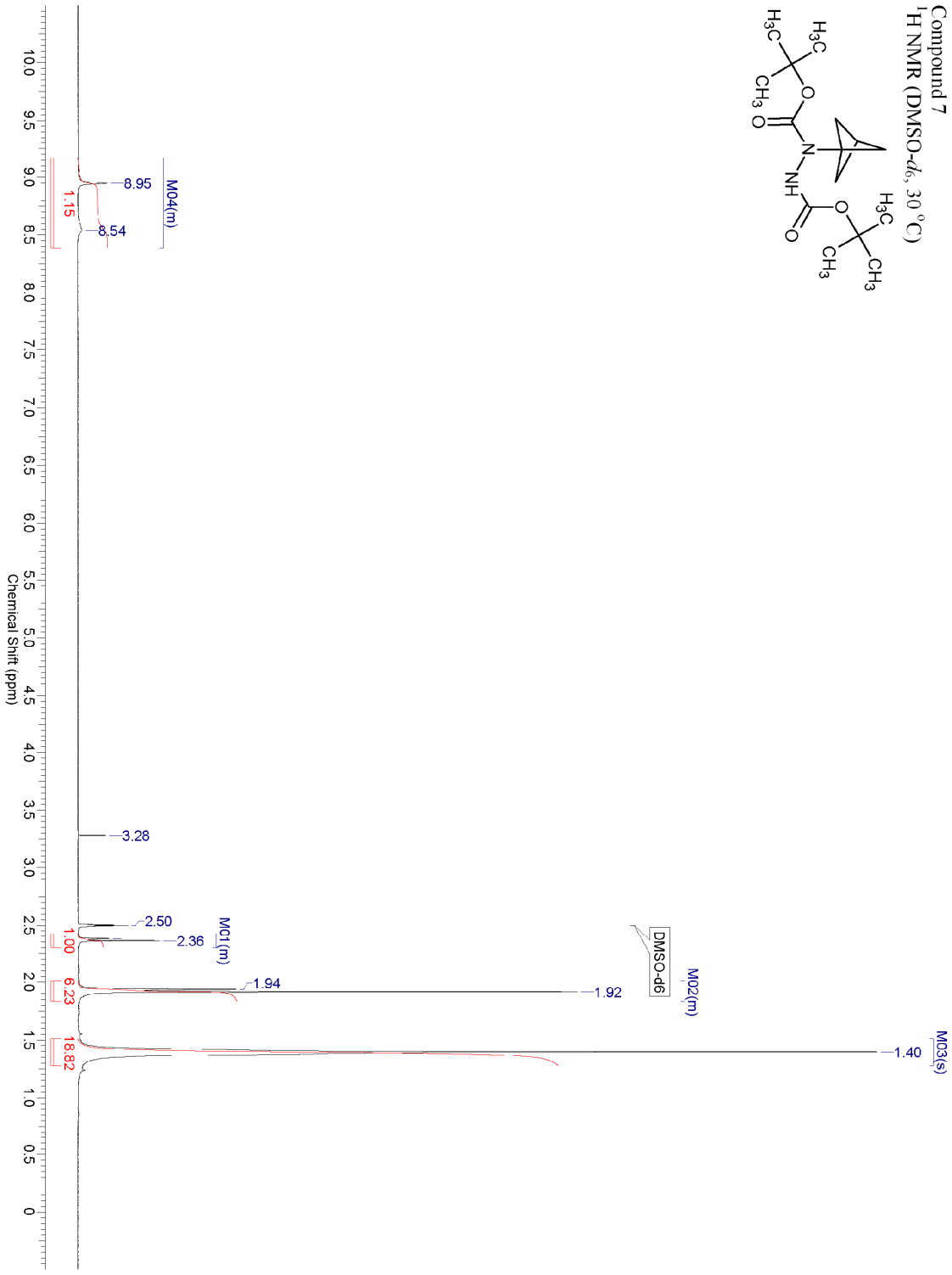
Bicyclo[1.1.1]pentan-1-ylhydrazine hydrochloride (8). To an ethyl acetate solution of di-*tert*-butyl 1-(bicyclo[1.1.1]pentan-1-yl)hydrazine-1,2-dicarboxylate (**7**, 11.03 g, 36.97 mmol) was added HCl (277 mL, 1.10 mol, 4M in dioxane) at rt. The reaction was stirred at rt. LC/MS analysis after 21 h indicates the reaction is complete. The mixture was concentrated and dried to give 5.99 g (94.7%, ~2 eq of HCl by ^{1}H NMR analysis) of **8** as an off-white solid; ^{1}H NMR (600 MHz, DMSO-d_6, δ) 1.82 (s, 6H) 2.45 (s, 1H) 6.75 - 11.32 (m, 5H). Trituration in heptane/EtOAc (3:1) followed by filtration and drying the solids under vacuum gave a white solid in which ^{1}H NMR spectrum indicated ~1 eq of HCl. Differential scanning calorimetry (DSC) of **8** showed a very high thermal potential of -1528 J/g with an onset temperature of 111 °C.[4] mp 205 °C dec. ^{1}H NMR (600 MHz, DMSO-d_6, δ): 1.81 (s, 6H) 2.43 (s, 1H) 4.94 - 7.59 (m, 1H) 9.36 (br. s., 3H). ^{13}C NMR (151 MHz, DMSO-d_6, δ) 22.35 (s, 1C, *C*H) 50.23 (s, *C*H_2, 3C) 54.80 (br. s., 1C, *C*N). IR: 3391 (w, br), 3221 (w), 2911 (vs, br), 2704 (m), 1583 (m), 1531 (m), 1295 (m), 1232 (m), 1200 (m), 860 (m) cm^{-1}. HRMS (TOF/ESI, *m*/*z*): $[M+H]^+$ Calcd for $C_5H_{11}N_2$ *m*/*z* 99.0917; Found 99.0916. Anal. Calcd for $C_5H_{10}N_2$:HCl (1:1.37 ratio): C, 40.58; H, 7.74; Cl, 32.74; N, 18.93. Found C, 40.25; H, 7.67; Cl, 32.48; N, 18.71.



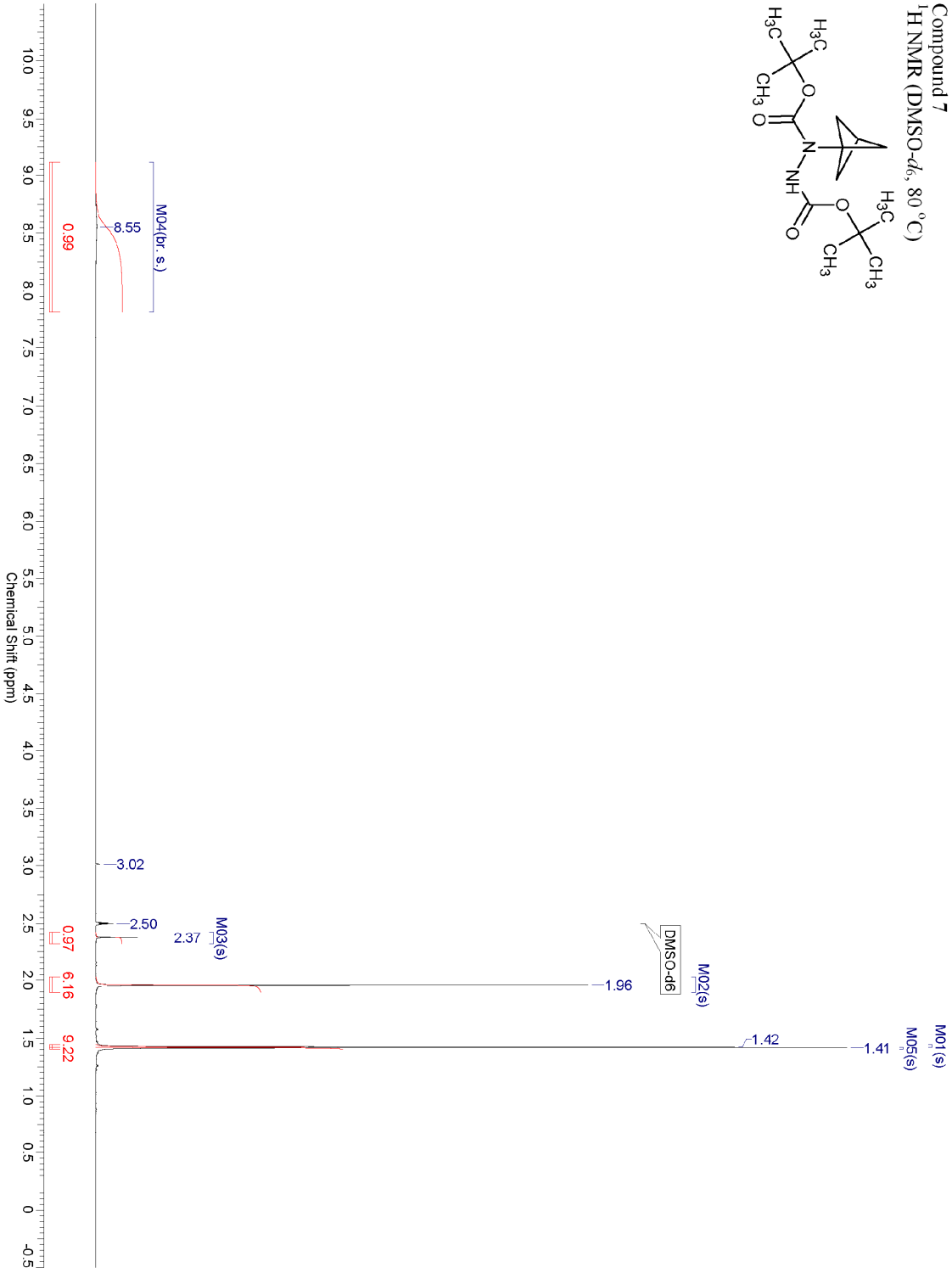
Bicyclo[1.1.1]pentan-1-amine hydrochloride (1). To a wet slurry of platinum (IV) oxide (795 mg, 3.50 mmol, 0.10 eq) in methanol (minimal amount, ~5 mL) was added a solution of bicyclo[1.1.1]pentan-1-ylhydrazine hydrochloride (**8**; 5.99 g, 35.0 mmol) in methanol (350 mL, 0.1 M). The mixture was subjected to 3 bar of hydrogen at 25 ^{o}C for 24 h. LC/MS analysis indicated the reaction to be complete. The mixture was filtered through filter paper and the filtrate was concentrated. The solid residue was washed with ether and then triturated in *i*PrOH/DCM (~10/1) solution and filtered. The filtrate was concentrated to give 3.3552 g (80%) of **1** as a white solid. Differential scanning calorimetry (DSC) of **1** showed a very high thermal potential of -2015 J/g with an onset temperature of 193 ^{o}C.[4] mp 247-251 ^{o}C (255 ^{o}C dec) [lit.[5] 242-244 ^{o}C]. ^{1}H NMR (600 MHz, D_2O, δ) 2.04 (s, 6H, CH_2) 2.60 (s, 1H, CH). [lit.[6] ^{1}H NMR (δ) 2.06 (s, 6H, CH_2) 2.61 (s, 1H, CH)], ^{13}C NMR (151 MHz, D_2O with TSP, δ) 25.94 (s, 1C, CH) 47.64 (s, 1C, CN) 53.62 (s, 3C, CH_2). [lit.[7] ^{13}C NMR (D_2O, δ) 26.09 (CH), 47.69 (CN), 53.75 (CH_2)]. ^{1}H NMR (600 MHz, DMSO-d_6, δ) 1.97 (s, 6H, CH_2) 2.57 (s, 1H, CH) 8.97 (br. s., 3H, $^{+}NH_3$). ^{13}C NMR (151 MHz, DMSO-d_6, δ) 23.74 (s, 1C, *C*H) 45.53 (s, 1C, *C*N) 51.08 (s, 3C, *C*H_2). IR: 3392 (s, br), 2999 (vs, br), 2848 (vs, br), 2023 (w), 1599 (m), 1465 (m), 1246 (s), 1016 (s). HRMS (TOF/ESI, *m*/*z*): $[M+H]^+$ Calcd for C_5H_9N *m*/*z* 84.0808; Found 84.0811.

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

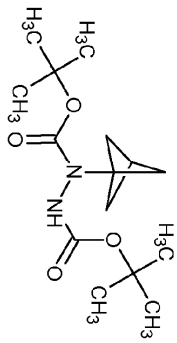



Compound 7
^{1}H NMR (DMSO-d_6, 30 °C)
Chemical Shift (ppm)
8.95
8.54
M04(m)
1.15
3.28
2.50
2.36
M01(m)
1.00
1.94
1.92
DMSO-d6
M02(m)
6.23
18.82
1.40
M03(s)

Compound 7
^{1}H NMR (DMSO-d_6, 80 °C)

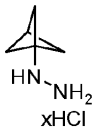


Compound 7
^{13}C NMR (DMSO-*d*$_6$, 80 °C)



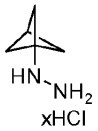
Compound **8**

^{1}H NMR (DMSO-d_6, 27 °C)



Compound **8**

^{13}C NMR (DMSO-d_6, 27 °C)



Compound **1**

^{1}H NMR (D_2O, 27 °C)

Compound **1**
^{13}C NMR (D_2O, 27 °C)
Internal Standard 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt (TSP)

Compound **1**

^{1}H NMR (DMSO-d_6, 27 °C)

Compound **1**

^{13}C NMR (DMSO-d_6, 27 °C)

References

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