Electronic Supplementary Material (ESI) for ChemComm.


**Supporting Information**

# Decarboxylative Hydrazination of Unactivated Carboxylic acids Driven by Cerium Photocatalysis

Veera Reddy Yatham, Peter Bellotti and Burkhard König*

Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, D-93053 Regensburg, Germany

*e-mail: Burkhard.Koenig@chemie.uni-regensburg.de

## Table of contents

**General Considerations:**

**Reagents:** Unless otherwise stated, all reactions were conducted in 10 ml crimp glass vials purchased from VWR International. All carboxylic acids, cerium catalysts and reagents were purchased from commercial sources (Sigma-Aldrich, Fluka, Merck, TCI, Fluorochem and ACROS Organics) and used as received. $CeCl_3 \cdot 7H_2O$ was grinded before use using a pottery mortar until a fine white powder was obtained. All Anhydrous solvents were purchased from ACROS Organics (AcroSeal™) and stored under molecular sieves in brown bottles equipped with septa. The solvents were withdrawn using a syringe under a positive nitrogen pressure. Dinitrogen ($N_2$) was dried by passing it through a Drierite® ($Ca_2SO_4$) laboratory gas drying unit. Carboxylic acids **1k, 1u, 1v** were all prepared following reported literature protocols.[1,2]

**Analytical Methods:** All NMR spectra were recorded at 294 K using a Bruker Avance 300 (300.13 MHz for $^1H$, 75.48 MHz for $^{13}C$), a Bruker Avance III 400 (400.13 MHz for $^1H$, 100.62 MHz for $^{13}C$) and Ascend 400 (400.30 MHz for $^1H$, 100.66 MHz for $^{13}C$) using DEU400 NMR tubes from Deutero GmbH. The following deuterated solvents were used (minimal deuteration in brackets): $CDCl_3$ (Sigma-Aldrich, 99.8%), $CD_3OD$ (Deutero GmbH, 99.8%) and $CD_2Cl_2$ (Deutero GmbH, 99.8%). All chemical shifts were reported in δ-scale as parts per million [ppm] (multiplicity, coupling constant *J*, number of protons, assignment if clear) relative to the solvent residual peaks as the internal standard ($CDCl_3$: 7.26 ppm for $^1H$, 77.16 ppm for $^{13}C$; $CD_3OD$: 4.87 ppm for $^1H$, 49.00 ppm for $^{13}C$, $CD_2Cl_2$: 5.32 ppm for $^1H$, 54.00 ppm for $^{13}C$). [3]The multiplicity was reported for first order coupling patterns and coupling constants *J* were given in Hertz [Hz]. If possible, the scalar coupling *J* through *n*-bonds was listed as "$^nJ$". $^1H$-$^{13}C$-HSQC spectra were acquired using the *hsqcedetgp* sequence (multiplicity-edited HSQC using echo-antiecho), $^1H$-$^1H$-COSY using the *cosygpqf* sequence, $^1H$-$^{13}C$-HMBC using the *hmbcetgpl2nd* sequence (HMBC with 2nd order low pass *J*-filter). Abbreviations used for signal multiplicity: $^1H$ NMR: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, ddt = double of doublets of triplets, dt = doublet of triplets, dq = double of quartets, hept = heptet and m = multiplet. High

[1] N. Gavande, H.-L. Kim, M.R. Donnareddy, G.A.R. Johnston, M. Chebib, J.R. Hanrahan, *ACS Med. Chem. Lett.*, **2013**, 4 (4), 402-407

[2] C.L. Joe, A.G. Doyle, *Angew. Chem. Int. Ed.*,**2016**, 55 (12), 4040-4043

[3] H.E. Gottlieb, V. Kotiyar, A. Nudelman, *J. Org. Chem.*, **1997**, 62 (61), 7512-7515

resolution mass spectra (HRMS) were obtained from the central analytic mass spectrometry facilities (JeolAccuTOF GCX or Agilent Q-TOF 6540 UHD) of the Faculty of Chemistry and Pharmacy, Universität Regensburg, and are reported according to the IUPAC recommendations 2013.[4] FT-IR spectra were acquired using an Agilent Cary 630 bench-top spectrometer. Unless otherwise stated, the spectra were recorded under neat conditions and the characteristic signals were reported in wavenumbers ($cm^{-1}$), rounded at the nearest unit. When possible, the characteristic stretch vibrations for the functional groups (amides and carbonyls) were highlighted. Analytical TLC was performed on silica gel coated alumina plates (Macherey-Nagel TLC sheets ALUGRAM® Xtra SIL G/UV254) and visualized under UV light irradiation (254 nm) or alternatively stained with an ethanolic solution of phosphomolybdic acid (10 g of PMA in 100 ml of absolute ethanol) or basic $KMnO_4$ (1.5 g $KMnO_4$, 10 g $K_2CO_3$, 200 mg NaOH in 200 ml $H_2O$) and gently heated using an heat-gun. Melting points were measured using a Stanford research Systems MPA100 melting point apparatus. The results are reported in ranges from the onset to the melt of all the sample, with the solvent from which the compound was dried in brackets. Optical rotations were measured using an Anton Paar MCP500 polarimeter (10.0 cm cell path) at 20.0°C with at 589 nm wavelength in analytical grade chloroform (Fischer scientific, contains amylene as stabilizer).

**Experimental procedures:** Purification by column chromatography was performed according to the report of Still *et al.*[5] with Merck silica gel 60M (40-63 μm, 230-440 mesh) as stationary phase using glass columns or plastic cartridges on a Biotage®Isolera TM Spektra One device. Hexane (reagent grade, Sigma-Aldrich) and ethyl acetate (purified by distillation from technical grade) were used as mobile phase. Solvent removal under reduced pressure was performed using Büchi Rotavapor® R-100 rotary evaporators equipped with water baths at 40 ºC. Photochemical reactions were irradiated with 455 nm LEDs (OSRAM Oslon® SSL 80 royal-blue LEDs ($\lambda_{max}$= 455 nm (± 15 nm), 3.5 V, 700 mA), which were installed on a passive cooling system at the bottom (7 mm from the bottom-plane of the vials) of a custom-made 6-vials reactor (aluminium), which was equipped with a liquid cooling system (25ºC) and a magnetic stirrer (≈ 250 rpm) (see **Figure 1**).

[4] K.K. Murray, R.K. Boyd, M.N. Eberlin, G.J. Langley, L. Li, Y. Naito, *Pure Appl. Chem.*, **2013**, 85 (7), 1515-1609.

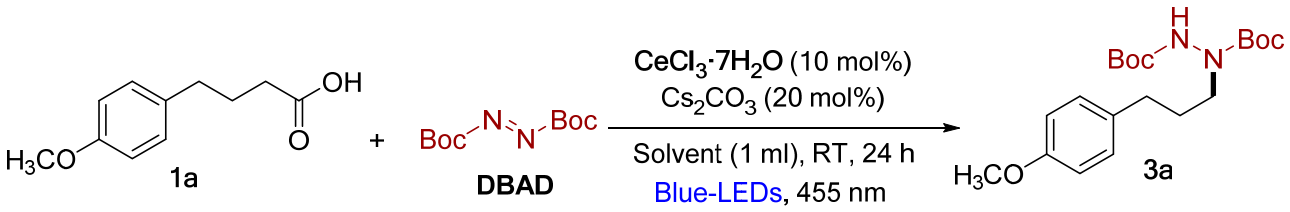
[5] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, **1978**, 43 (14), 2923-2925.

## Optimization details

**General procedure for screening reactions:** A 10 mL glass vial was charged with carboxylic acid (0.1 mmol), Ce-photocatalyst (10 mol%), DBAD (1.5 equiv.), $Cs_2CO_3$ (20 mol%) and a PTFE-coated stirring bar. The glass vial was closed with a septum. Solvent (1 mL) was added and the glass vial was purged with $N_2$ using an hypodermic needle. The reactions were placed in a pre-programed temperature (25°C) controlled blue LED reactor (as shown in **Figure 1**) and the reaction mixture was irradiated with a 455 nm blue LED. After 24 hours, the reaction was quenched with a saturated solution of $NaHCO_3$ (1 mL) then extracted with EtOAc. A sample of this solution was analyzed by $^1H$ NMR using benzoyl benzoate as the internal standard to determine the yield.


**Figure 1: Blue LED reactor with magnetic stirring plate**

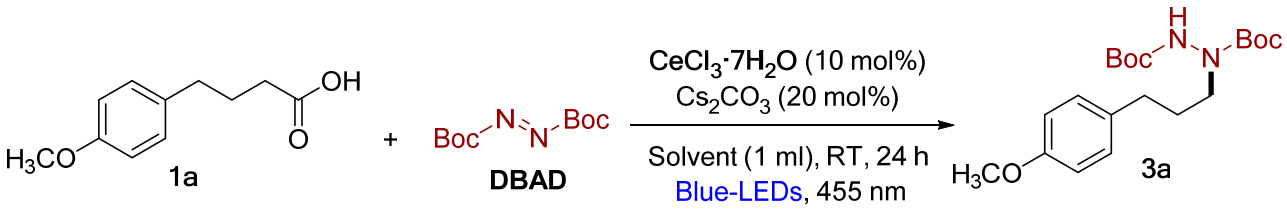
## Table S1: Screening of Solvents




| Entry | Deviation from standard conditions | 3a (%)[a] |
|---|---|---|
| 1 | $CH_3CN$ | 90 |
| 2 | $CH_2Cl_2$ | 85 |
| 3 | $CHCl_3$ | 66 |
| 4 | Toluene | 54 |
| 5 | THF | 42 |
| 6 | DMA | 42 |
| 7 | NMP | 17 |
| 8 | Dioxane | 50 |
| 9 | EtOAc | 52 |
| 10 | DCE | 86 |
| 11 | DMSO | 61 |
| 12 | Benzene | 48 |
| 13 | Acetone | 40 |

[a]Determined by $^1$H NMR, using Benzoyl benzoate as internal standard

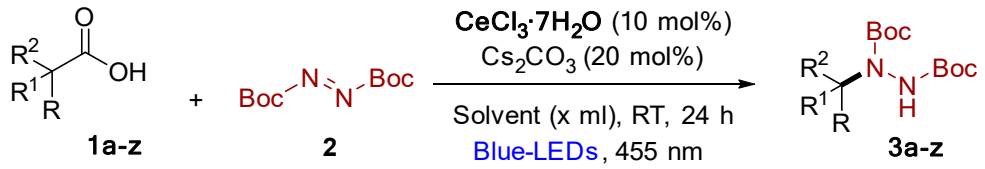
**Table S2: Screening of other reaction parameters**




| Entry | Deviation from standard conditions | 3a (%)[a] |
|---|---|---|
| 1 | $(NH_4)_2Ce(NO_3)_6$ instead of $CeCl_3{\cdot}7H_2O$ | 35 |
| 2 | $(^nBu_4N)_2CeCl_6$ instead of $CeCl_3{\cdot}7H_2O$ | 50 |
| 3 | $CeCl_3{\cdot}7H_2O$ (5 mol%) instead of 10 mol% | 56 |
| 4 | Blue LEDs (400 nm) | 64 |
| 5 | Green LEDs (525 nm) | 20 |
| 6 | DBAD (2 equiv.) | 85 |

[a]Determined by $^1H$ NMR, using Benzoyl benzoate as internal standard

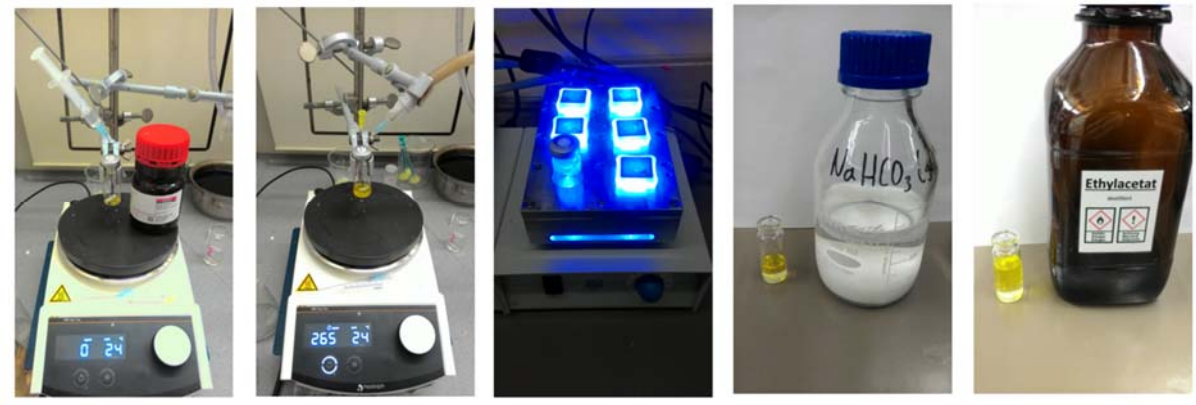
## General procedure for Decarboxylative hydrazination of carboxylic acids



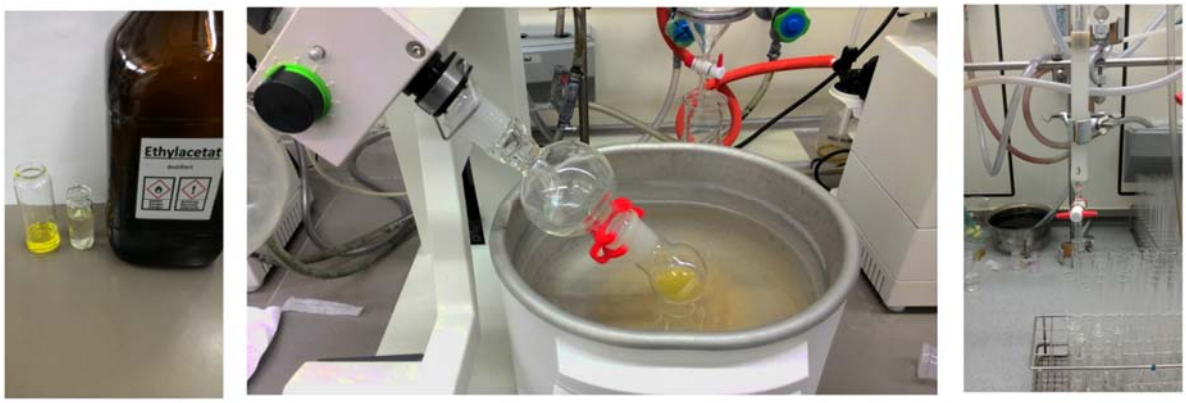

**General procedure for the de-carboxylative hydrazination of carboxylic acids (GP1):** A 10 mL glass vial equipped with a teflon-coated stirring bar was charged with carboxylic acid **1a-z** (0.2-0.3 mmol), $CeCl_3 \cdot 7H_2O$ (10 mol%), DBAD (1.5 equiv.) and $Cs_2CO_3$ (20 mol%). The crimp glass vial was sealed with a PTFE septum, then MeCN (1 ml) was added and the vial purged with $N_2$ using an hypodermic needle. The reaction was placed in a pre-programed temperature (25°C) controlled blue LED reactor (as shown in **Figure 1**) and the reaction mixture was irradiated with a 455 nm blue LED. After 24 hours, the reaction was quenched with a saturated solution of $NaHCO_3$ (1 ml), then extracted 2 times with AcOEt (5 ml each time). The combined organic layers were concentrated under reduced pressure. The product**3a-z** was purified by flash chromatography on silica (hexane:AcOEt 10:1, followed by hexane:AcOEt 10:4).

Visual representation of the reaction set-up


**Left:** The catalyst ($CeCl_3 \cdot 7H_2O$) (*left*), DBAD (*center-left*), $Cs_2CO_3$ (*center-right*)and substrate (*right*, *for instance cyclopropylacetic acid*) are weighted at open air. **Center**: the species are charged in a crimp-top vial equipped with a PTFE stirring bar. **Right**: the crimp vial is sealed with a PFTE septum.

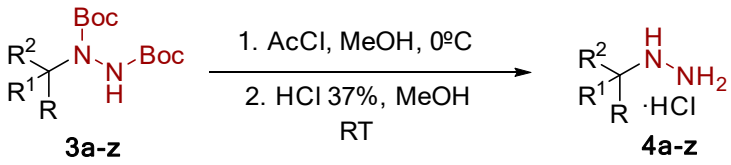



**Left**: the solvent (usually MeCN) is added using a syringe. **Center-left**: The vial is filled with $N_2$ using an hypodermic needle (*$N_2$ inlet on the right, outlet on the left*). **Center**: The reaction is irradiated at 455 nm. **Center-right**: The reaction is quenched with a saturated solution of $NaHCO_3$ (1 ml). **Right**: AcOEt (5 ml) is added and the layers separated.




**Left**: The water layer is extracted once more (5 ml) with AcOEt (*on the left the organic layer*). **Center**: The solvent is removed under reduced pressure. **Right:** The crude is purified by column chromatography.

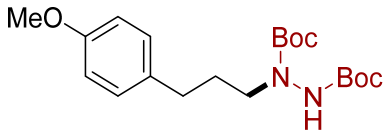
## General procedure for the deprotection of hydrazine derivatives to hydrazinium hydrochloride




**General procedure for deprotection of Boc-protected hydrazines (GP2):** In a 10 mL glass vial equipped with a teflon-coated stirring bar, methanol (0.1 M) was charged, then cooled-down to 0ºC and acetyl chloride (30.0 equiv.) was slowly added dropwise (**WARNING**: *addition must be extremely slow in order to prevent the solvent from violently boil*), then the corresponding Boc-protected hydrazine **3a-z** (1.0 equiv.) was added in one portion, then HCl

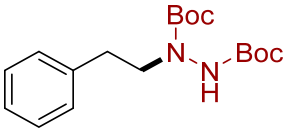
37% (50 µl/ml of MeOH). The reaction was sealed using a PTFE septum, then stirred at room temperature until disappearance of the starting material. The solvent was removed under reduced pressure, then further dried using the lyophilizer, to afford the corresponding hydrazine hydrochloride **4a-z**.

**Synthesis and characterization of products:**

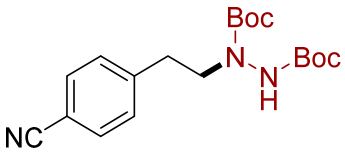



**di-*tert*-butyl 1-(3-(4-methoxyphenyl)propyl)hydrazine-1,2-dicarboxylate (3a):** Following the general procedure **GP1**, two reactions of **1a** (0.2 mmol each one) afforded **3a** as an off-white semi-solid in 80% yield (120 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers.* $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, $^{3}J$ = 7.7 Hz, 2H, 3-ArH), 6.82 (d, $^{3}J$ = 7.8 Hz, 2H, 2-ArH), 6.30 – 5.75 (br m, 1H, NH), 3.78 (s, 3H, OMe), 3.47 (br, 2H, -$CH_2$N), 2.59 – 2.57 (t, $^{3}J$ = 7.4 Hz, 2H), 1.89 – 1.85 (quint, $^{3}J$ = 7.4 Hz, 2H). 1.47 (m, 9H, C($CH_3$)$_3$), 1.45 (s, 9H, C($CH_3$)$_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 157.7, 155.3 (br s), 154.2, 151.0 (br s), 133.7 (br s), 129.2, 113.7, 83.5, 80.9 (br s), 55.2, 48.9 (br s), 32.1, 28.2, 27.9, 24.7. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{20}H_{32}N_2O_5$+ H] 381.2384; found: 381.2381. FT-IR (neat, $cm^{-1}$): 3325 (stretch N-H), 2978, 2933, 1707 (stretch C=O), 1513, 1367, 1245, 1148, 1036.

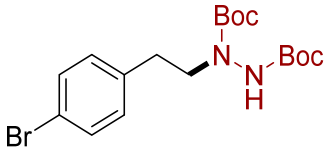
For large scale the concentration of **1a** was increased to 0.25 M and the reaction time was increased to 72 hours yielded **3a** in 75% yield.



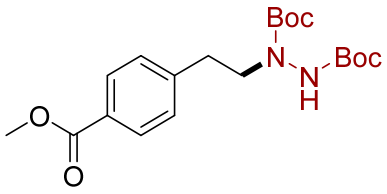

**di-*tert*-butyl 1-phenethylhydrazine-1,2-dicarboxylate (3b)**: Following the general procedure **GP1**, with the substrate concentration increased to 0.25 M and the reaction time was increased to 36 hours, **1b** (150 mg, 1 mmol) afforded **3b** as a white solid in 54% yield (181 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers.* Mp: 84-86°C (from DCM). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.10 (m, 5H, ArH), 6.50 – 6.00 (br m, 1H, NH), 3.78 – 3.60 (br m, 2H, $CH_2$N), 2.88 (br t, $^{3}J$ = 7.7 Hz, 1H, Ar$CH_2$), 1.47 (s, 9H, C($CH_3$)$_3$), 1.44 – 1.35 (br m, 9H, C($CH_3$)$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.6 (br s), 155.2, 139.2, 128.9, 128.6, 126.4, 81.3 (br s), 52.3 (br s), 51.1 (br s), 34.8-33.6 (br m), 28.3, 28.3. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{18}H_{28}N_2O_4$ + H] 337.2122; found: 337.2120. $[M+Na]^+$ calc. for [$C_{18}H_{28}N_2O_4$ + Na] 359.1941; found: 359.1941. FT-IR (neat, $cm^{-1}$): 3325 (stretch N-H), 3265, 2981, 2933, 1744 (stretch C=O), 1703 (stretch C=O), 1677 (stretch C=O), 1495, 1405, 1364, 1249, 1148.



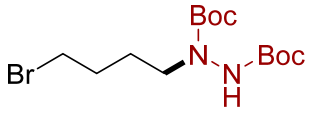

**di-*tert*-butyl 1-(4-cyanophenethyl)hydrazine-1,2-dicarboxylate (3c):** Following the general procedure **GP1**, two reactions of **2c** (0.2 mmol each one) afforded **3c** as an off-white solid in 57% yield (83 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. Mp: 92-93°C (from hexane:AcOEt). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, $^{3}J$ = 7.8 Hz, 2H, 3-ArH), 7.32 (d, $^{3}J$ = 7.9 Hz, 2H, 2-ArH), 6.60 – 5.90 (br m, 1H, NH), 3.76 – 6.62 (br m, 2H, $CH_2N$), 2.94 (t, $^{3}J$ = 7.5 Hz, 2H, $ArCH_2$), 1.48 – 1.35 (m, 18H, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.2 – 155.2 (br m), 155.1, 145.0, 132.3, 129.7, 119.0, 110.3, 81.6, 51.8 (br s), 50.5 (br s), 35.1 – 33.8 (br m), 28.3, 28.2. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{19}H_{27}N_3O_4 + H]$ 362.2074; found: 362.2072. FT-IR (neat, $cm^{-1}$): 3269 (stretch N-H), 2978, 2933, 2229 (stretch CN), 1733 (stretch C=O), 1669 (stretch C=O), 1368, 1245, 1148.



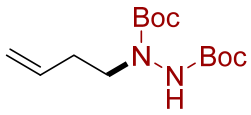

**di-*tert*-butyl 1-(4-bromophenethyl)hydrazine-1,2-dicarboxylate (3d):** Following the general procedure **GP1**, two reactions of **1d** (0.2 mmol each one) afforded **3d** as a white solid in 51% yield (85 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. Mp: 132-133°C (from hexane:AcOEt). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, $^{3}J$ = 8.4 Hz, 2H, 3-ArH), 7.07 (d, $^{3}J$ = 7.9 Hz, 2H, 2-ArH), 6.60 – 6.10 (br m, 1H, NH), 3.72 – 6.58 (br m, 2H, $CH_2N$), 2.83 (br t, $^{3}J$ = 7.6 Hz, 2H, $ArCH_2$), 1.46 (s, 9H, $C(CH_3)_3$), 1.44 – 1.39 (br m, 9H, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.0 – 155.2 (br m), 138.2, 131.6, 130.6, 120.2, 81.4 (br m), 52.1 (br s), 50.8 (br s), 34.2 – 33.0 (br m), 28.3, 28.3. HRMS (ESI+) m/z: $[M+Na]^+$ calc. for $[C_{18}H_{27}N_2O_4{}^{79}Br + Na]$ 437.1046; found: 437.1042. calc. for $[C_{18}H_{27}N_2O_4{}^{81}Br + Na]$ 439.1028; found: 439.1024. FT-IR (neat, $cm^{-1}$): 3306 (stretch N-H), 2974, 2930, 1703 (stretch C=O), 1394, 1364, 1249, 1152.



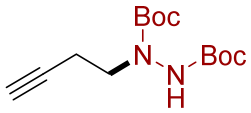

**di-*tert*-butyl 1-(4-(methoxycarbonyl)phenethyl)hydrazine-1,2-dicarboxylate (3e)**: Following the general procedure **GP1**, two reactions of **1e** (0.2 mmol each one) afforded **3e** asa white waxy semi-solid in 59% yield (93 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, $^{3}J$ = 8.0 Hz, 2H, 3-ArH), 7.32 – 7.21 (m, 2H, 2-ArH - *overlaps with the solvent signal*), 6.60 – 6.00 (br m, 1H, NH), 3.88 (s, 3H, $OCH_3$), 3.78 – 3.60 (br m, 2H, $CH_2N$), 2.93 (br t, $^{3}J$ = 7.5 Hz, 2H, $ArCH_2$), 1.48 – 1.36 (m, 18H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.1, 156.1–153.9 (m), 144.8, 129.9, 128.9, 128.4, 81.9– 81.1 (br m), 52.1, 50.7 (br), 34.6– 33.7 (br m), 28.3, 28.3, 28.0. HRMS (ESI+) m/z: $[M+Na]^+$ calc. for $[C_{20}H_{30}N_2O_6 + Na]$ 417.1996; found: 417.1994. $[M+NH_4]^+$ calc. for $[C_{20}H_{30}N_2O_6 + NH_4]$ 412.2442; found: 412.2440. FT-IR (neat, $cm^{-1}$): 3250 (stretch N-H), 2978, 2933, 1703 (broad, stretch C=O), 1390, 1275, 1241, 1148, 1103.



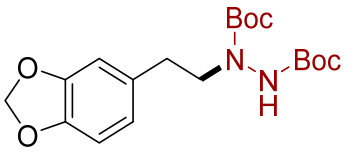

**di-*tert*-butyl 1-(4-bromobutyl)hydrazine-1,2-dicarboxylate (3f):** Following the general procedure **GP1**, two reactions of **1f** (0.1 mmol each one) afforded **3f** as white semi-solid in 40% yield (36 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.31 (br s, 1H, NH), 3.46 – 3.41 (m, 4H, $CH_2N$, $CH_2Br$), 1.92 – 1.85 (m, 2H, $CH_2$), 1.74 – 1.63 (m, 2H, $CH_2$), 1.45 (br s, 18H, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.4 (br s), 82.0 – 80.5 (br m), 48.4 (br s), 33.5 (br s), 29.9, 28.3, 26.2. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{14}H_{27}{}^{79}BrN_2O_4 + H]$ 367.1227; found: 367.1218. FT-IR (neat, $cm^{-1}$): 3295 (stretch N-H), 2978, 2933, 1797 (stretch C=O), 1696 (stretch C=O), 1502, 1401, 1368, 1275, 1148.




**di-*tert*-butyl 1-(but-3-en-1-yl)hydrazine-1,2-dicarboxylate (3g):** Following the general procedure **GP1**, two reactions of **1g** (0.2 mmol each one) afforded **3g** as an off-white solid in 60 % yield (68 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. Mp: 78-80°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.50 – 6.14 (br m, 1H, NH), 5.76 (ddt, $^{3}J$ = 17.0, 10.2, 6.8 Hz, 1H, C=CH), 5.05 (dq, $^{3}J$ = 17.2 Hz, $^{4}J$ = 1.7 Hz, 1H, *cis*-C=$CH_2$), 5.00 (d, $^{3}J$ = 10.2 Hz, 1H, *trans*-C=$CH_2$, *broadening due to $^{4}J$ visible*), 3.60 – 3.40 (br m, 2H, $CH_2N$), 2.31 (q, $^{3}J$ = 7.1 Hz, 2H, *allyl*-$CH_2$, *broadening due to $^{4}J$ visible*), 1.45 (s, 9H, $C(CH_3)_3$), 1.44 – 1.39 (br m, 9H, $CH_3$, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.7 – 155.2 (br m), 116.6, 81.1 (br s), 50.2 (br s), 48.8, 32.6-31.8 (br m), 28.3. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{14}H_{26}N_2O_4$+ H] 287.1965; found: 287.1961. FT-IR (neat, $cm^{-1}$): 3310 (stretch N-H), 2978, 2933, 1703 (stretch C=O), 1491, 1394, 1364, 1252, 1148.

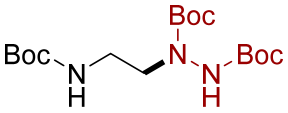



**di-*tert*-butyl 1-(but-3-yn-1-yl)hydrazine-1,2-dicarboxylate (3h):** Following the general procedure **GP1**, two reactions of **1h** (0.2 mmol each one) afforded **3h** as an off-white solid in 57% yield (65 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.50 – 6.15 (br m, 1H, NH), 3.65 – 3.50 (br m, 2H, $CH_2N$), 2.46 (td, $^{3}J$ = 5.1 Hz, $^{4}J$ = 1.8 Hz, *propargyl*-$CH_2$), 1.94 (t, $^{4}J$ = 1.8 Hz, 2H, *alkyne*-CH) 1.45 (br s, 18H, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.1 (br), 82.2 – 80.8 (br m), 70.0 – 69.3 (br m), 50.0 – 48.3 (br m), 28.2, 17.6. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{14}H_{24}N_2O_4$+ H] 285.1809; found: 285.181. FT-IR (neat, $cm^{-1}$): 3310 (stretch N-H), 2974, 2926, 2855, 1703 (stretch C=O), 1490, 1394, 1368, 1297, 1252, 1156, 1059.

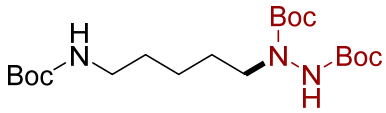



**di-tert-butyl 1-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)hydrazine-1,2-dicarboxylate (3i):** Following the general procedure **GP1**, two reactions of **1i** (0.2 mmol each one) afforded **3i** as

an off-white solid in 40% yield (60 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 6.72 – 6.61 (m, 3H, ArH), 6.31 – 6.14 (br m, 1H, NH), 5.89 (s, 2H, $OCH_2O$), 3.70 – 3.45 (br m, 2H, $CH_2N$), 2.78 (br t, $^{3}J$ = 7.5 Hz, 2H, $ArCH_2$), 1.46-1.42 (m, 18H, $C(CH_3)_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.1 – 154.3 (br m), 147.6, 146.0, 132.9, 121.6, 109.2, 108.3, 100.8, 82.0 – 80.5 (br m), 53.4 – 50.7 (br m), 34.4 – 33.0 (br m), 28.4 – 27.9 (m). HRMS (ESI+) m/z: $[M+Na]^+$ calc. for $[C_{19}H_{28}N_2O_6 + Na]$ 403.1840; found: 403.1837. FT-IR (neat, $cm^{-1}$): 3325 (stretch N-H), 2978, 2933, 1703 (stretch C=O), 1491, 1442, 1394, 1368, 1244, 1148, 1040.

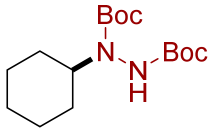



**di-*tert*-butyl 1-(2-((tert-butoxycarbonyl)amino)ethyl)hydrazine-1,2-dicarboxylate (3j)**: Following the general procedure **GP1**, two reactions of **1j** (0.2 mmol each one) afforded **3j** as a colorless glass in 52% yield (78 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.45 (br m, 1H, NH), 5.60 – 5.07 (br m, 1H, NH), 3.59 – 3.41 (br m, 2H, $CH_2N$), 3.36 – 3.14 (br m, 2H, $CH_2N$), 1.47 – 1.38 (m, 27H, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.5 (br s), 155.5 (br s), 81.7 (br s), 81.2 (br s), 79.2 (br s), 51.0 (br s), 49.2 (br s), 38.2 (br s), 28.5, 28.3. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{17}H_{33}N_3O_6 + H]$ 376.2442; found: 376.2446. $[M+Na]^+$ calc. for $[C_{17}H_{33}N_3O_6 + Na]$ 398.2262; found: 398.2260. FT-IR (neat, $cm^{-1}$): 3321 (stretch N-H), 2978, 2937, 1696 (stretch C=O), 1506, 1394, 1364, 1249, 1144.

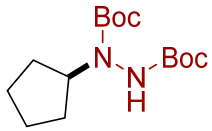



**di-*tert*-butyl 1-(5-((tert-butoxycarbonyl)amino)pentyl)hydrazine-1,2-dicarboxylate (3k):** Following the general procedure **GP1**, two reactions of **1k** (0.2 mmol each one) afforded **3k** as a colorless gum in 46% yield (77 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.79 – 6.11 (br m, 1H, NH), 4.66 (br m, 1H, NH), 3.55 – 3.26 (br m, 2H, $CH_2N$), 3.23 – 2.94 (br m, 2H, $CH_2N$), 1.61 – 1.45 (m, 4H, $CH_2$), 1.45 – 1.39 (m, 27H, $C(CH_3)_3$), 1.38 – 1.22 (m, 2H, $CH_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.3, 155.6, 156.1 – 155.0 (br s), 81.6 – 80.6 (br m), 79.1 (br s), 50.9 – 48.7 (br m), 40.2 (br s), 29.8, 28.5, 28.3, 24.0. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{20}H_{39}N_3O_6 + H]$ 418.3912; found: 418.3915. $[M+Na]^+$ calc. for $[C_{20}H_{39}N_3O_6 + Na]$

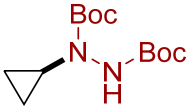
440.2731; found: 440.2729. FT-IR (neat, $cm^{-1}$): 3310 (stretch N-H), 2978, 2933, 2870, 1689 (stretch C=O), 1513, 1394, 1364, 1245, 1144.




**di-*tert*-butyl 1-*cyclo*hexylhydrazine-1,2-dicarboxylate (3l):** Following the general procedure **GP1**, two reactions of **1l** (0.2 mmol each one) afforded **3l** as an off-white solid in 85% yield (106 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers and conformational flexibility of the cyclohexyl ring*. Mp: 144-146°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.20 –5.90 (br m, 1H, NH), 4.10 – 3.70 (br m, 1H, CHN), 1.73 – 0.90 (m, 28H, $C(CH_3)_3$, *cyclohexyl*-$CH_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.7 – 155.5 (br m), 154.9 – 154.0 (br m), 80.9 (br s), 80.7 (br s) 57.0 – 55.8 (br m), 30.2, 28.3, 28.3, 25.6, 25.5. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{16}H_{30}N_2O_4$ + H] 315.2278; found: 315.2278. FT-IR (neat, $cm^{-1}$): 3310 (stretch N-H), 2974, 2930, 2859, 1696 (stretch C=O), 1517, 1394, 1315, 1252, 1148.

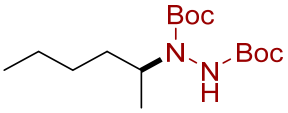



**di-*tert*-butyl 1-*cyclo*pentylhydrazine-1,2-dicarboxylate (3m):** Following the general procedure **GP1**, two reactions of **1m** (0.2 mmol each one) afforded **3m** as an off-white solid in 80% yield (96 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers and conformational flexibility of the cyclopenyl ring*. Mp: 148-150°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.30 – 6.02 (br m, 1H, NH), 4.60 – 4.30 (br m, 1H, CHN), 1.74 – 1.40 (m, 26H, $C(CH_3)_3$, *cyclopentyl*-$CH_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.9 (br s), 155.1, 81.2 (br s), 80.8 (br s) 59.0 – 57.2 (br m), 29.0, 28.3, 28.2, 23.7. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{15}H_{28}N_2O_4$+ H] 301.2122; found: 301.2118. FT-IR (neat, $cm^{-1}$): 3310 (stretch N-H), 2974, 2870, 1700 (stretch C=O), 1513, 1401, 1364, 1249, 1152, 1122.

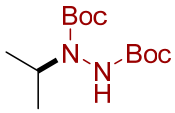



**di-*tert*-butyl 1-*cyclo*propylhydrazine-1,2-dicarboxylate (3n):** Following the general procedure **GP1**, two reactions of **1n** (0.2 mmol each one) afforded **3n** as an off-white solid in

75% yield (80 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. Mp: 150-154°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.50 – 6.18 (br m, 1H, NH), 2.87 – 2.81 (br m, 1H, CHN), 1.40 (br s, 18H, $C(CH_3)_3$), 0.65 (d, $^{3}J$ = 4.0 Hz, 4H, $CH_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.1 (br s), 155.5, 81.2 (br s), 80.9 (br s) 31.8 (br s), 28.2, 27.9, 7.3. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{13}H_{24}N_2O_4$+ H] 273.1809; found: 273.1806. FT-IR (neat, $cm^{-1}$): 3347 (stretch N-H), 3299, 2978, 2933, 1722 (stretch C=O), 1498, 1368, 1245, 1144.

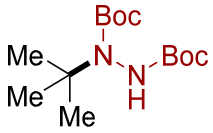



**di-*tert*-butyl 1-(hexan-2-yl)hydrazine-1,2-dicarboxylate (3o):** Following the general procedure **GP1**, two reactions of **3o** (0.2 mmol each one) afforded **3o** as an off-white solid in 87% yield (114 mg*). Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. Mp: 65-66°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.10 – 5.85 (br m, 1H, NH), 4.30 – 3.90 (br m, 1H, CHN), 1.44 (s, 9H, $C(CH_3)_3$), 1.43 (s, 9H, $C(CH_3)_3$), 1.24 (br s, 6H, 3C,4C,5C-$CH_3$), 1.06 (d, $^{3}J$ = 6.6 Hz, 3H, 1C-$CH_3$), 0.85 (t, $^{3}J$ = 6.0 Hz, 3H, 6C-$CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.0 – 155.0 (br m), 80.8 (br s), 55.0 – 52.2 (br m), 34.1, 31.8, 28.3, 28.2, 26.2, 22.7, 14.1. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{17}H_{34}N_2O_4$+ H] 331.2591; found: 331.2590. FT-IR (neat, $cm^{-1}$): 3280 (stretch N-H), 2974, 2930, 2859, 1737 (stretch C=O), 1670 (stretch C=O), 1517, 1409, 1364, 1241, 1156, 1111.

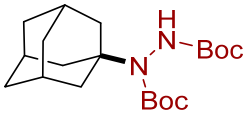



**di-*tert*-butyl 1-*iso*propylhydrazine-1,2-dicarboxylate (3p)**: Following the general procedure **GP1**, with the substrate concentration increased to 0.25 M and the reaction time was increased to 36 hours, isobutyric acid **1p** (91 µl, 1 mmol) afforded **3p** as a white solid in 79% yield (218 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. Mp: 111-113°C (from DCM). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 5.96 (br m, 1H, NH), 4.50 – 4.20 (br m, 1H, CHN), 1.45 (s, 9H, $C(CH_3)_3$), 1.44 (br s, 9H, $C(CH_3)_3$), 1.08 (d, $^{3}J$ = 6.7 Hz, 6H, $^{i}Pr$-$CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.0 – 155.4 (br m), 154.8 (br s), 81.5 – 80.5 (br m), 50.0 – 47.5 (br m), 28.4, 28.3, 19.9. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{13}H_{26}N_2O_4$ + H] 275.1965; found: 275.1962. $[M+Na]^+$ calc. for

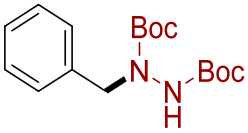
[$C_{13}H_{26}N_2O_4$ + Na] 297.1785; found: 297.1783. FT-IR (neat, $cm^{-1}$): 3276 (stretch N-H), 2978, 2933, 1741 (stretch C=O), 1670 (stretch C=O), 1521, 1409, 1364, 1241, 1156, 1096.




**di-*tert*-butyl 1-(*tert*-butyl)hydrazine-1,2-dicarboxylate (3q):** Following the general procedure **GP1**, two reactions of **1q** (0.2 mmol each one) afforded **3q** as an off-white solid in 90% yield (102 mg*). Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. Mp: 65-66°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.30 – 5.80 (br m, 1H, NH), 1.44 (s, 9H, *Boc*-$CH_3$), 1.43 (s, 9H, *Boc*-$CH_3$), 1.36 (s, 9H, *Hydrazine*-$CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.5, 156.2, 154.8, 154.3, 81.3, 80.7 (br s), 59.4 (br s), 28.6, 28.4, 28.3. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{14}H_{28}N_2O_4$ + H] 289.2122; found: 289.2117. FT-IR (neat, $cm^{-1}$): 3310 (stretch N-H), 2978, 2933, 1737 (stretch C=O), 1685 (stretch C=O), 1521, 1364, 1271, 1156, 1088.

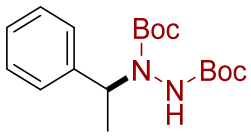



**di-*tert*-butyl 1-((3s,5s,7s)-adamantan-1-yl)hydrazine-1,2-dicarboxylate (3r):** Following the general procedure **GP1**, two reactions of **1r** (0.2 mmol each one) afforded **3r** as white semi-solid in 65% yield (92 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.20 – 5.80 (br m, 1H, NH), 2.14 – 2.01 (m, 9H), 1.66 – 1.59 (m, 6H), 1.45 (s, 9H, $C(CH_3)_3$), 1.43 (s, 9H, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.6, 156.4, 154.6, 154.2, 81.5 – 80.5 (br m), 60.1, 40.32, 36.5, 30.2, 28.4. HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{20}H_{34}N_2O_4$+ H] 367.2591; found: 367.2591. FT-IR (neat, $cm^{-1}$): 3332 (stretch N-H), 2967, 2907, 2848, 1703 (stretch C=O), 1495, 1454, 1364, 1275, 1241, 1156.

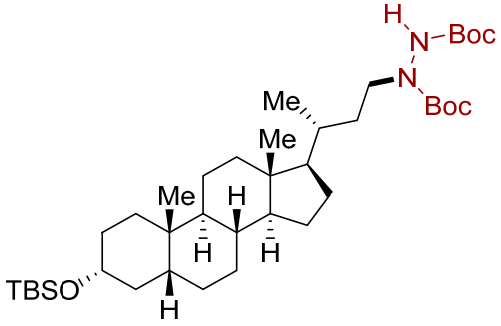



**di-*tert*-butyl 1-benzylhydrazine-1,2-dicarboxylate (3s):** Following the general procedure **GP1** with the following modification: the system was degassed by bubbling $N_2$ through the

solution for 5 minutes. Two reactions of **3s** (0.2 mmol each one) afforded **3s** as an off-white solid in 40% yield (50 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H, ArH), 6.36 – 6.92 (br m, 1H, NH), 4.72 – 4.32 (br m, 2H, $PhCH_2N$), 1.50 – 1.40 (m, 18H, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.0 – 154.8 (br m), 137.3, 128.6, 127.6, 82.0 – 81.2 (br m), 55.0 – 52.6 (br m), 28.3. HRMS (ESI+) m/z: $[M+Na]^+$ calc. for $[C_{17}H_{26}N_2O_4 + H]$ 345.1785; found: 345.1784. FT-IR (neat, $cm^{-1}$): 3276 (stretch N-H), 2982, 2930, 1726 (stretch C=O), 1674 (stretch C=O), 1521, 1413, 1364, 1252, 1148.

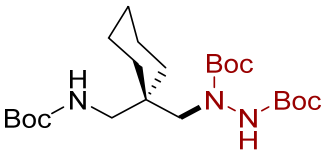



**di-*tert*-butyl 1-(1-phenylethyl)hydrazine-1,2-dicarboxylate (3t):** Following the general procedure GP1 with the following modification: the system was degassed by bubbling $N_2$ through the solution for 5 minutes. Two reactions of **1t** (0.2 mmol each one) afforded **3t** as an off-white solid in 43% yield (57 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 5H, ArH), 6.20 – 5.80 (br m, 1H, NH), 5.70 – 5.23. (br m, 1H, ArCH), 1.60 – 1.35 (m, 21 H, $C(CH_3)_3$, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.0 – 155.2 (br m), 154.8 (br), 141.5, 128.4, 127.4, 127.2, 81.3 (br), 80.8 (br), 54.8 (br), 28.3, 28.2, 16.9 (br). HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{18}H_{28}N_2O_4 + H]$ 337.2122; found: 337.2121. $[M+Na]^+$ calc. for $[C_{18}H_{28}N_2O_4 + Na]$ 359.1941; found: 359.1944. FT-IR (neat, $cm^{-1}$): 3314 (stretch N-H), 2978, 2933, 1700 (stretch C=O), 1476, 1390, 1312, 1241, 1152.

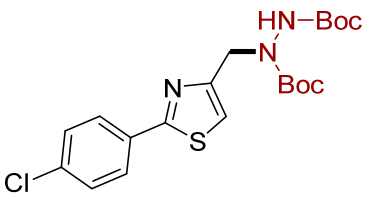



**di-*tert*-butyl 1-((R)-3-((3R,5R,8R,9S,10S,13R,14S,17R)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)butyl)hydrazine-1,2-**

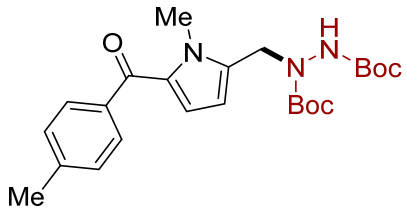
**dicarboxylate (3u):**Following the general procedure **GP1** with DCM (1 ml) instead of MeCN, two reactions of **1u** (0.2 mmol each one) afforded **3u** as a white foam in 28% yield (75 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers. Only distinguishable signals are reported in the $^{1}H$ NMR. One $^{13}C$ NMR signal (23-C) is only detectable indirectly using the HSQC sequence, due to signal broadening in presence of amide rotamers (see picture for details).* Mp: 46-47°C (from hexane:AcOEt). $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 6.45 – 6.04 (br m, 1H, NH), 3.57 (tt, $^{3}J$ = 10.8, 4.6 Hz, 1H, 3-C), 3.51 – 3.32 (m, 2H, $CH_2N$) 1.46 (m, 18H, $C(CH_3)_3$), 0.88 (s, 9H, $C(CH_3)_3$-silyl), 0.62 (s, 3H, 18-C), 0.05 (s, 6H, $Si(CH_3)_2$). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 155.6 (br), 81.2, 73.0, 56.5, 56.3, 42.9, 42.4, 40.3, 40.3, 37.1, 36.0, 35.7, 34.7, 31.2, 28.7–28.4 (m), 28.3, 27.4, 26.5, 26.1, 24.3, 23.5, 20.9, 18.9, 18.5, 12.1, -4.5. HRMS (ESI+) m/z: $[M+Na]^+$ calc. for $[C_{39}H_{72}N_2O_5Si + Na]$ 699.5103; found: 699.5098. FT-IR (neat, $cm^{-1}$): 3325 (stretch N-H), 2930, 2859, 1707 (stretch C=O), 1454, 1368, 1252, 1148, 1077.




**di-*tert*-butyl 1-((1-(((*tert*-butoxycarbonyl)amino)methyl)*cyclo*hexyl)methyl)hydrazine-1,2-dicarboxylate (3v):** Following the general procedure **GP1** with additional DCM (0.5 ml) to improve the solubility of the substrate, two reactions of **1v** (0.2 mmol each one) afforded **3v** as a white sticky foam in 50% yield (92 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers, as well as the conformational flexibility of the cyclohexyl moiety*. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 6.68 – 5.35 (br m, 2H, NH), 3.89 – 2.60 (br m, 4H, $CH_2N$), 1.58 – 1.27 (m, 37H, $C(CH_3)_3$, $CH_2$). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 156.7 (br), 155.1 (br), 82.0 – 81.0 (br m), 78.7 (br), 56.5 (br), 44.5 (br), 39.0, 33.0 – 31.0 (br m), 28.6, 28.3, 28.2, 26.3, 21.5. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{23}H_{43}N_3O_6 + H]$ 458.3225; found: 458.3228. $[M+Na]^+$ calc. for $[C_{23}H_{43}N_3O_6 + Na]$ 480.3044; found: 480.3039. FT-IR (neat, $cm^{-1}$): 3310 (stretch N-H), 2978, 2930, 2866, 1692 (stretch C=O), 1510, 1454, 1394, 1364, 1282, 1252, 1148.

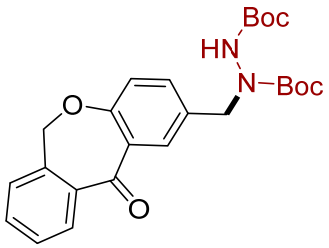


**di-*tert*-butyl 1-((2-(4-chlorophenyl)thiazol-4-yl)methyl)hydrazine-1,2-dicarboxylate (3w):** Following the general procedure **GP1**, with the following modification: DMSO was used as solvent and the system was degassed by bubbling $N_2$ for 5 minutes. Two reactions of **1w** (0.2 mmol each one) afforded **3w** as white semi-solid in 30% yield (50 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers.* $^1$H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 2H, 3-ArH), 7.40 – 7.35 (m, 2H, 2-ArH), 7.21 – 7.15 (br m, 1H, *thiazole*-CH), 6.60 – 6.30 (br s, 1H, NH), 4.85 – 4.60 (br m, 2H, $ArCH_2N$), 1.53 –1.38 (m, 18H, $C(CH_3)_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.9, 156.0 – 154.8 (br m), 154.0 (br), 136.0, 132.0, 129.2, 127.8, 116.3, 81.6 (br s), 81.3 (br s), 52.0 – 48.8 (br m), 20.2. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{20}H_{26}ClN_3O_4S + H]$ 440.1405; found: 440.1407. FT-IR (neat, $cm^{-1}$): 3317 (stretch N-H), 2978, 2933, 1707 (stretch C=O), 1495, 1394, 1368, 1249, 1148, 1003.

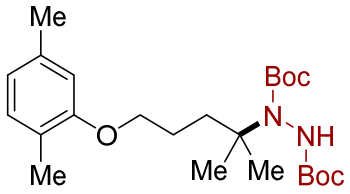



**di-*tert*-butyl 1-((1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)methyl)hydrazine-1,2-dicarboxylate (3x):**

Following the general procedure **GP1**, with the following modification: DMSO was used as solvent, the system was degassed by bubbling $N_2$ for 5 minutes and no $Cs_2CO_3$ was added (the substrate is the sodium salt). Two reactions of tolmetin sodium salt·$2H_2O$ **1x** (0.2 mmol each one) afforded **3x** as an off-white semi-solid in 40% yield (70 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers.* $^1$H NMR (300 MHz, $CD_2Cl_2$) δ 7.68 (d, $^3J$ = 8.1 Hz, 2H, 2-ArH), 7.26 (d, $^3J$ = 8.1 Hz, 2H, 2-ArH), 6.90 – 6.50 (br m, 2H, *pyrrole*-CH), 6.16 (br, 1H, NH), 4.80 – 4.58 (br m, 2H, $ArCH_2N$), 3.94 (s, 3H, $NCH_3$), 2.42 (s, 3H, $ArCH_3$), 1.49 – 1.46 (br s, 18 H, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CD_2Cl_2$) δ 186.3, 156.4 (br s), 155.7 – 155.3 (br m), 142.6, 137.9, 137.7, 132.8, 129.9, 129.2, 122.1, 111.4 – 110.7 (br m), 82.3 – 81.3 (br m), 82.1, 44.9 (br), 33.7, 28.5, 21.8. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{24}H_{33}N_3O_5 + H]$ 444.2493; found: 444.2492. FT-IR (neat, $cm^{-1}$): 3317 (stretch N-H), 2978, 2933, 1707 (stretch C=O), 1626 (stretch C=O), 1484, 1368, 1252, 1148, 1044.

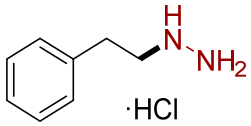



**di-*tert*-butyl 1-((11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)methyl)hydrazine-1,2-dicarboxylate (3y):** Following the general procedure **GP1**, with the following modification: DMSO was used as solvent and the system was degassed by bubbling $N_2$ for 5 minutes. Two reactions of **1y** (0.2 mmol each one) afforded **3y** as an off-white semi-solid in 56% yield (100 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers.* $^1$H NMR (300 MHz, $CDCl_3$) δ 8.08 (br s, 1H, ArH), 7.82 (dd, $^3J$ = 7.5 Hz, $^4J$ = 1.2 Hz, 1H, ArH), 7.50 (td, $^3J$ = 7.5 Hz, $^4J$ = 1.5 Hz, 1H, ArH), 7.44 – 7.38 (m, 2H, ArH), 7.32 – 7.30 (m, 1H, ArH), 6.97 (d, $^3J$ = 8.4 Hz, 1H, ArH), 6.60 – 6.20 (br m, 1H, NH), 5.16 (s, 2H, $ArCH_2O$), 4.70 – 4.32 (br m, 2H, $CH_2N$) 1.45 – 1.41 (br s, 18H, $C(CH_3)_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.8, 160.7, 155.8 (br s), 155.2 (br s), 140.4, 135.5, 132.8, 131.5, 131.1, 129.4, 129.2, 127.8, 124.9, 121.0, 82.5 – 80.5 (br m), 73.5, 53.7 (br), 52.2 (br), 28.22, 28.16. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{25}H_{30}N_2O_6 + H]$ 455.2177; found: 455.2178. FT-IR (neat, $cm^{-1}$): 3329 (stretch N-H), 2978, 2933, 1707 (stretch C=O), 1648 (stretch C=O), 1610 (stretch C=O), 1491, 1368, 1297, 1241, 1148, 1047, 1017.

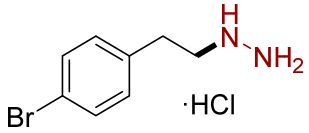



**di-*tert*-butyl 1-(5-(2,5-dimethylphenoxy)-2-methylpentan-2-yl)hydrazine-1,2-dicarboxylate (3z):** Following the general procedure **GP1**, two reactions of **1z** (0.1 mmol each one) afforded **3z** as a white semi-solid in 72% yield (62 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers.* $^1$H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.99 (m, 1H, ArH), 6.66 – 6.62 (m, 2H, ArH), 6.30 – 5.85 (br m, 1H, NH), 3.93 (t, $^3J$ = 4.5 Hz , 1H, $OCH_2$), 2.31 (s, 3H, $ArCH_3$), 2.18 (s, 3H, $ArCH_3$), 2.10 – 2.07

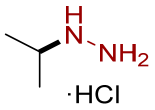
(m, 1H), 1.88 – 1.74 (m, 3H), 1.48 – 1.46 (m, 21H), 1.32 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.1, 156.8 – 156.0 (br m), 155.0 – 154.2 (br m), 136.5, 130.4, 123.6, 120.7, 112.1, 81.5, 80.9 (br s), 80.7 (br s), 68.2, 61.9, 36.9, 28.4, 28.3, 27.0, 24.9, 21.5, 15.9. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{24}H_{40}N_2O_5 + H]$ 437.301; found: 437.3007. FT-IR (neat, $cm^{-1}$): 3332 (stretch N-H), 2978, 2930, 1703 (stretch C=O), 1613 (stretch C=O), 1588, 1509, 1476, 1390, 1252, 1156, 1081, 1044.



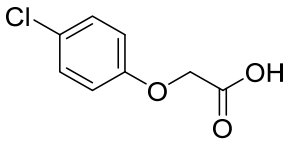

**[2-(phenyl)ethyl]hydrazine·HCl– Phenelzine·HCl (6b)**: According to the general procedure for the Boc-deprotection **GP2**, **3b** (64 mg, 0.19 mmol) reacted to afford the corresponding hydrazine hydrochloride salt **6b** as an off-white solid in quantitative yield (33 mg). *The reference peak overlaps with one multiplet of the product.* $^1$H NMR (300 MHz, $CD_3OD$) δ 7.37 – 7.19 (m, 5H, ArH), 3.35 – 3.24 (m, 2H, $CH_2N$), 2.98 (t, $^3J$ = 8.0 Hz, 2H, $ArCH_2$). $^{13}$C NMR (101 MHz, $CD_3OD$) δ 138.3, 129.8, 129.7, 128.0, 53.6, 32.5. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_8H_{12}N_2 + H]$ 137.1073; found: 137.1073.




**[2-(4-bromophenyl)ethyl]hydrazine·HCl (6d)**: According to the general procedure for the Boc-deprotection **GP2**, **3d** (27.7 mg, 6.7 µmol) reacted to afford the corresponding hydrazine hydrochloride salt **6d** as a light-yellow solid (17.0 mg, quantitative yield). Mp 110-112°C (dec., from MeOH). *In the case of aromatic multiplets, only the $^3J$ coupling constant could be obtained and was therefore reported.* $^1$H NMR (300 MHz, $CD_3OD$) δ 7.42 – 7.32 (m, $^3J$ = 8.4 Hz, 2H, 3-ArH), 7.16 – 7.05 (m, $^3J$ = 8.4 Hz, 2H, 2-ArH), 3.18 – 3.10 (m, 2H, $CH_2N$), 2.82 (t, $^3J$ = 7.9 Hz, 2H, $ArCH_2$). $^{13}$C NMR (75 MHz, $CD_3OD$) δ 137.8, 132.9, 131.8, 121.7, 53.0, 32.2. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_8H_{11}{}^{79}BrN_2 + H]$ 215.0178; found: 215.0181. $[M+H]^+$ calc. for $[C_8H_{11}{}^{81}BrN_2 + H]$ 217.0158; found: 217.0159.



**Isopropylhydrazine·HCl (6p)**: According to the general procedure for the Boc-deprotection**GP2**, **3p** (64 mg, 0.19 mmol) reacted to afford the corresponding hydrazine hydrochloride salt **4p** as a white solid in quantitative yield (46 mg). *One multiplet overlaps with the residual solvent signal, but the deconvolution was possible (see attached spectra for details).* $^{1}$H NMR (300 MHz, $CD_3OD$) δ 3.32 (hept, $^{3}J$ = 6.6 Hz, 1H, CHN), 1.30 (d, $^{3}J$ = 6.6 Hz, 6H, $CH_3$). $^{13}$C NMR (101 MHz, $CD_3OD$) δ 54.9, 17.8. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_3H_{10}N_2 + H]$ 75.0917; found: 75.0919.

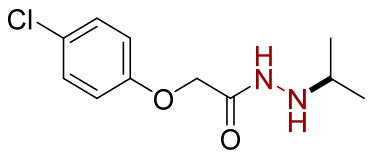


**2-(4-chlorophenoxy)acetic acid:** The compound was synthesized using a modified version of the synthesis reported by Vitelino *et al.*[6]

In a round-bottom flask equipped with a PTFE-coated stirring bar and a reflux condenser, 4-chlorophenol (2.11 g. 16.4 mmol, 1.0 equiv.), $K_3PO_4$ (8.71 g, 41.0 mmol, 2.5 equiv.) and methyl 2-bromoacetate (2.49 ml, 24.6 mmol, 1.5 equiv.) were dissolved in acetone (7 ml) and the reaction was heated-up at 60 ºC for 17 hours, then water (22 ml) was added and the acetone was removed under reduced pressure. The aqueous solution was heated-up at 95 ºC for 60 minutes, then one NaOH pallet (approx. 200 mg) was added and the reaction was stirred for an additional hour, then cooled-down to room temperature. HCl 37% was added until pH 1 was reached, then the resulting precipitated solid was recovered by filtration and washed once with water (30 ml) and hexane (30 ml). The white solid (*containing residual methyl bromoacetate*) was triturated with 15 ml of AcOEt, then filtered and washed with additional 15 ml of AcOEt. The white solid was dried under reduced pressure, to afford pure 2-(4-chlorophenoxy)acetic acid.

$^{1}$H NMR (300 MHz, $CD_3OD$) δ 7.28 – 7.19 (m, 2H), 6.96 – 6.86 (m, 2H), 4.48 (s, 2H). *The experimental data are in accordance with the literature.*[6]

[6] K. Belecki, M. Berliner, R.T. Bibart, C. Meltz, K. Ng, J. Phillips, D.H. Brown Ripin, M. Vitelino*, Org. Process. Res. Dev.*, **2007**, 11 (4), 754-761

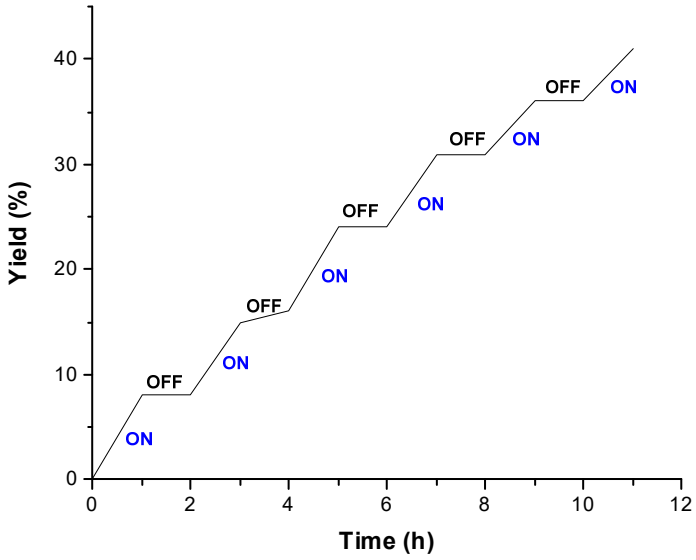



2-**(4-chlorophenoxy)-*N*'-isopropylacetohydrazide (Iproclozide) (7p)**: In a round-bottom flask equipped with a PTFE stirring bar and a reflux condenser, CDI (50 mg, 0.31 mmol, 1.1 equiv.) was dissolved in dry THF:DMF (1:1, 2 ml) under nitrogen atmosphere, then 2-(4-chlorophenoxy)acetic acid (52 mg, 0.28 mmol, 1.0 equiv.) was added in one portion and the reaction was stirred at room temperature for 60 minutes, then **6p**(40 mg, 0.36 mmol, 1.3 equiv.) in dry DMF (1 ml) was added in one portion, followed by $Et_3N$ (66 µl, 0.47 mmol, 1.7 equiv.). The reaction was stirred at 80°C overnight, then cooled-down to room temperature. The residual THF was removed under reduced pressure, then the residue was taken-up with DCM (10 ml) and water (10 ml) and the layers were separated. The water layer was extracted once with DCM (10 ml), then the combined organic layers were washed twice with water (10 ml each time) and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the crude was purified by flash chromatography on silica (hexane:AcOEt 3:7) to afford **7p** as an off-white semi-solid in 38% yield over two steps (25 mg).

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H, 3-ArH), 6.88 – 6.82 (m, 2H, 2-ArH), 4.54 (s, 1H, $OCH_2C(O)$), 3.15 (hept, $^3J$ = 6.3 Hz, 1H, NCH), 1.05 (d, $^3J$ = 6.3 Hz, 6H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.0, 155.8, 129.9, 127.4, 116.0, 67.4, 51.6, 20.8. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{11}H_{15}N_2O_2Cl + H]$ 243.0895; found: 243.0897. FT-IR (neat, $cm^{-1}$): 3295 (stretch N-H), 2971, 2930, 2874, 1659 (stretch C=O), 1584, 1491, 1439, 1368, 1296, 1226, 1170, 1092, 1054.

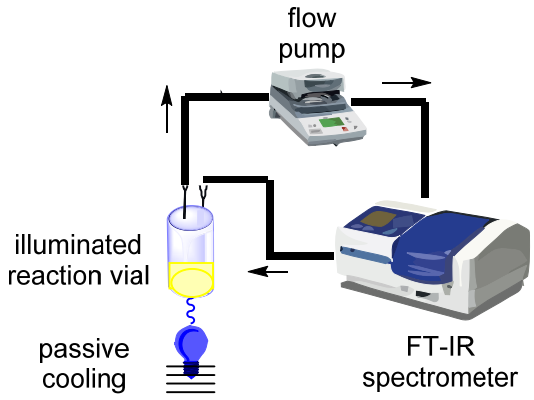
## Mechanistic studies

**ON/OFF experiment:** A 10 mL glass vial was charged with carboxylic acid (0.3 mmol), $CeCl_3 \cdot 7H_2O$ (10 mol%), DBAD (1.5 equiv.), $Cs_2CO_3$ (20 mol%) and stirring bar, then glass vial was sealed with a PTFE septum. Solvent (3 mL), benzoyl benzoate (0.3 mmol, internal standard) was added and the reaction was purged by fluxing nitrogen through an hypodermic needle. The reactions were placed in a pre-programed temperature controlled blue LED reactor (as shown in **Figure 1**) and the reaction mixture was irradiated with a 455 nm blue LED. After the selected time has expired, a small aliquot was removed. The aliquots were quenched with $NaHCO_3$, then extracted with EtOAc (2 x 1 ml). The combined organic layers were concentrated under reduced pressure and then analyzed by $^1H$ NMR to determine the yield.




The above reaction profile upon the alternating irradiation shows that the reaction can only proceed in presence of light, whereas the catalytic activity is inhibited under darkness, thus confirming the previous results from the conditions screening.

***In-situ* Infrared spectroscopy:**




A custom-made set-up (see simplified scheme) allowed the monitor of the $CO_2$ evolution by means of IR spectroscopy. The system set-up was described below. The reaction mixture was prepared according to **GP1** for **1a** in a standard crimp-cap vial and irradiated through the bottom plane with a single 455 nm LEDs (OSRAM Oslon® SSL 80 royal□blue LEDs (□$_{max}$= 455 nm (± 15 nm), 3.5 V, 700 mA) mounted on a passive cooling system. The reaction was stirred using a standard magnetic stirring plate (approx. 250 rpm). An hypodermic needle was immersed in the reaction and attached through a PTFE tube (ø= 2 mm) to an Ismatec® IPC dispensing pump (flow rate: 0.5 ml·min$^{-1}$). The pump was connected using a PTFE tube (ø = 2 mm) to a IR sample holder (see picture below) inserted into a Varian 3100 FT-IR Excalibur Series IR spectrometer. The sample holder outlet was connected through a PTFE tube (ø= 2 mm) to a needle which re-injected the solution into the reaction vial. The IR spectra were collected at 1 hour intervals and analysed using a Varian proprietary suite.


**Figure 2**: IR chamber for *in-situ* acquisition. The inlet and outlet are highlighted.

As visible in the pictures below, the $CO_2$ evolution can be detected monitoring the signal at 2342 reciprocal centimetres, which could be attributed to the asymmetric stretching of the molecule. Over time, the amount of carbon dioxide in solution increases, as visible by the plot absorbance vs. time, thus indicating the progression of the reaction.

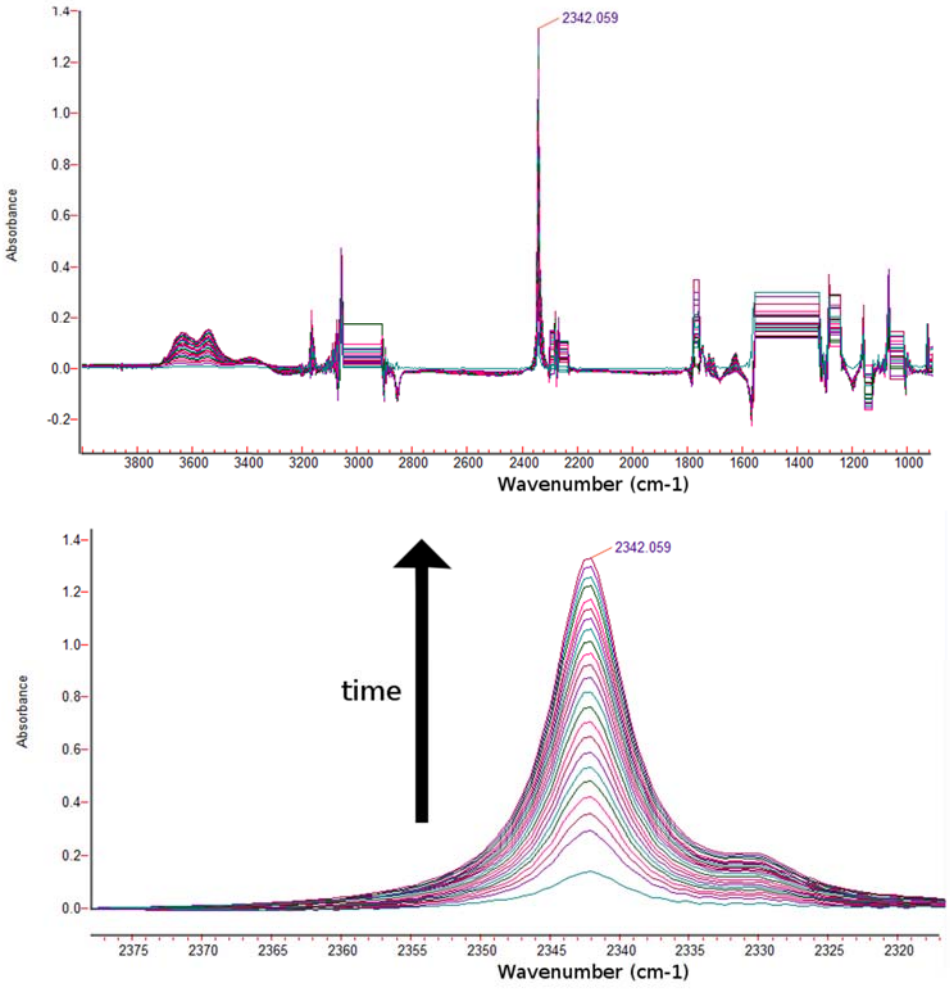
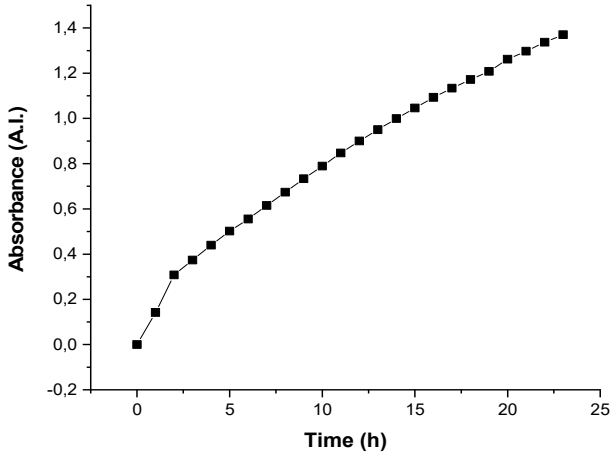
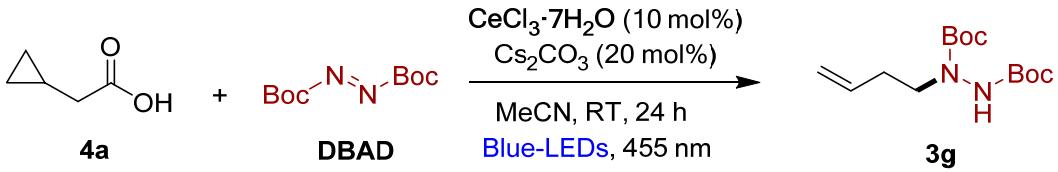



**Figure 3**: (*upper*) Full FT-IR spectrum of the reaction solution at different reaction times. (*lower*) Enlarged section of the upper spectrum, highlighting the asymmetric stretch of $CO_2$ at different reaction times.



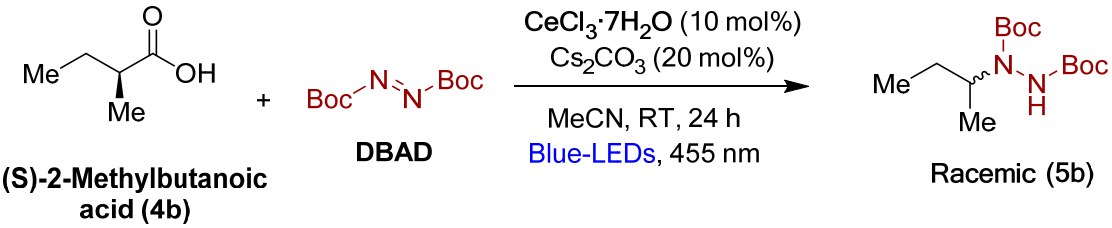
As reported in the above graph, no evolution of $CO_2$ could be detected when the reaction is not irradiated (time = 0 h). While it could be hypothesized that the small amount of base (20 mol %) could partially decompose to form $CO_2$, the evolution must have stopped after a limited amount of time, which was not the case. For this reason, we believe that the carbon dioxide evolution represents a strong indication of the decarboxylative event.

**Radical clock experiment**



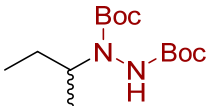

Following the general procedure **GP1**, two reactions of **4a** (0.2 mmol each one) afforded **3g** as an off-white solid in 57 % yield (64 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. Mp: 78-80°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.50 – 6.14 (br m, 1H, NH), 5.76 (ddt, $^{3}J$ = 17.0, 10.2, 6.8 Hz, 1H, C=CH), 5.05 (dq, $^{3}J$ = 17.2 Hz, $^{4}J$ = 1.7 Hz, 1H, *cis*-C=$CH_2$), 5.00 (d, $^{3}J$ = 10.2 Hz, 1H, *trans*-C=$CH_2$, *broadening due to $^{4}J$ visible*), 3.60 – 3.40 (br m, 2H, $CH_2N$), 2.31 (q, $^{3}J$ = 7.1 Hz, 2H, *allyl*-$CH_2$, *broadening due to $^{4}J$ visible*), 1.45 (s, 9H, $C(CH_3)_3$), 1.44 – 1.39 (br m, 9H, $CH_3$, $C(CH_3)_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 155.7 – 155.2 (br m), 116.6, 81.1 (br s), 50.2 (br s), 48.8, 32.6-31.8 (br m), 28.3. HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{14}H_{26}N_2O_4$+ H] 287.1965; found: 287.1961. FT-IR (neat, $cm^{-1}$): 3310, 2979, 2933, 1703, 1491, 1364, 1252, 1148.

**Decarboxylative hydrazination (*S*)-2-Methylbutanoic acid**




Following the general procedure **GP1**, two reactions of (S)-2-Methylubutanoic acid (0.2 mmol each one) afforded the corresponding Boc-protected hydrazine as an off-white solid in 79 % yield (90 mg). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 6.20 – 5.50 (br m, 1H, 3-ArH), 4.30 – 3.80 (br m, 1H, CHN), 1.47 (s, 9H, *boc*-$CH_3$), 1.46 (s, 9H, *boc*-$CH_3$), 1.41-1.19 (m, 2H, $CH_2$) 1.09 (d, $^{3}J$ = 6.8 Hz, 3H, $CH_3$) 1.00-0.76 (br, 2H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.0 – 154.6 (br m), 80.8 (br), 56.8-53.6 (br m), 28.4, 28.3, 27.2 (br), 17.7 (br), 11.2 (br). HRMS (ESI+) m/z: $[M+H]^+$ calc. for $[C_{14}H_{28}N_2O_4$+ H] 289.2122; found: 289.2116.

Synthesis of an authentic racemic sample:




(±)

**(±)-di-*tert*-butyl 1-(*sec*-butyl)hydrazine-1,2-dicarboxylate (5b)**: In an oven-dried Schlenk flask equipped with a PTFE stirring bar, magnesium turnings (378 mg, 15.6 mmol, 1.7 equiv.) were added, then the flask was further flame-dried under vacuum. The flask was purged three times with $N_2$, then dry THF (30 ml) was added, followed by a small iodine crystal. The suspension was vigorously stirred until the yellow colour fainted (*approx. 5 minutes*), then (±)-2-bromobutane (1.5 ml, 13.7 mmol, 1.5 equiv.) was slowly added controlling the exothermic process with a water bath, then upon completion of the addition the reaction was stirred for 30 minutes. The solution was cooled-down to -78°C, then DBAD (2.11 g, 9.2 mmol, 1.0 equiv.) in dry THF (10 ml) was added dropwise (*immediate discoloration of the dripped solution was observed*) and the reaction was gently warmed-up at room temperature for 30 minutes. The reaction was quenched by the addition of a saturated $NH_4Cl$ solution (30 ml), diluted with water (20 ml) and AcOEt (50 ml). The layers were separated and the water layer was extracted once with AcOEt (30 ml), then the combined layers were washed with magnesium sulphate and the solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica (hexane:AcOEt 95:5 to 9:1), affording the corresponding Boc-protected hydrazine **5b** as a white crystalline solid (1.21 g, 28% yield). *Signal broadening and additional splitting could be observed due to the presence of amide rotamers*. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.20 – 5.50 (br m, 1H, 3-ArH), 4.30 – 3.80 (br m, 1H, CHN), 1.47 (s, 9H, *boc*-$CH_3$), 1.46 (s, 9H, *boc*-$CH_3$), 1.41-1.19 (m, 2H, $CH_2$) 1.09 (d, $^3J$ = 6.8 Hz, 3H, $CH_3$) 1.00-0.76 (br m, 2H, $CH_3$).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 157.0 – 154.6 (br m), 80.8 (br), 56.8-53.6 (br m), 28.4, 28.3, 27.2 (br), 17.7 (br), 11.2 (br). HRMS (ESI+) m/z: $[M+H]^+$ calc. for [$C_{14}H_{28}N_2O_4$+ H] 289.2122; found: 289.2116. FT-IR (neat, $cm^{-1}$): 3288 (stretch N-H), 2974, 2933, 1737 (stretch C=O), 1677 (stretch C=O), 1521, 1405, 1364, 1238, 1156, 1103.

Optical rotation of an authentic racemic sample:

$[\alpha]_{589}$ (293.15 K, $CHCl_3$) = +0.23 degrees·$dm^{-1}$ (0.3 g/ 100 ml)

Optical rotation of the reaction sample:

$[\alpha]_{589}$ (293.15 K, $CHCl_3$) = -0.60 degrees·$dm^{-1}$ (0.3 g/ 100 ml)

Within the experimental error, no significant difference in the optical rotation of an independently synthesized sample and the reaction product could be detected. Therefore, it must be concluded that racemization occurs during the reaction.

**UV-Vis experiments**

In order to verify whether the interaction with the substrate carboxylic acids **1a-z** and cerium (IV) could lead to the overall LMCT process, which reduced the Ce(IV) species to Ce(III), a similar approach to the one reported by Zuo *et al.* was used.[7] $(^{n}Bu_4)_2Ce^{IV}Cl_6$ was chosen as a Ce(IV) source to ensure sufficient solubility in organic solvents and facilitate the detection of the species.

*Synthesis of* $(^{n}Bu_4)_2Ce^{IV}Cl_6$

In a round-bottom flask equipped with a teflon-coated stirring bar, tetrabutylammonium chloride (3.24 g, 11.7 mmol, 2.0 equiv.) and $Ce(SO_4)_2{\cdot}(H_2O)_n$ (2.36 g, 5.8 mmol, 1.0 equiv.) were charged, then HCl 37% (15 ml) was added at room temperature. After the formation of a yellow-orange precipitate, additional tetrabutylammonium chloride (324 mg, 1.2 mmol, 0.1 equiv.) was added and the reaction additionally stirred for 20 minutes. The suspension was cooled-down to 5°C using an ice-water bath, then the solid was collected by suction-filtration over a sintered funnel, then the yellow-orange solid was washed three times with the minimal amount of acetone (approx. 10 ml each time) and dried under high vacuum, to afford an intensely yellow powder (504 mg, 0.72 mmol, 12% yield).

*Preparation of a basic solution of* $(^{n}Bu_4)_2Ce^{IV}Cl_6$ *in* MeCN *(solution A).*

In a glass vial equipped with a teflon-coated stirring bar and a septum, $(^{n}Bu_4)_2Ce^{IV}Cl_6$ (1.1 mg, 1.3 μmol) and $Cs_2CO_3$ (7.0 mg, 21 μmol) were dissolved in MeCN (3 ml, analytical grade, Carl Roth) and the solution was degassed by bubbling argon for 10 minutes, under vigorous stirring.

*Preparation of a basic solution of* $(^{n}Bu_4)_2Ce^{IV}Cl_6$ and cyclohexylcarboxylic acid **1l** *in* MeCN *( solution B).*

In a glass vial equipped with a teflon-coated stirring bar and a septum, $(^{n}Bu_4)_2Ce^{IV}Cl_6$ (1.1 mg, 1.3 μmol), $Cs_2CO_3$ (7.0 mg, 21 μmol) and **1l** (51.2 mg, 0.4 mmol) were dissolved in MeCN (3 ml, analytical grade, Carl Roth) and the solution was degassed by bubbling argon for 10 minutes, under vigorous stirring.

[7] A. Hu, J.-J. Guo, H. Pan, H. Tang, Z. Gao, Z. Zuo, *J. Am. Chem. Soc*. **2018,** 140, 1612−1616

*Experimental procedure and sampling*

The UV-Vis measurement where performed using an Agilent Cary 100 spectrometer using a temperature-controlled (20.0 °C) fluorescence cuvette (1 cm optical pathway, both faces can transmit light) A single blue LED OSRAM Oslon® SSL 80 royal-blue LEDs ($\lambda_{max}$= 455 nm (± 15 nm), 3.5 V, 700 mA), equipped with a metallic passive cooling element, was placed approx. 2 mm away from one transmitting side of the cuvette, at 90° from the measuring beam. The spectra were recorded in the 200-550 nm range.

In order to record the spectra, the corresponding previously degassed solution was withdrawn using a syringe under argon atmosphere, filtered-off a Macherey-Nagel CHROMAFIL® O-20/15 MS PTFE filter and the cuvette sealed with a PTFE stopper. The acquisition routine was started (one scan every 30 seconds) and after a certain amount of time the illumination was started.

*Spectra acquisition in the absence of cyclohexylcarboxylic acid (***1l***).*

Solution A was used, each spectrum was acquired after 30 seconds from the previous. The first three spectra (**Figure 4**, different shades of green) were recorded in the absence of light irradiation, while the latter (**Figure 4**, different shades of red) have been recorded in the presence of 455 nm irradiation.

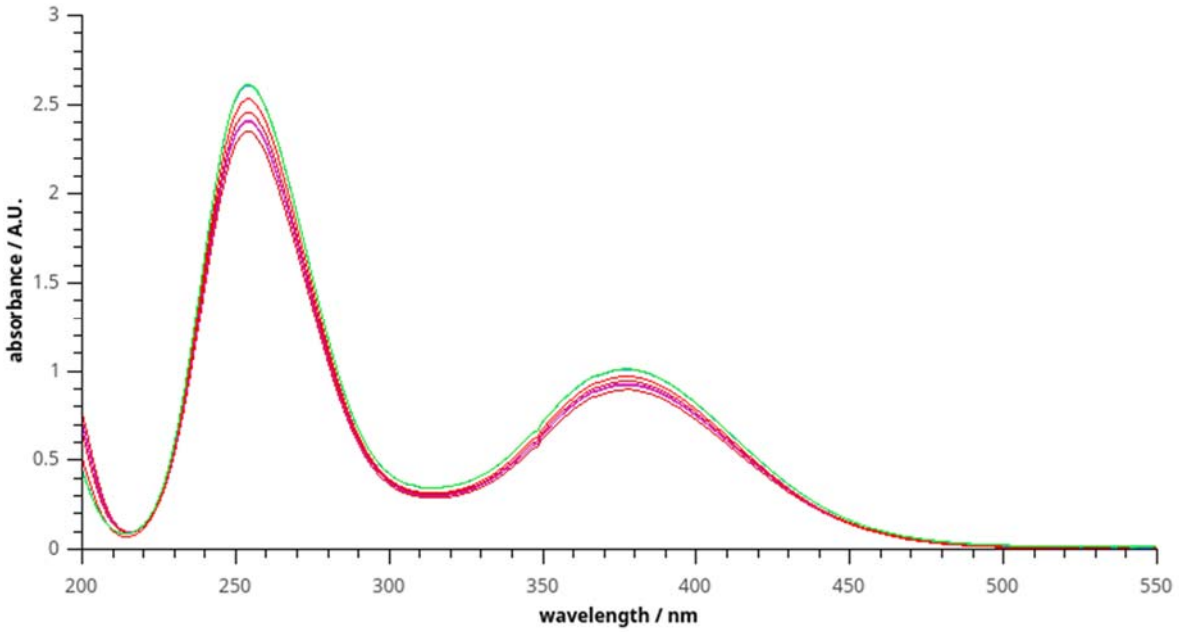



**Figure 4**: Overlay of the UV-Vis spectra of a basic solution of $(^{n}Bu_4)_2Ce^{IV}Cl_6$ in the absence of light (shades of green) and upon blue light irradiation (shades of red).

As visible in **Figure 4**, the typical Ce(IV) LMCT transition could be detected at around 380 nm. Without irradiation, the concentration of Ce(IV) species remained constant over time (green). By increasing the irradiation time, a slight decrease in the amount of Ce(IV) could be observed (red). The Ce(III) band, expected at approximately 340 nm, was most likely hidden by the other more intense transitions.

*Spectra acquisition in the presence of cyclohexylcarboxylic acid (**1l**).*

Solution B was used, each spectrum was acquired after 30 seconds from the previous. The first 10 acquisitions (**Figure 5**, different shades of red) have been recorded in the absence of light irradiation, while the latter (**Figure 5**, different shades of blue) were recorded under blue light irradiation.

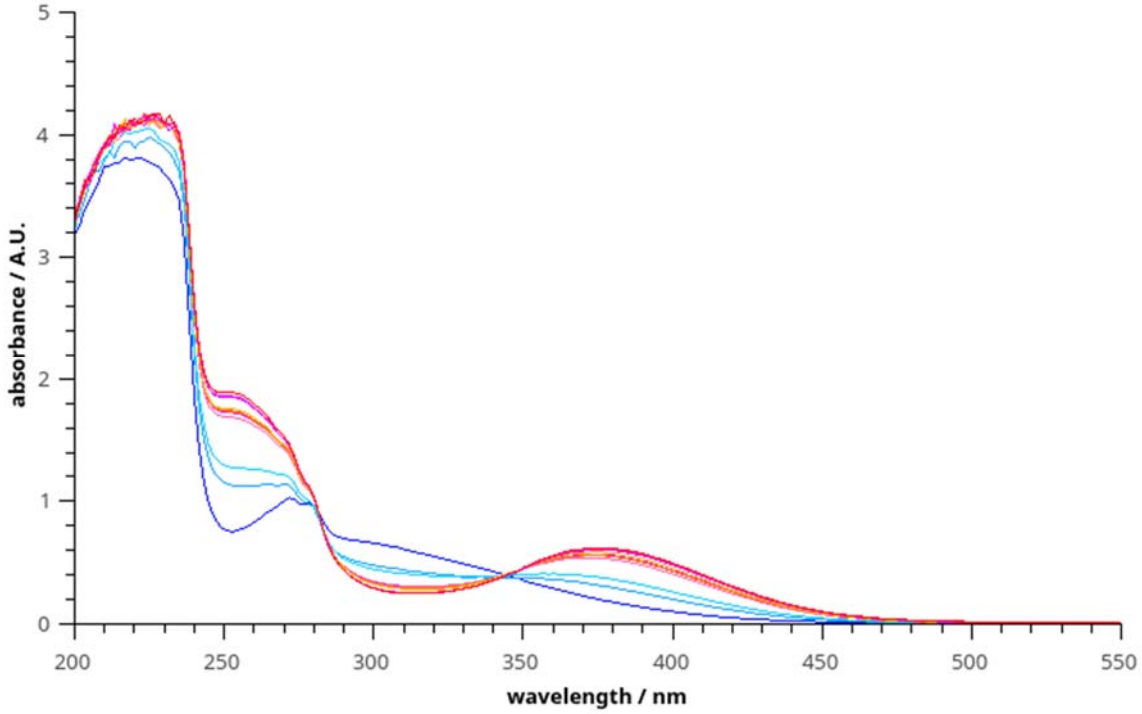



**Figure 5**: Overlay of the spectra in the presence of cyclohexylcarboxylic acid (**1l**). Orange-red: before the illumination with 455 nm light. Blue: after the illumination with 455 nm light.

In the presence of carboxylic acid **1l**, the concentration of Ce(IV) species remained almost constant without blue light irradiation (**Figure 5**, orange-red). The small modulation was most likely caused by the fact that, in order to operate the spectroscopic device, absolute darkness could not be reached. Upon irradiation with 455 nm light, an extremely fast reduction of the

Ce(IV) species ($\lambda_{max}$ ≈ 380 nm) to Ce(III) species (broad and partially overlapped peak at lower wavelengths) (**Figure 5**, blue) was observed.

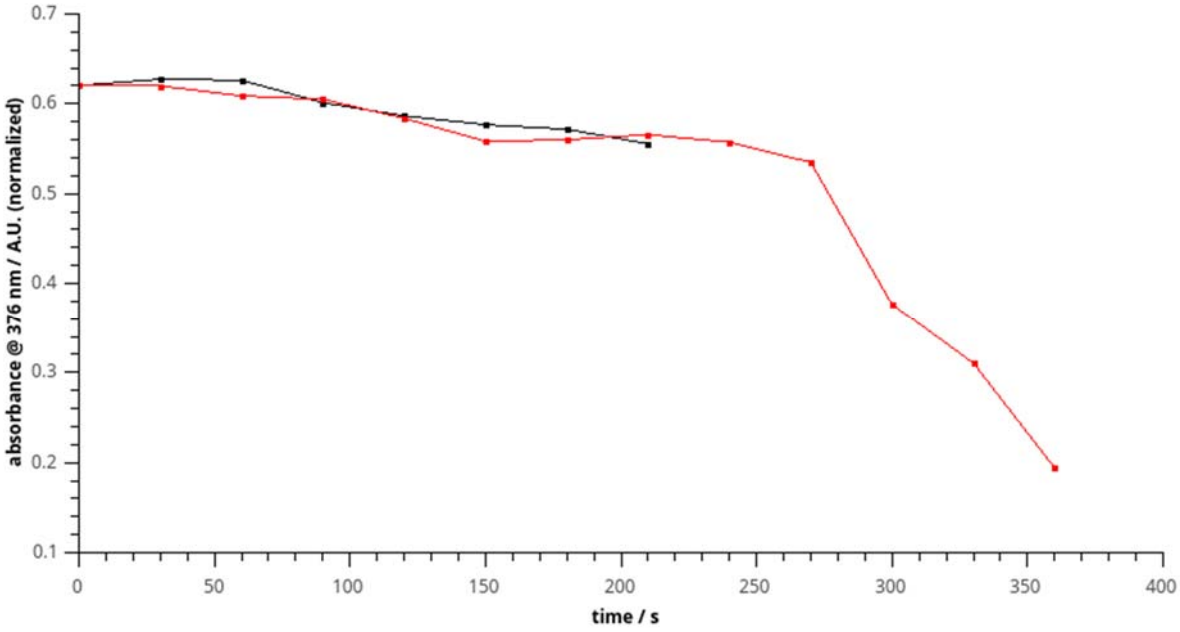



**Figure 6**: Overlay of the absorbance values (normalized at the same arbitrary unit) measured at 376 nm for the solution without **1l** (black) and with **1l** (red). For the single spectra, see **Figure 4** and **5**.

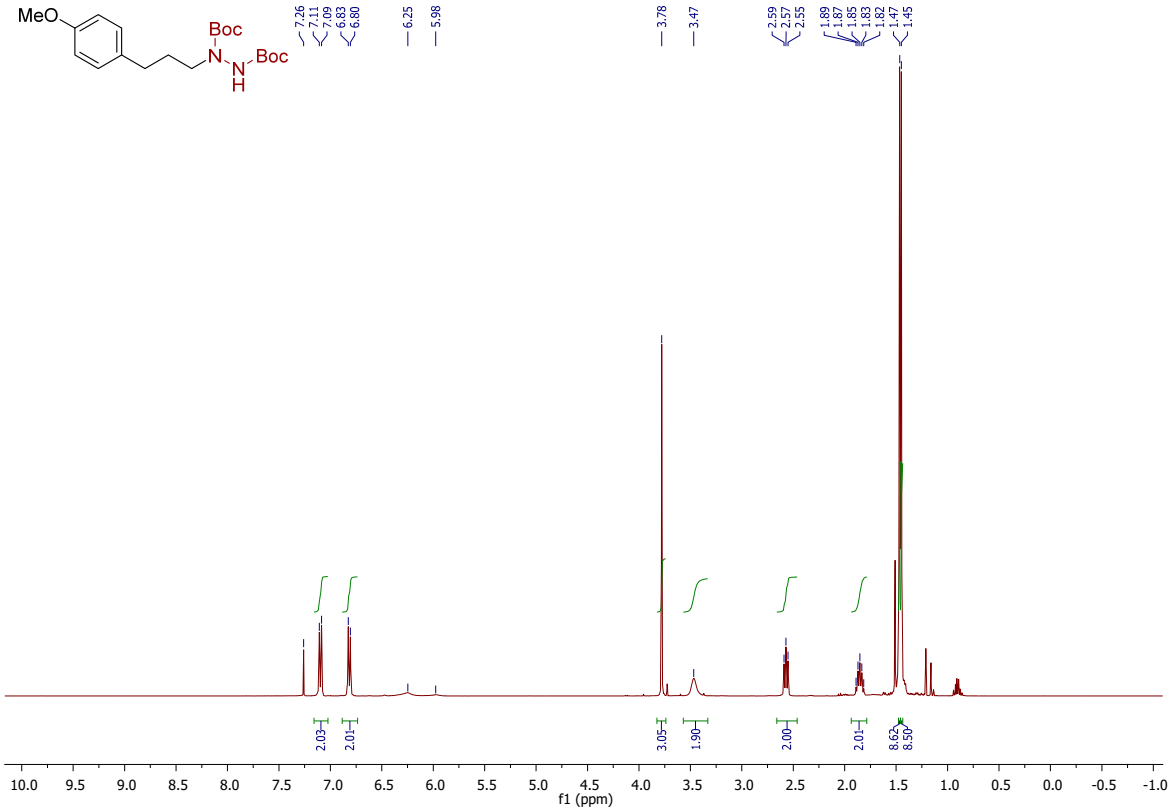
As visible in **Figure 6** (black line), in the absence of the carboxylic acid **1l** a very small consumption of Ce(IV) species occurs, both in the absence and presence of light. We might assume that the small reduction of the species is due to the coordinated solvent or the ammonium counterion.

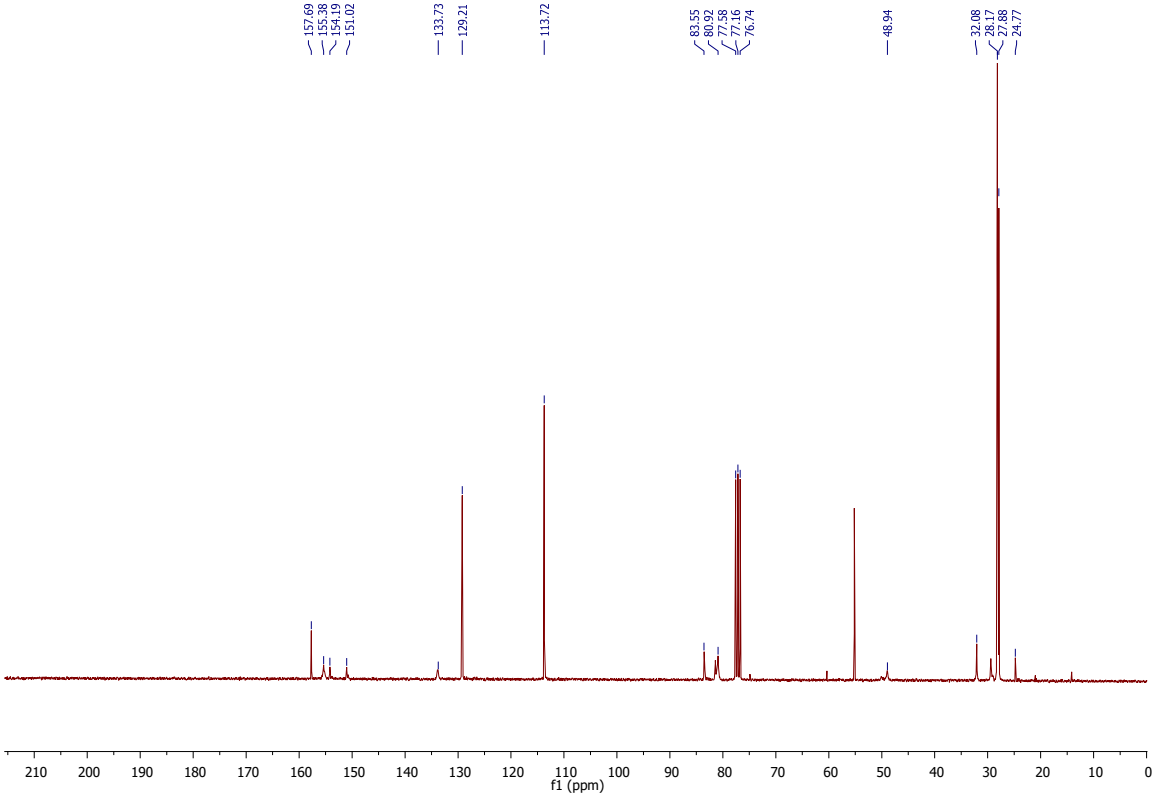
In the presence of **1l**, a similar profile could be observed in the absence of light, while when the illumination was switched-on the fast consumption of Ce(IV) was observed, with the increase of a new peak (most likely Ce(III)) at lower wavelengths.

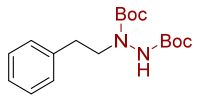
Because only the presence of the carboxylic acid **1l** and the irradiation at 455 nm caused the fast consumption of the Ce(IV) species, we showed that the substrate and the irradiation of the *in-situ* formed complex can perform the visible-light induced reduction of cerium, while this is not possible in the absence of **1l**. Moreover, the aforementioned observations corroborate the hypothesis that the Ce(IV) reduction (and thus the radical formation) can occur at a synthetically useful rate only upon irradiation.

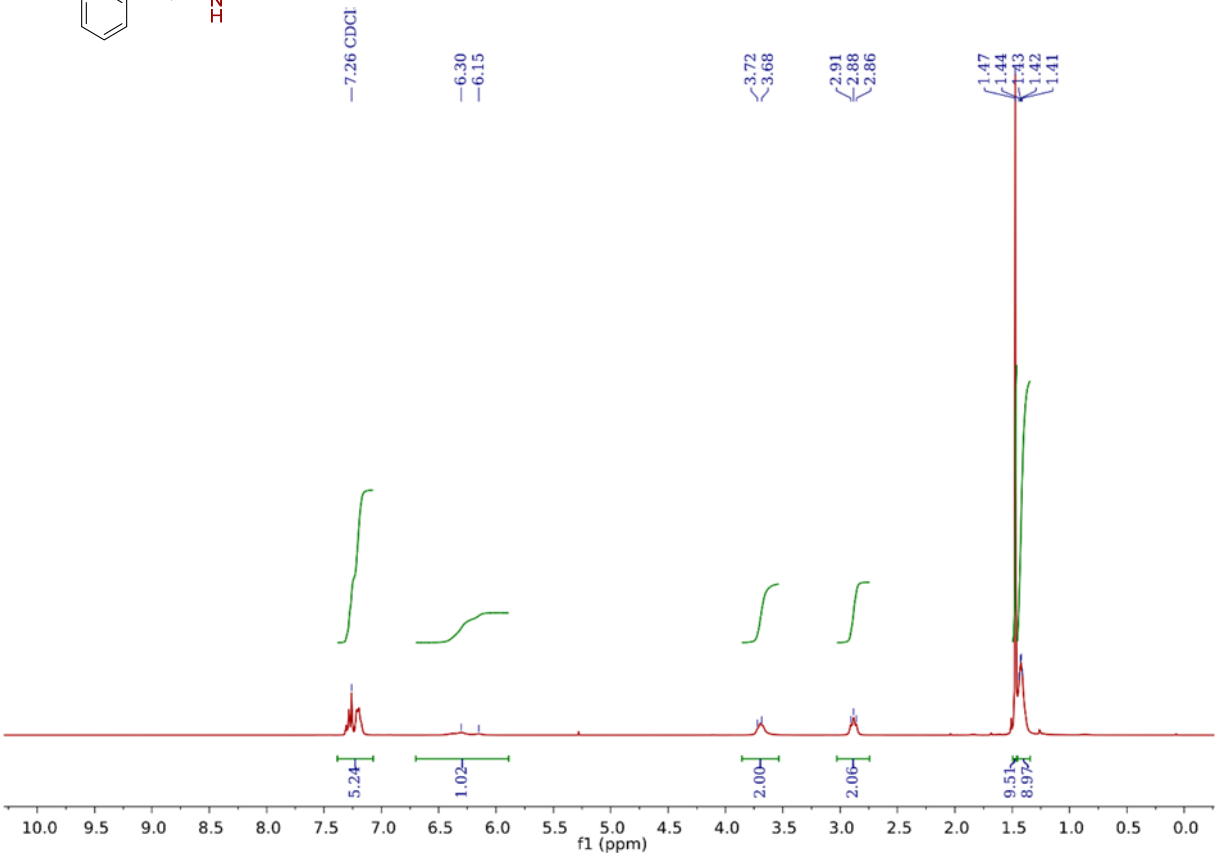
## NMR spectra

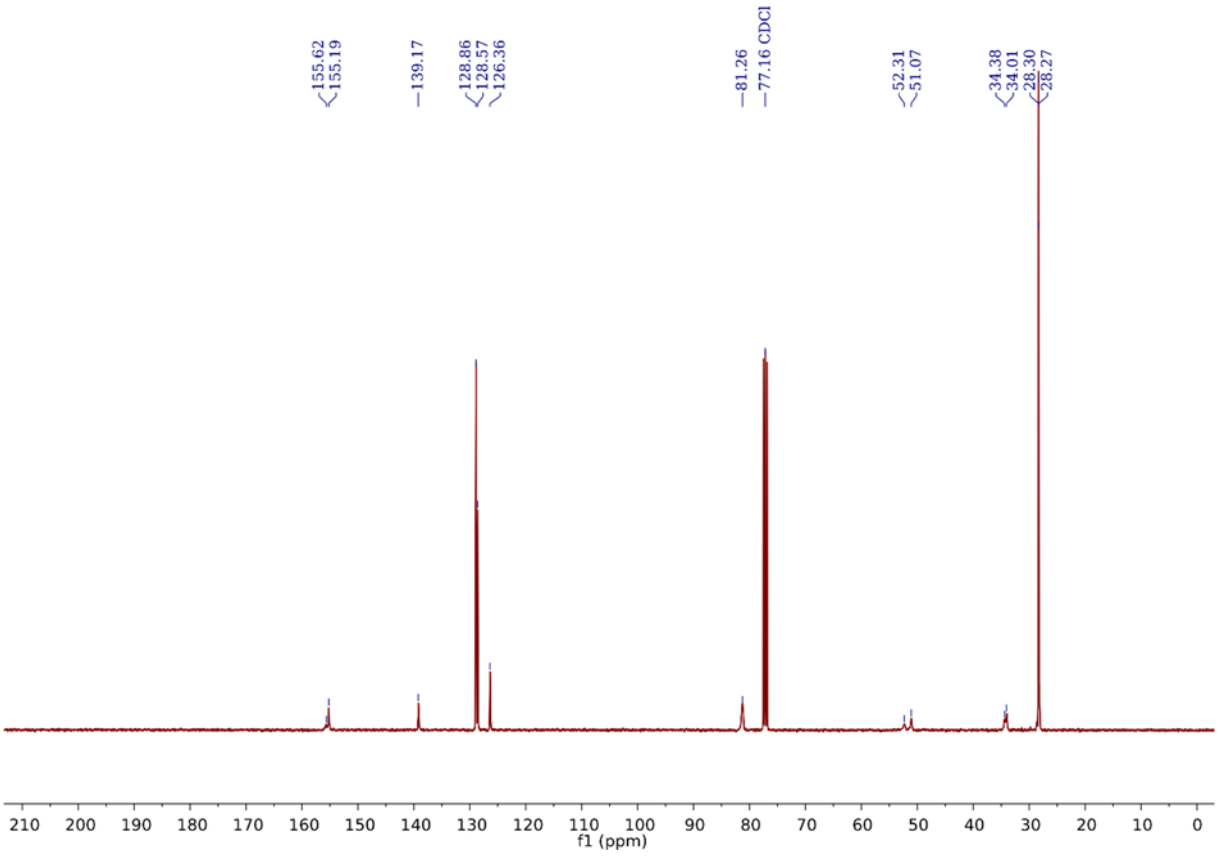
*Disclaimer*: Due to strong signal broadening, some signals in $^{13}C$ NMR show extremely small intensities, despite the highest possible concentration was used.

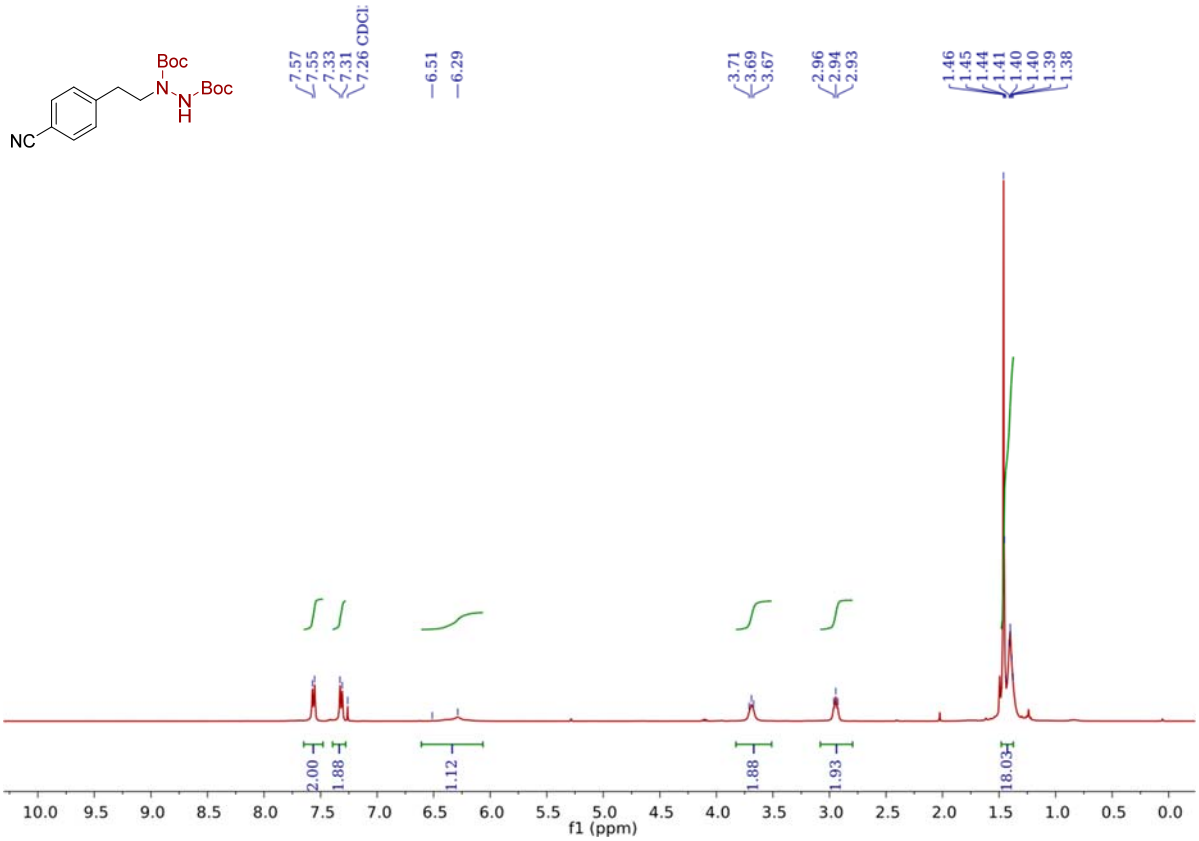


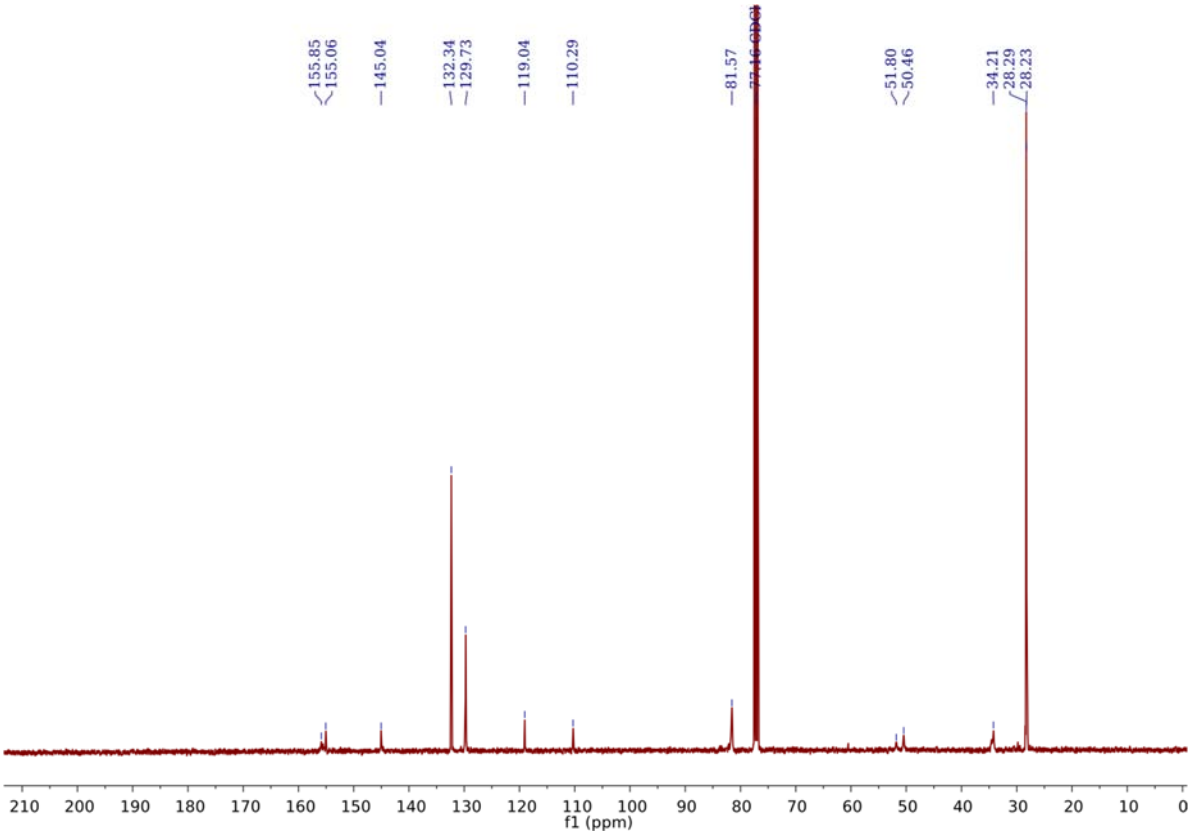



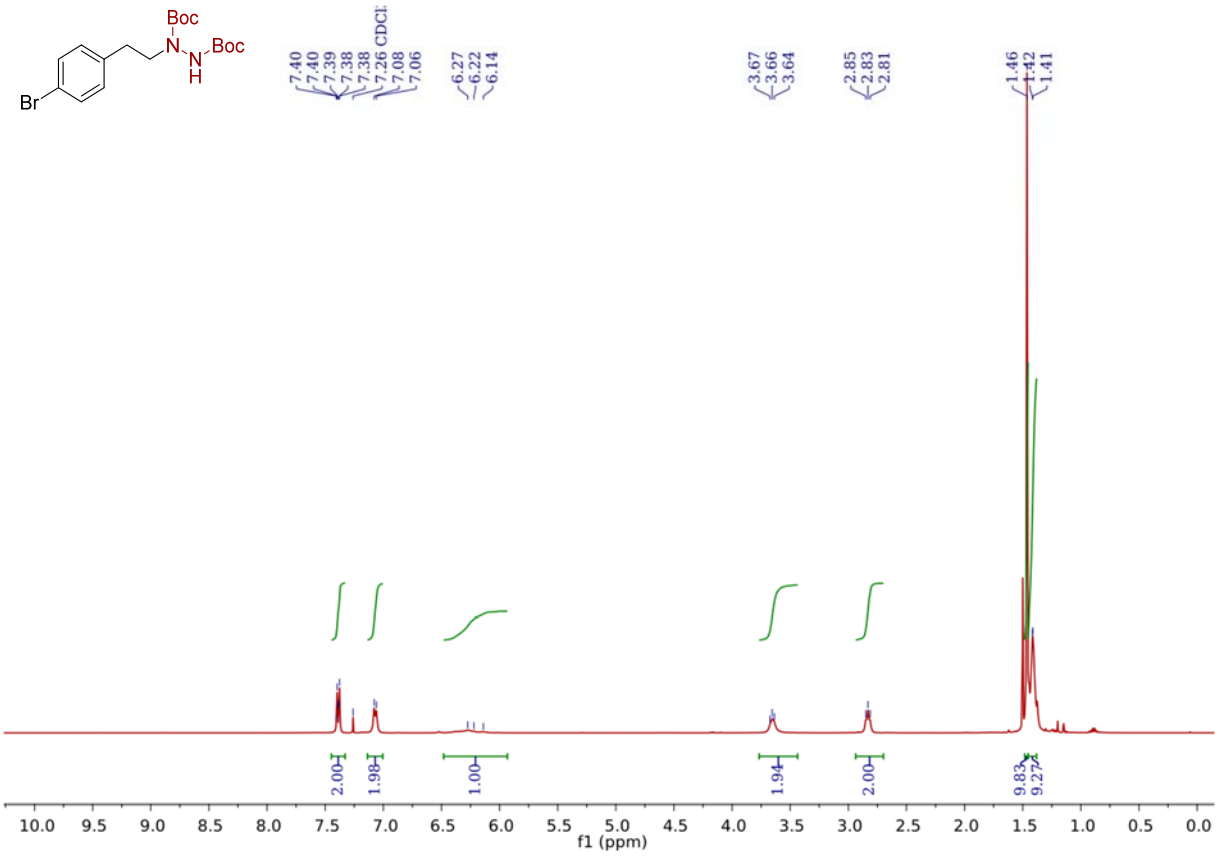

Boc
N
N
H
Boc

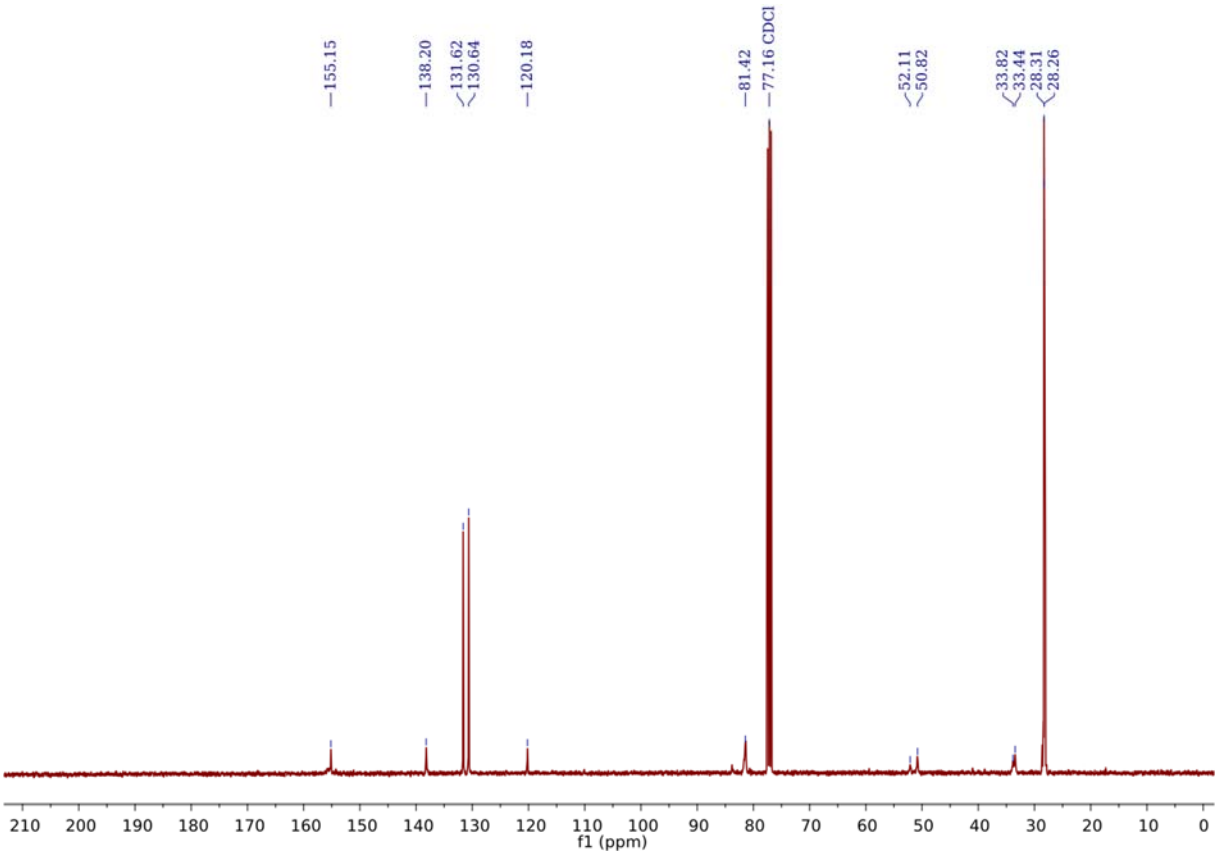

7.26 CDCl
6.30
6.15
3.72
3.68
2.91
2.88
2.86
1.47
1.44
1.43
1.42
1.41
5.24
1.02
2.00
2.06
9.51
8.97
f1 (ppm)

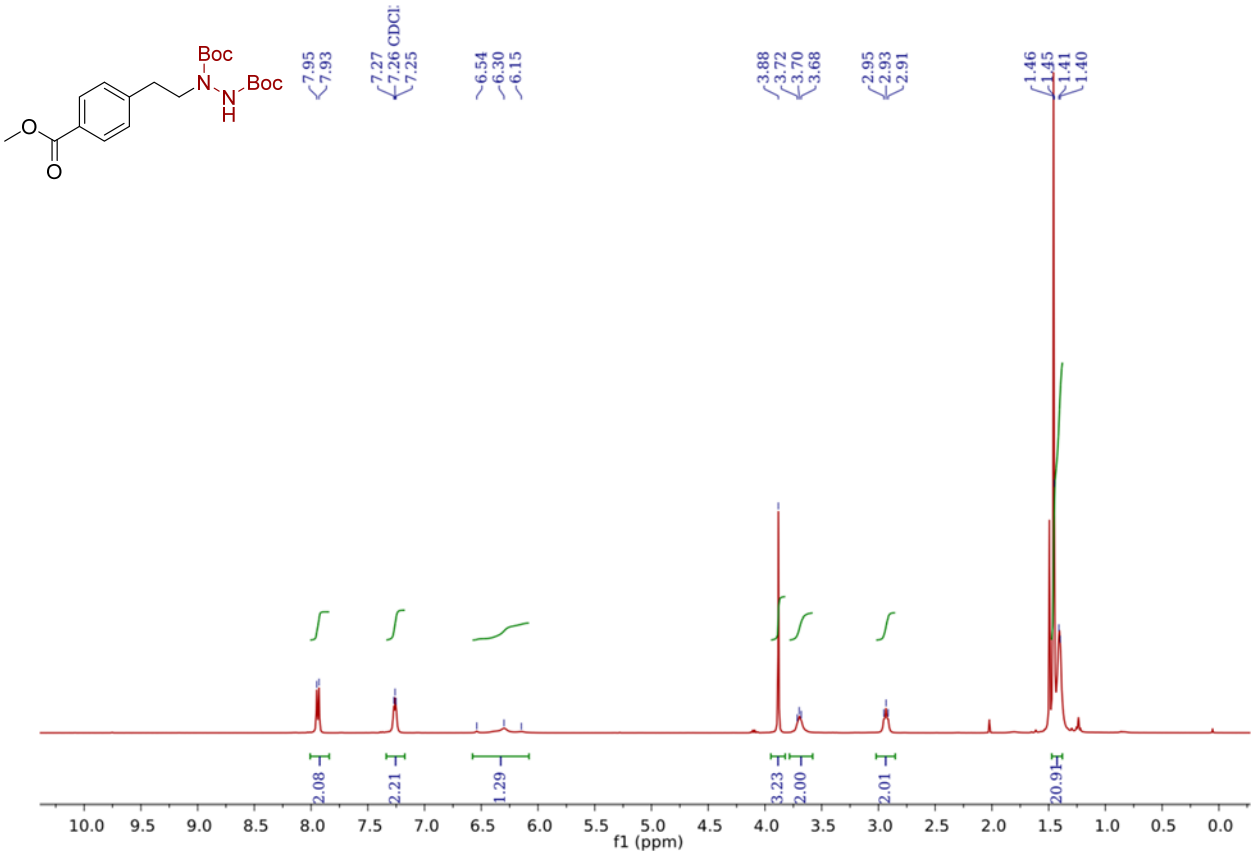

155.62
155.19
139.17
128.86
128.57
126.36
81.26
77.16 CDCl
52.31
51.07
34.38
34.01
28.30
28.27
f1 (ppm)

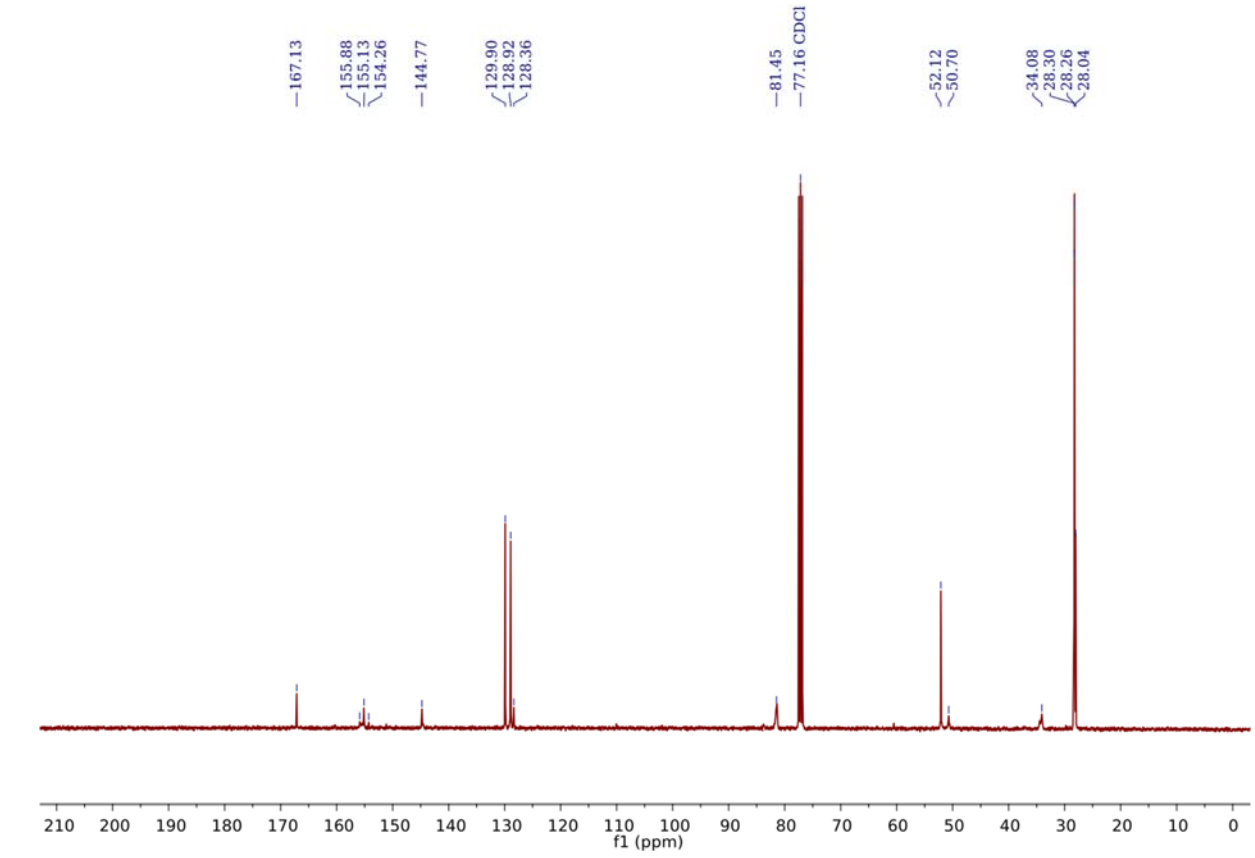

Boc
N
N
Boc
H
NC
7.57
7.55
7.33
7.31
7.26 CDCl3
6.51
6.29
3.71
3.69
3.67
2.96
2.94
2.93
1.46
1.45
1.44
1.41
1.40
1.40
1.39
1.38
2.00
1.88
1.12
1.88
1.93
18.03
f1 (ppm)

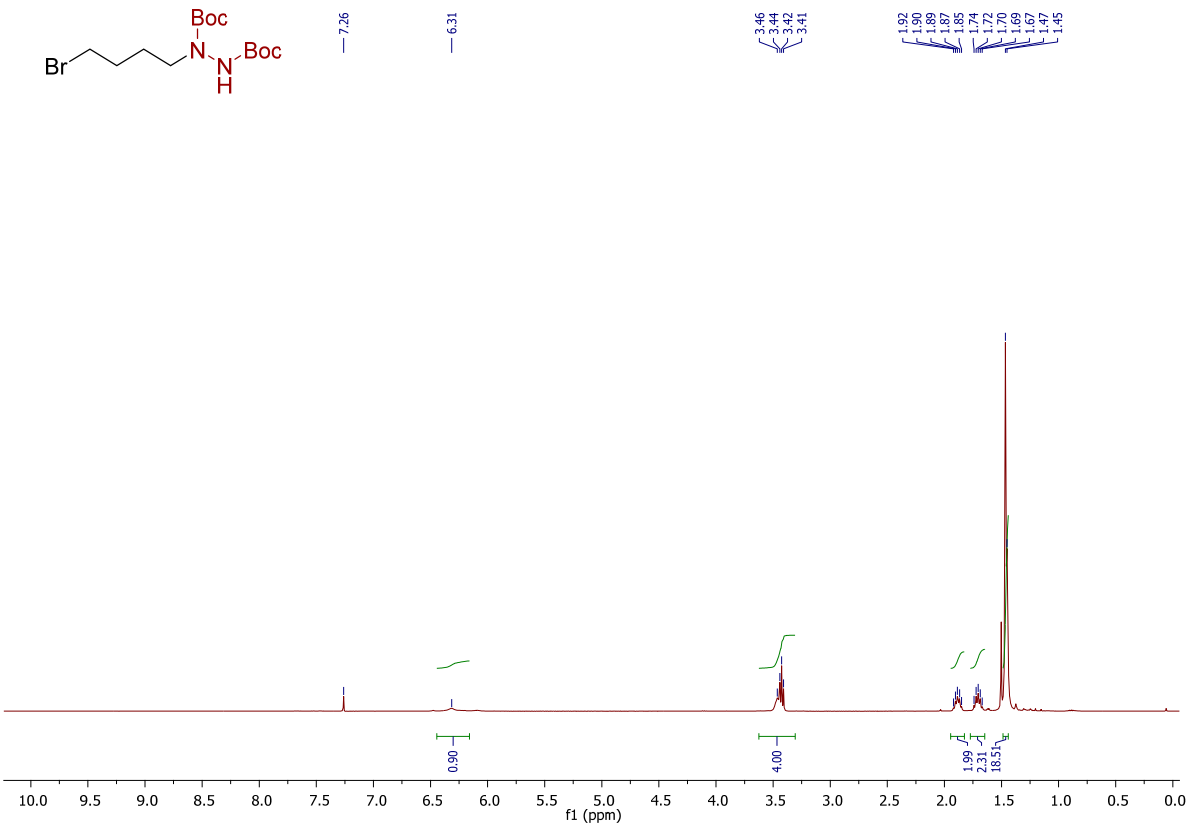

155.85
155.06
145.04
132.34
129.73
119.04
110.29
81.57
77.16 CDCl3
51.80
50.46
34.21
28.29
28.23
f1 (ppm)

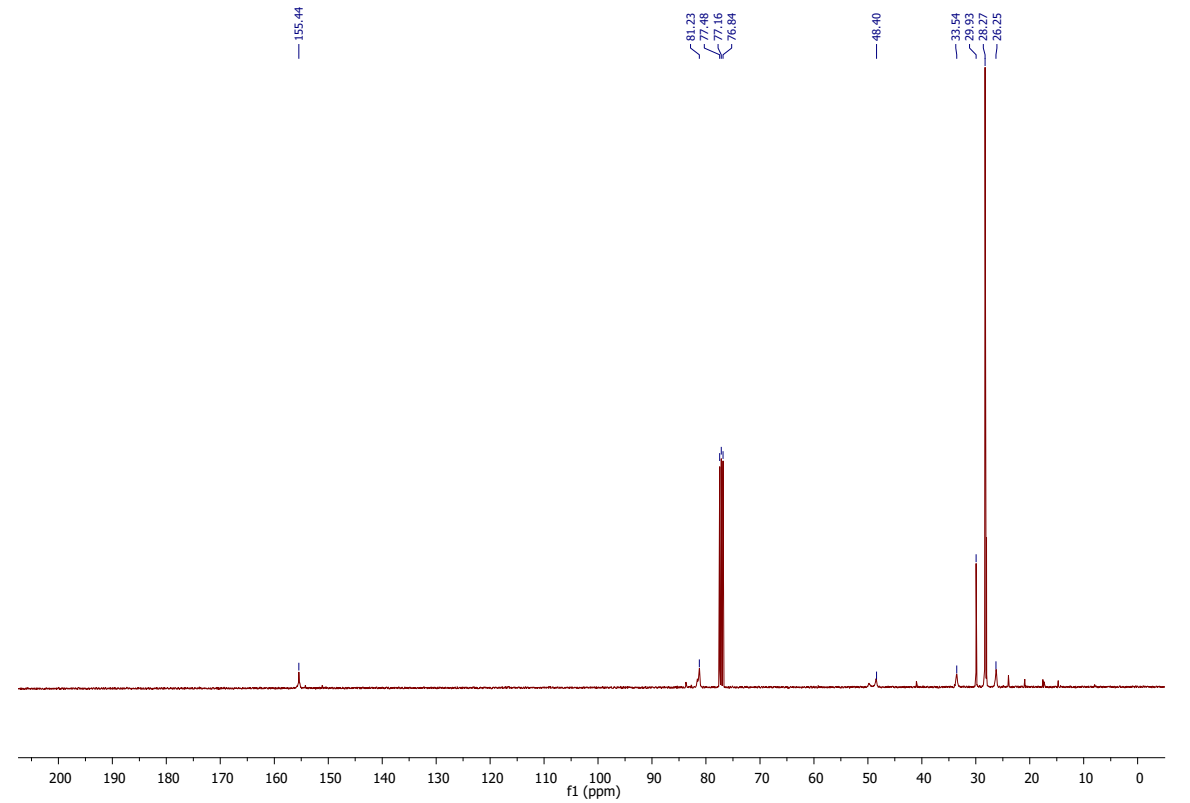

Boc
N
N
Boc
H
Br
7.40
7.40
7.39
7.38
7.38
7.26 CDCl
7.08
7.06
6.27
6.22
6.14
3.67
3.66
3.64
2.85
2.83
2.81
1.46
1.42
1.41
2.00
1.98
1.00
1.94
2.00
9.83
f1 (ppm)

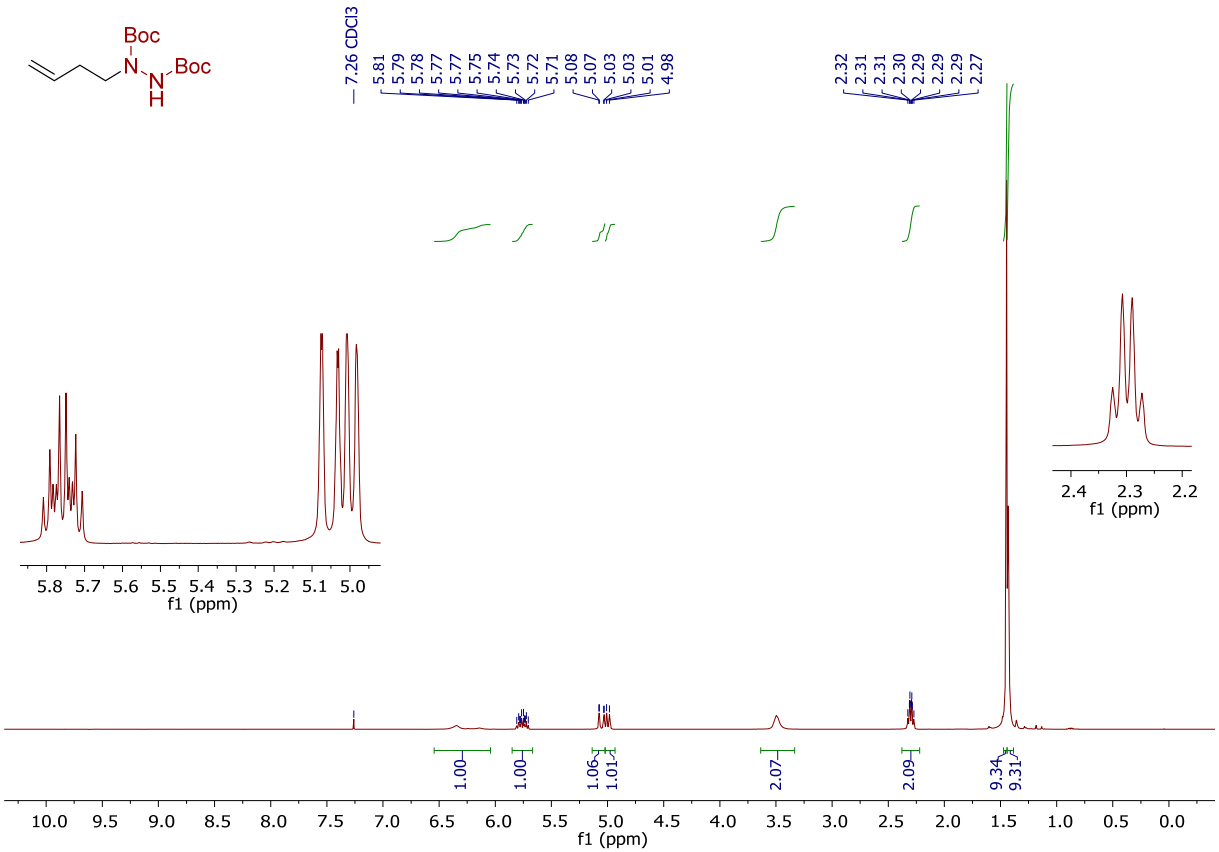

155.15
138.20
131.62
130.64
120.18
81.42
77.16 CDCl
52.11
50.82
33.82
33.44
28.31
28.26
f1 (ppm)

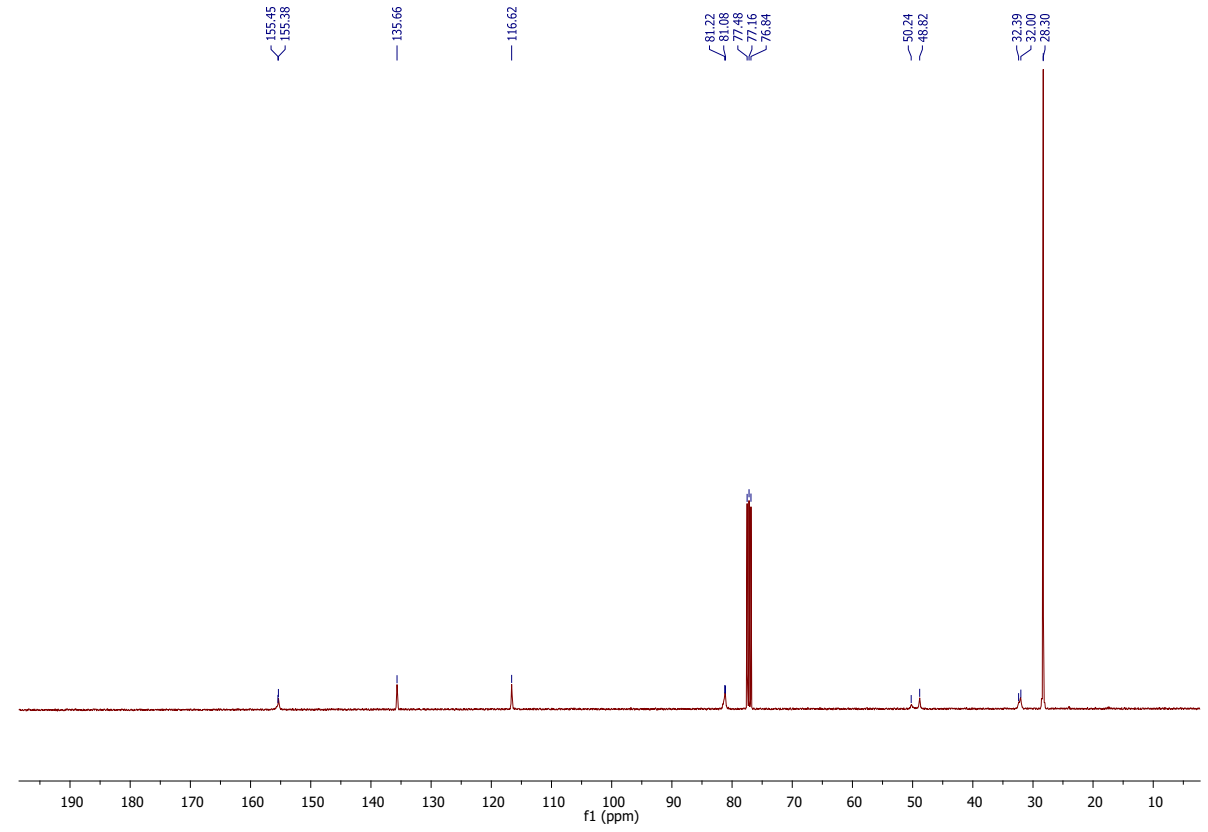

Boc
N
N
Boc
H
O
O
7.95
7.93
7.27
7.26 CDCl
7.25
6.54
6.30
6.15
3.88
3.72
3.70
3.68
2.95
2.93
2.91
1.46
1.45
1.41
1.40
2.08
2.21
1.29
3.23
2.00
2.01
20.91
f1 (ppm)

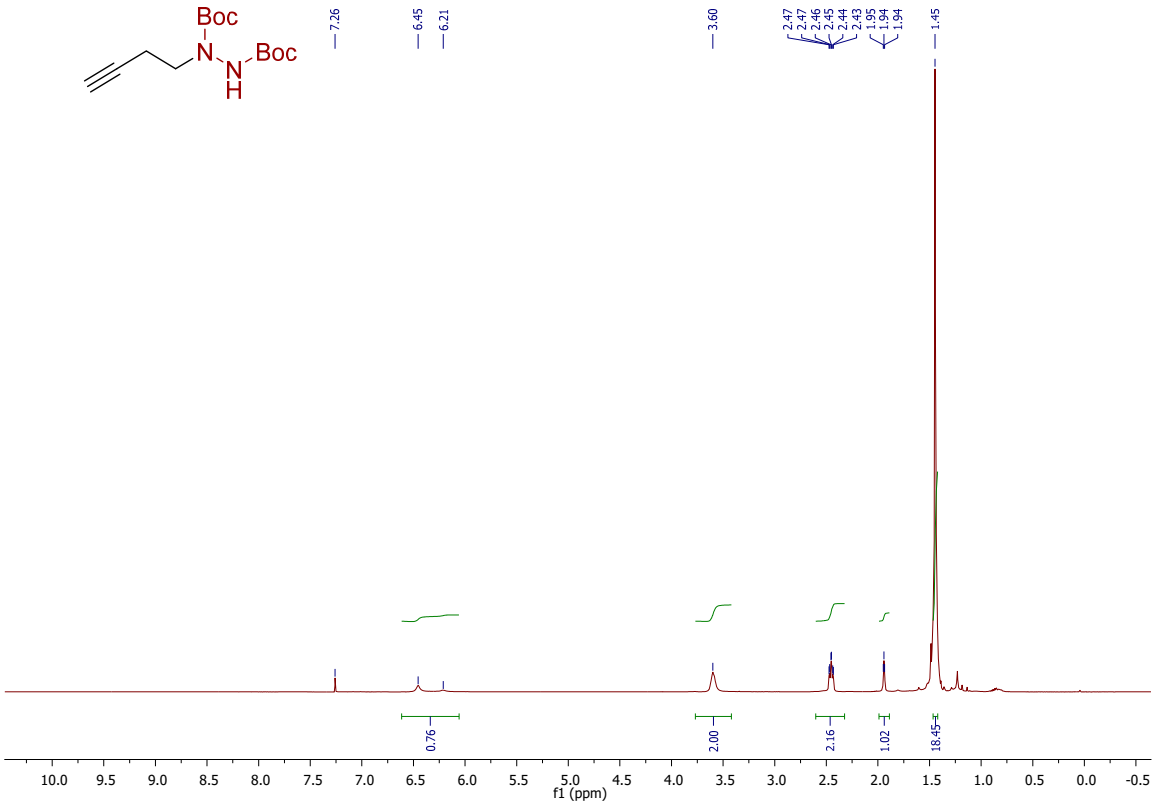

167.13
155.88
155.13
154.26
144.77
129.90
128.92
128.36
81.45
77.16 CDCl
52.12
50.70
34.08
28.30
28.26
28.04
f1 (ppm)

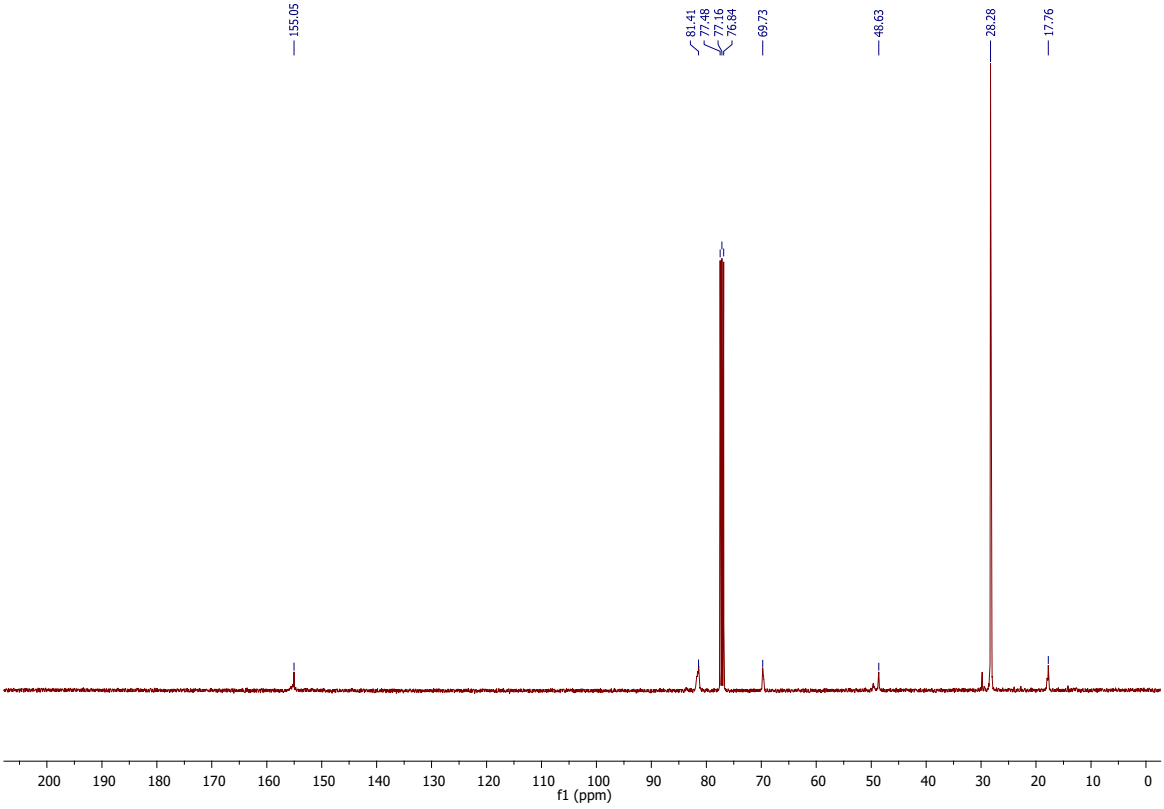

Boc
N
N
H
Boc
Br
7.26
6.31
3.46
3.44
3.42
3.41
1.92
1.90
1.89
1.87
1.85
1.74
1.72
1.70
1.69
1.67
1.47
1.45
0.90
4.00
1.99
2.31
18.51
f1 (ppm)

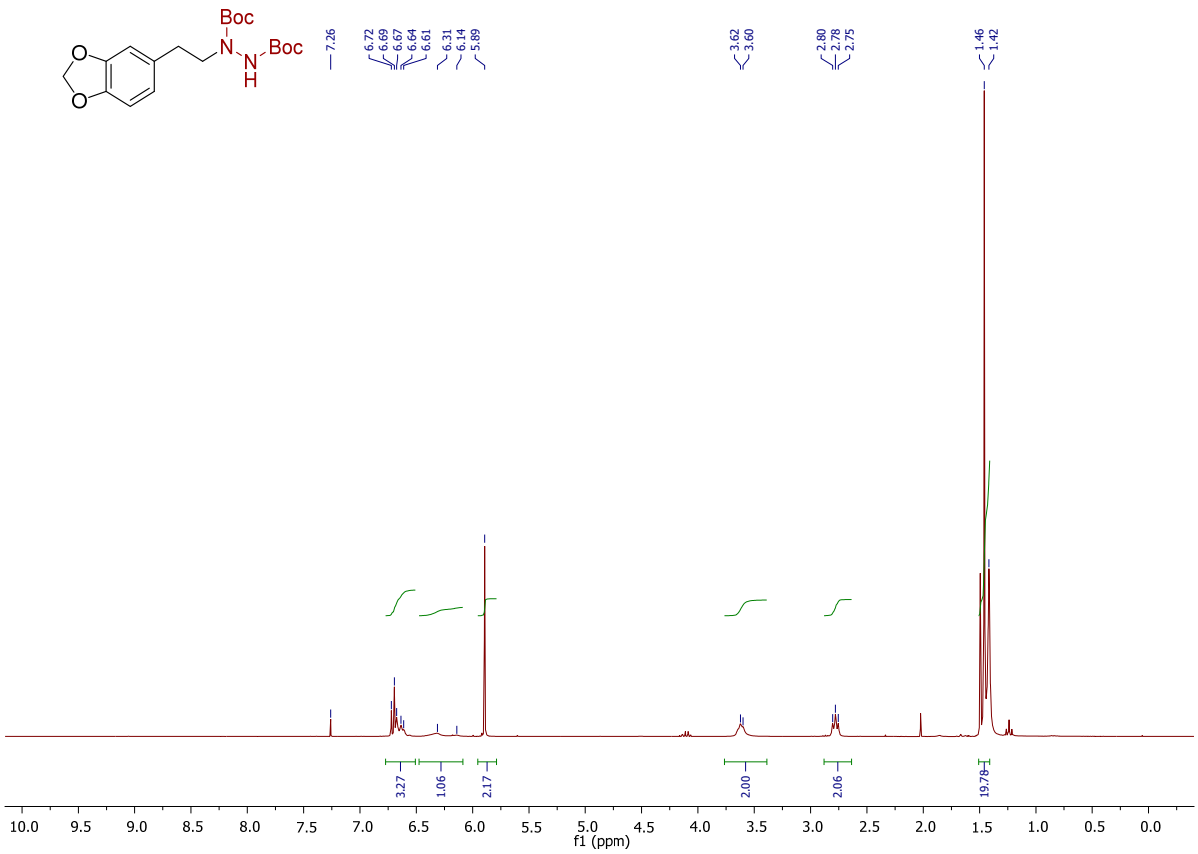

155.44
81.23
77.48
77.16
76.84
48.40
33.54
29.93
28.27
26.25
f1 (ppm)

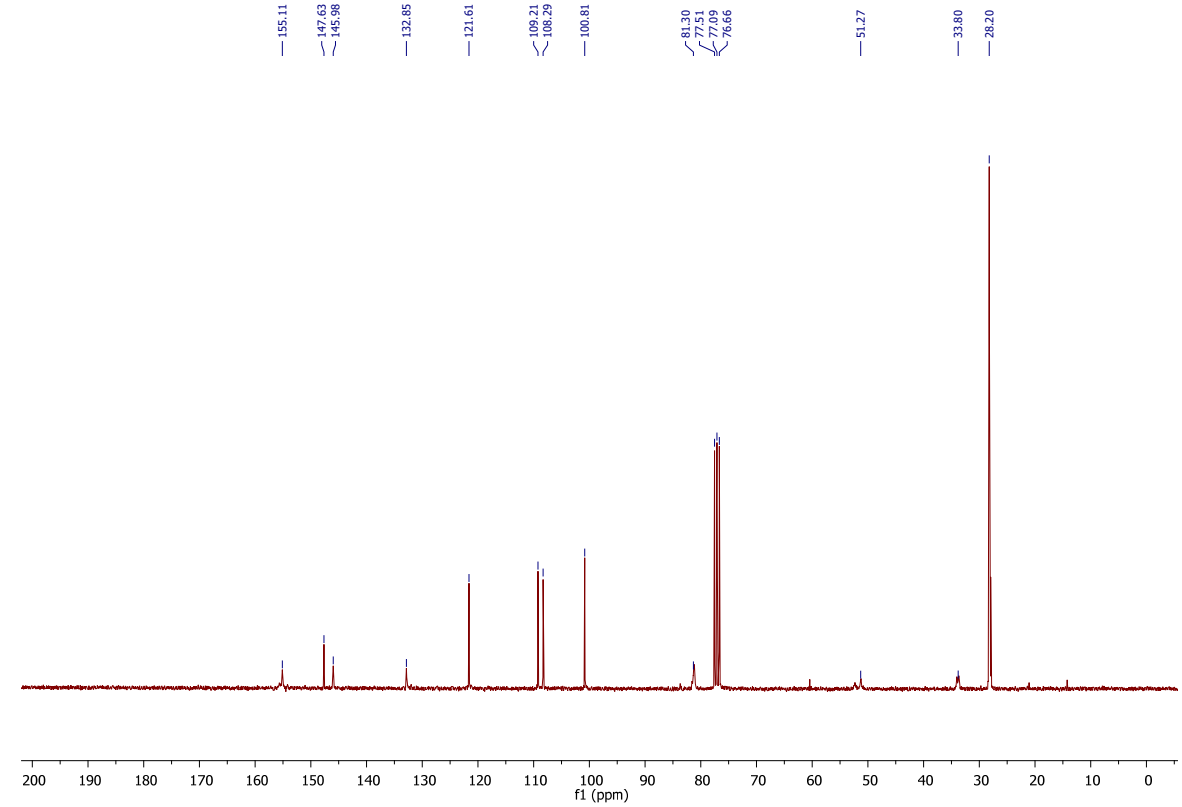

Boc
N
N
H
Boc
7.26 CDCl3
5.81
5.79
5.78
5.77
5.77
5.75
5.74
5.73
5.72
5.71
5.08
5.07
5.03
5.03
5.01
4.98
2.32
2.31
2.31
2.30
2.29
2.29
2.29
2.27
5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0
f1 (ppm)
2.4 2.3 2.2
f1 (ppm)
1.00
1.00
1.06
1.01
2.07
2.09
9.34
9.31
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

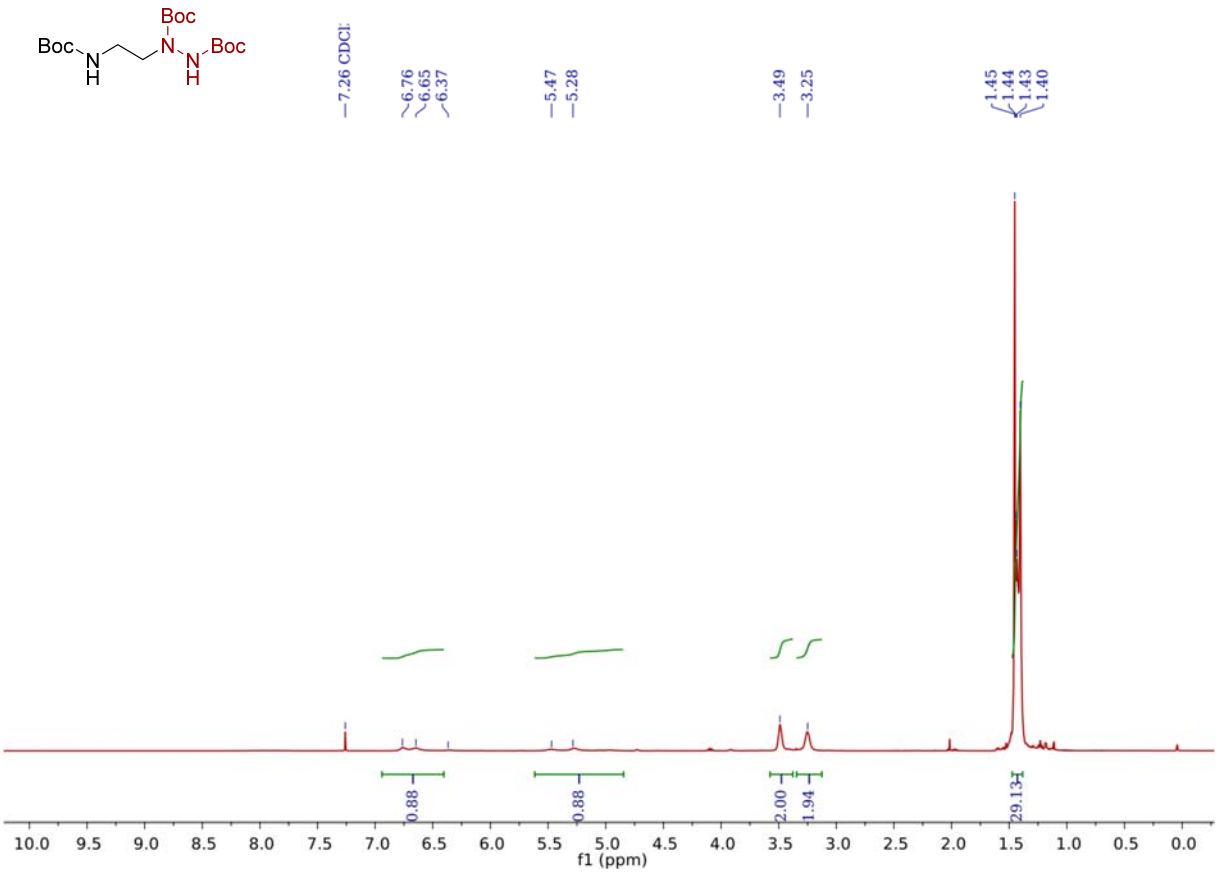

155.45
155.38
135.66
116.62
81.22
81.08
77.48
77.16
76.84
50.24
48.82
32.39
32.00
28.30
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

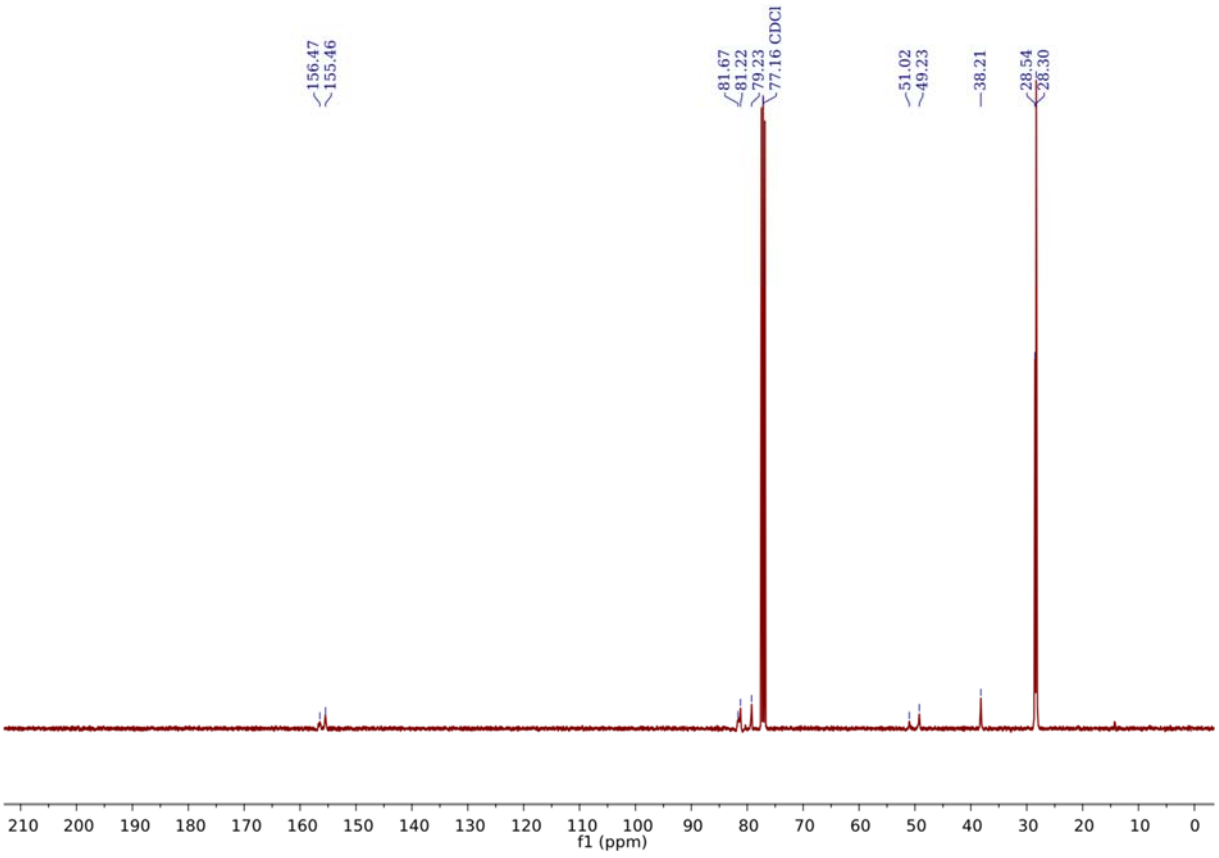

Boc
N
N
H
Boc
7.26
6.45
6.21
3.60
2.47
2.47
2.46
2.45
2.44
2.43
1.95
1.94
1.94
1.45
0.76
2.00
2.16
1.02
18.45
f1 (ppm)

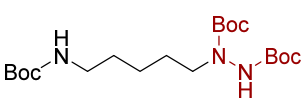

155.05
81.41
77.48
77.16
76.84
69.73
48.63
28.28
17.76
f1 (ppm)


Boc
N
N
Boc
H
O
O
7.26
6.72
6.69
6.67
6.64
6.61
6.31
6.14
5.89
3.62
3.60
2.80
2.78
2.75
1.46
1.42
3.27
1.06
2.17
2.00
2.06
19.78
f1 (ppm)

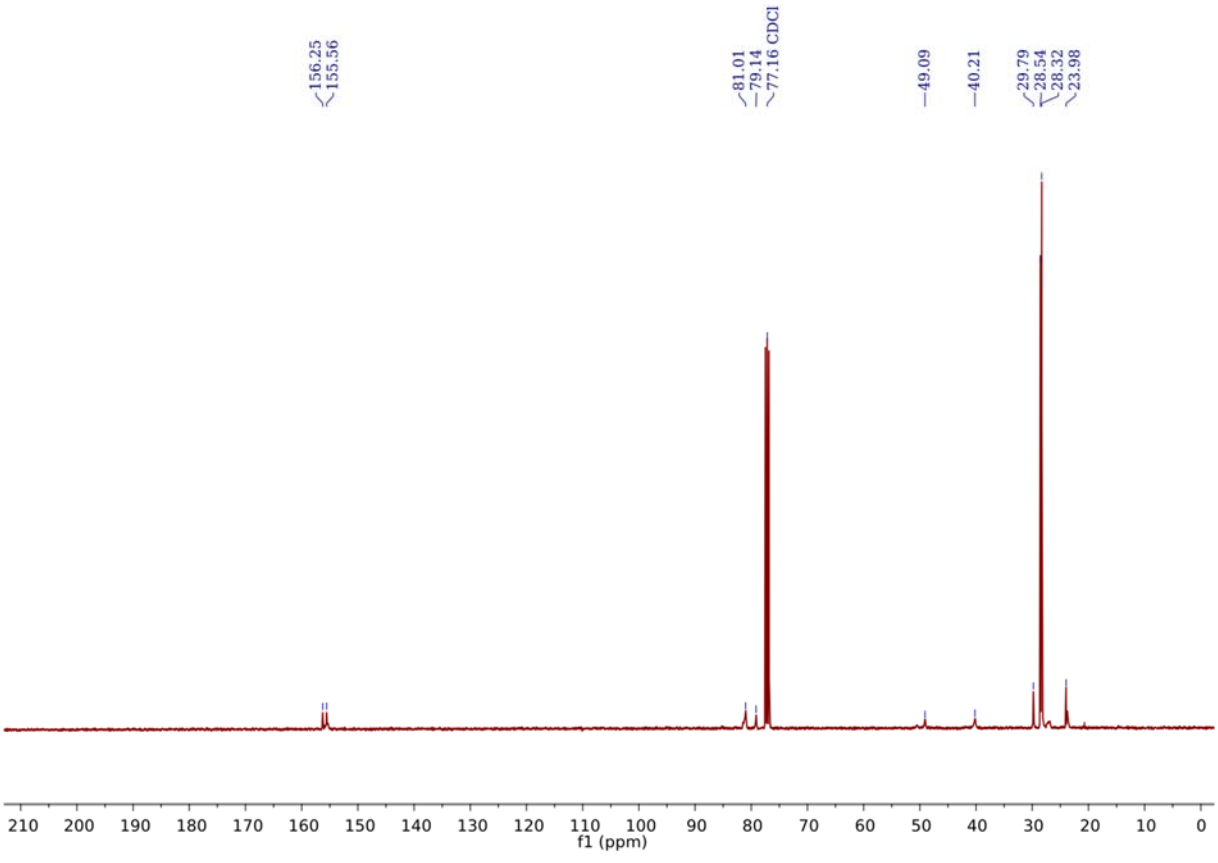

155.11
147.63
145.98
132.85
121.61
109.21
108.29
100.81
81.30
77.51
77.09
76.66
51.27
33.80
28.20
f1 (ppm)

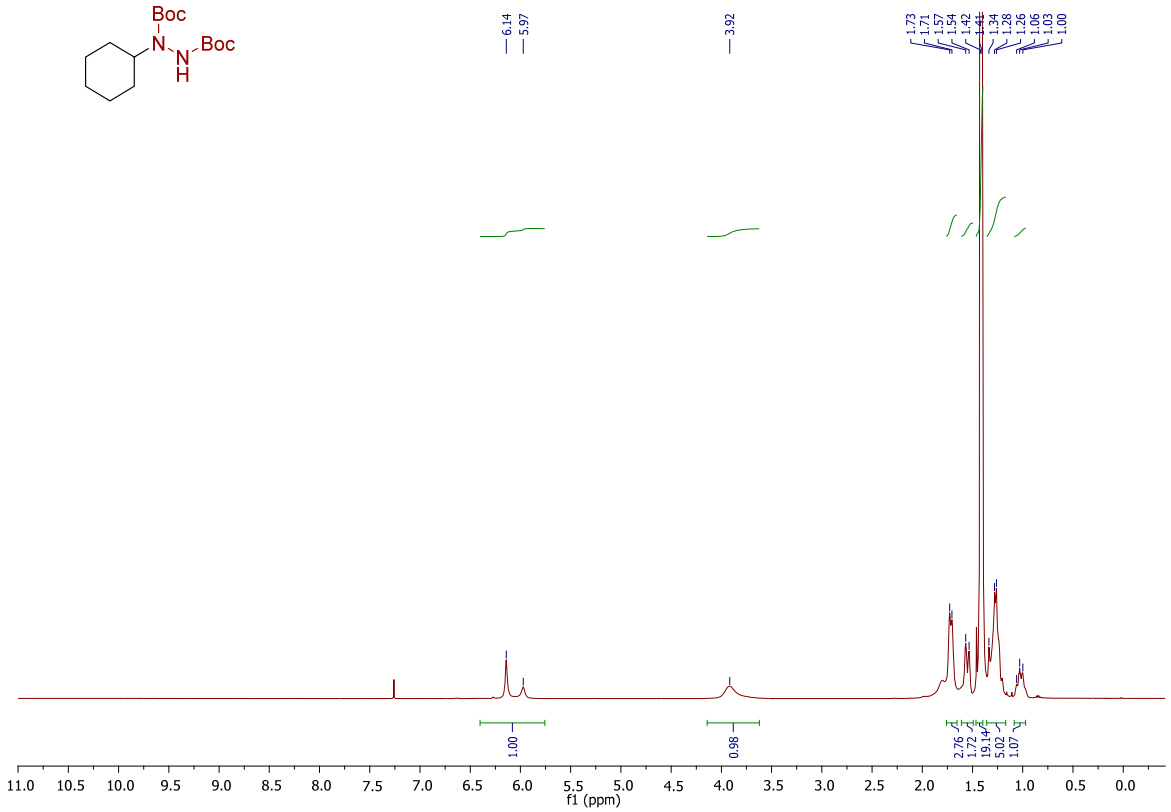

Boc
N
H
Boc
N
N
H
Boc
7.26 CDCl
6.76
6.65
6.37
5.47
5.28
3.49
3.25
1.45
1.44
1.43
1.40
0.88
0.88
2.00
1.94
29.13
f1 (ppm)

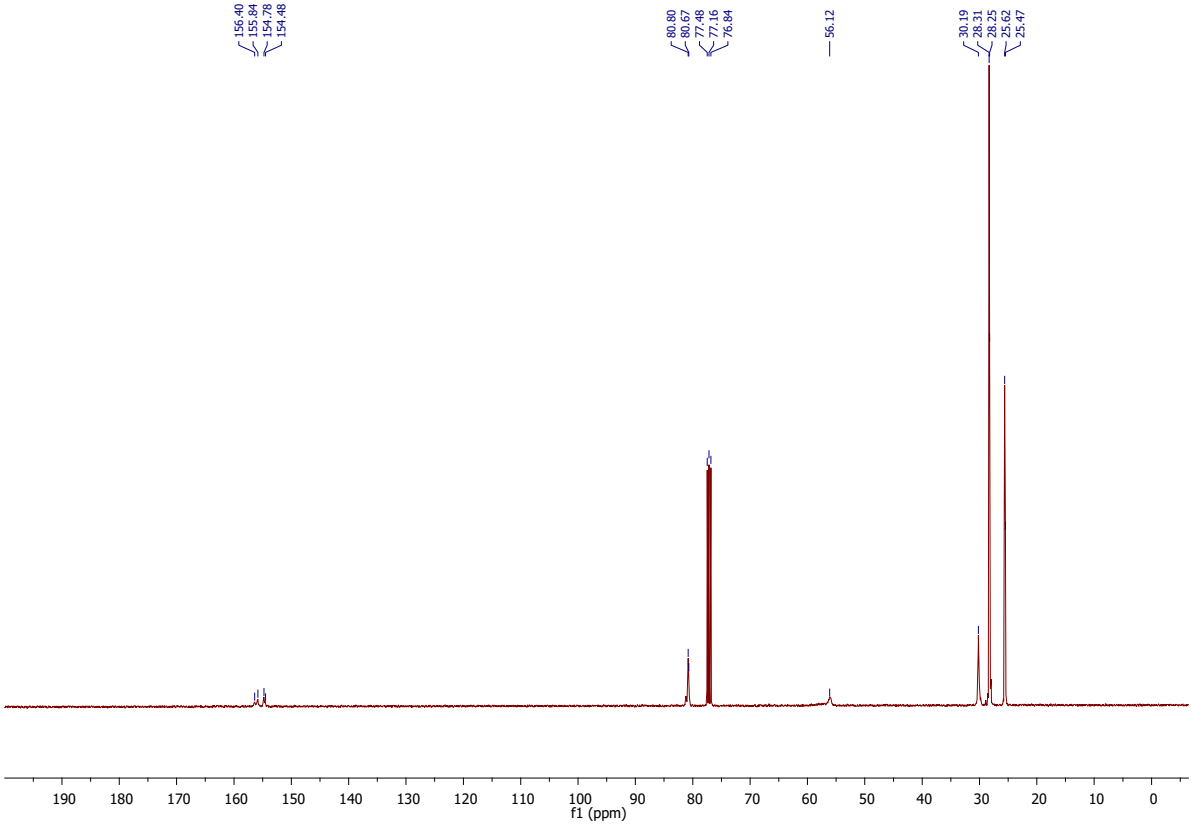

156.47
155.46
81.67
81.22
79.23
77.16 CDCl
51.02
49.23
38.21
28.54
28.30
f1 (ppm)

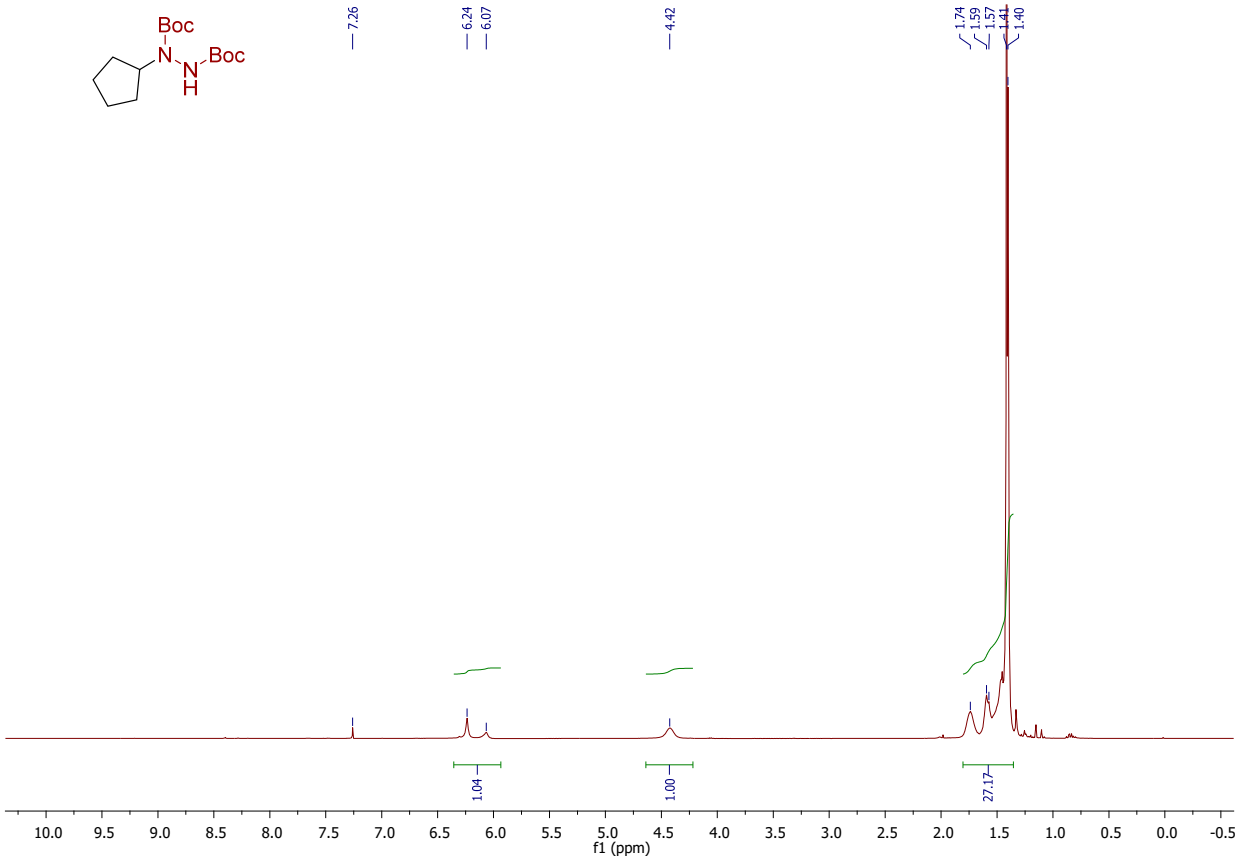

Boc
H
N
Boc
N
N
Boc
H

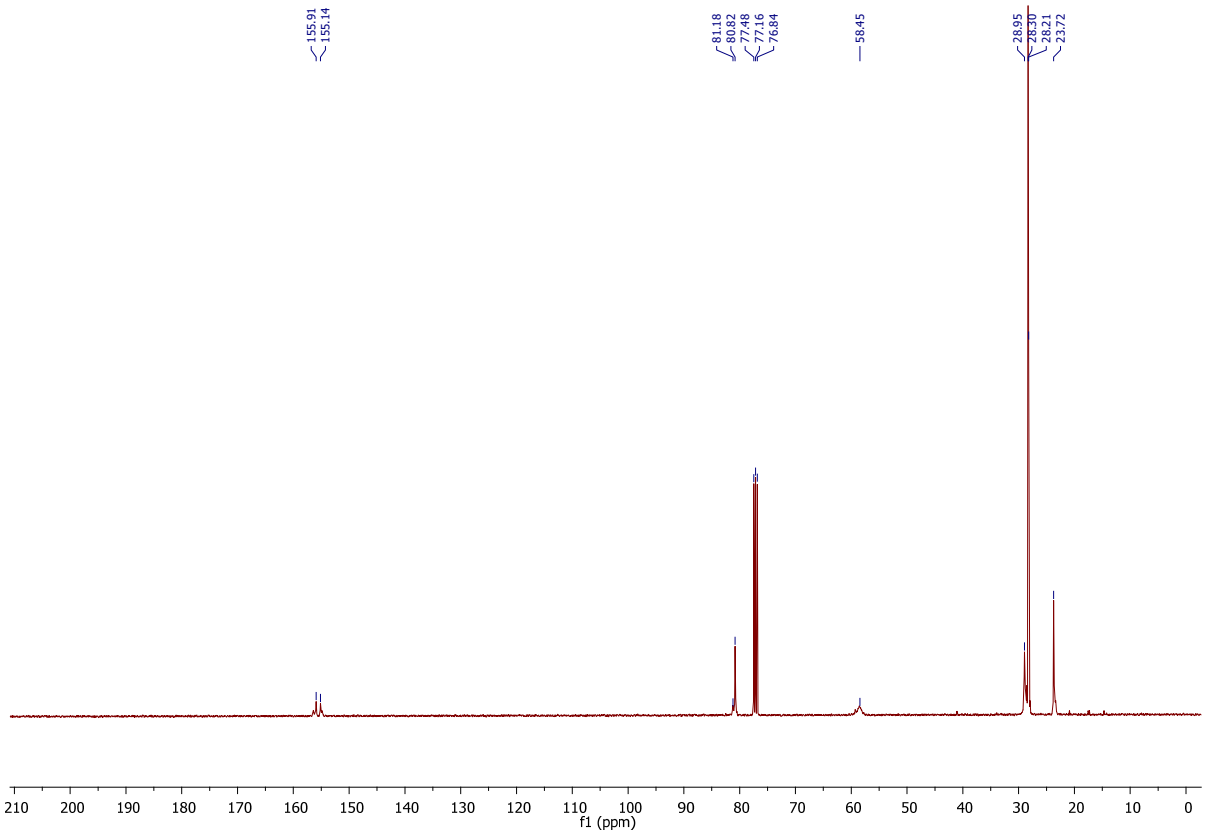

7.26 CDCl3
6.55
6.33
4.66
4.63
3.43
3.41
3.39
3.10
3.08
3.06
1.57
1.56
1.56
1.54
1.54
1.52
1.52
1.51
1.50
1.48
1.48
1.46
1.44
1.42
1.41
1.39
1.37
1.35
1.34
1.33
1.32
1.31
1.30
1.30
1.28
1.28
1.19
1.05
2.00
2.06
4.50
28.97
2.86
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

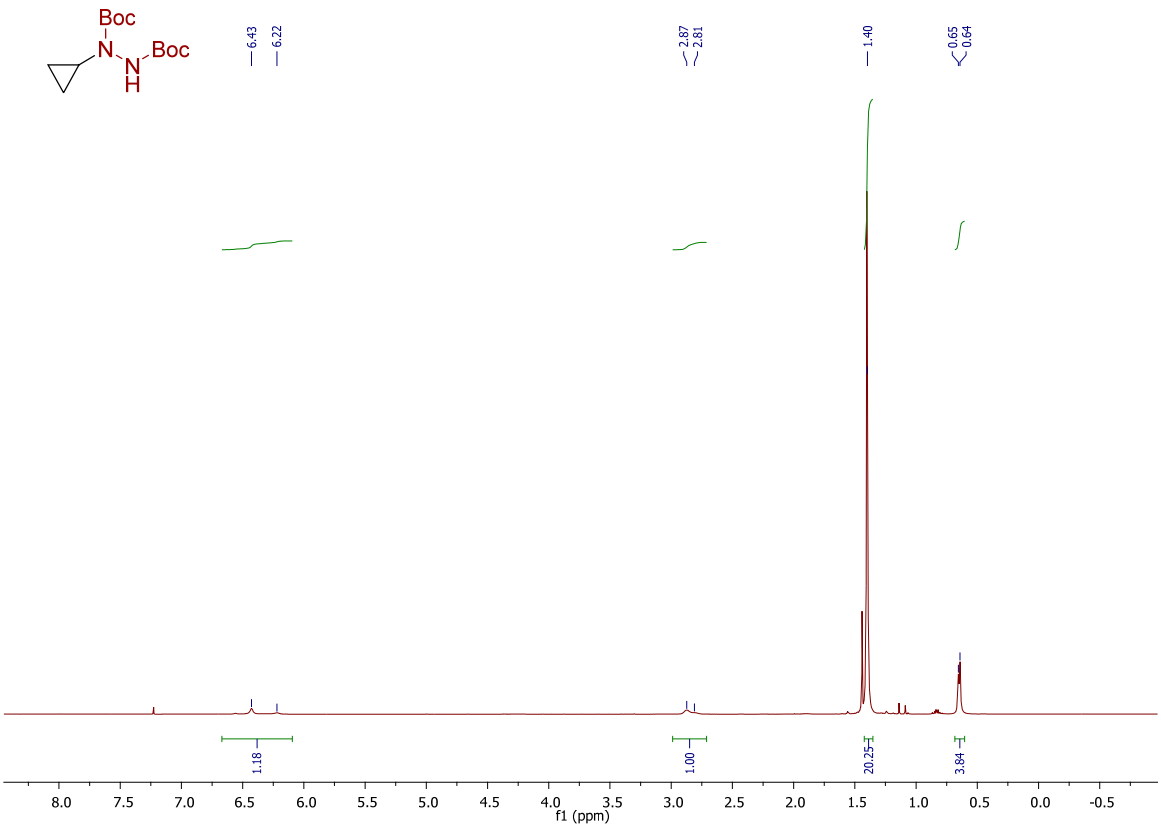

156.25
155.56
81.01
79.14
77.16 CDCl3
49.09
40.21
29.79
28.54
28.32
23.98
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

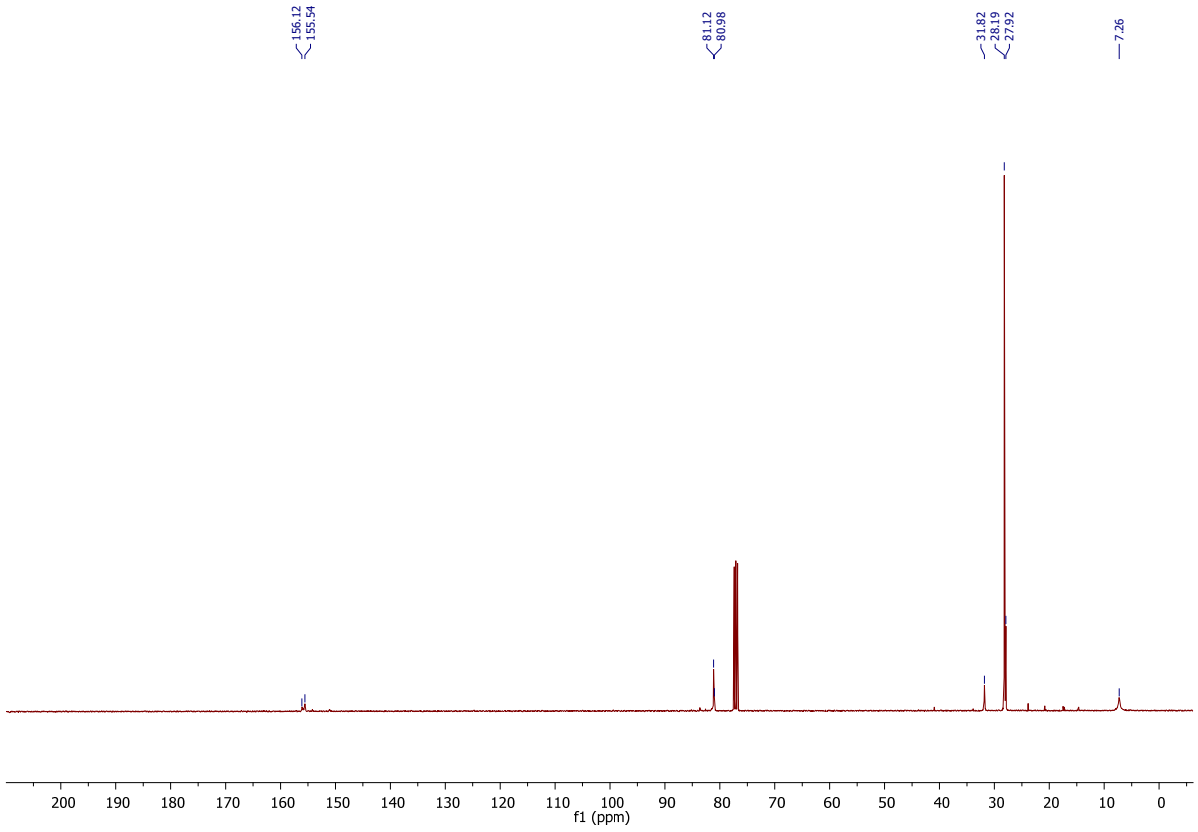

Boc
N
N
H
Boc
6.14
5.97
3.92
1.73
1.71
1.57
1.54
1.42
1.41
1.34
1.28
1.26
1.06
1.03
1.00
1.00
0.98
2.76
1.72
19.14
5.02
1.07
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

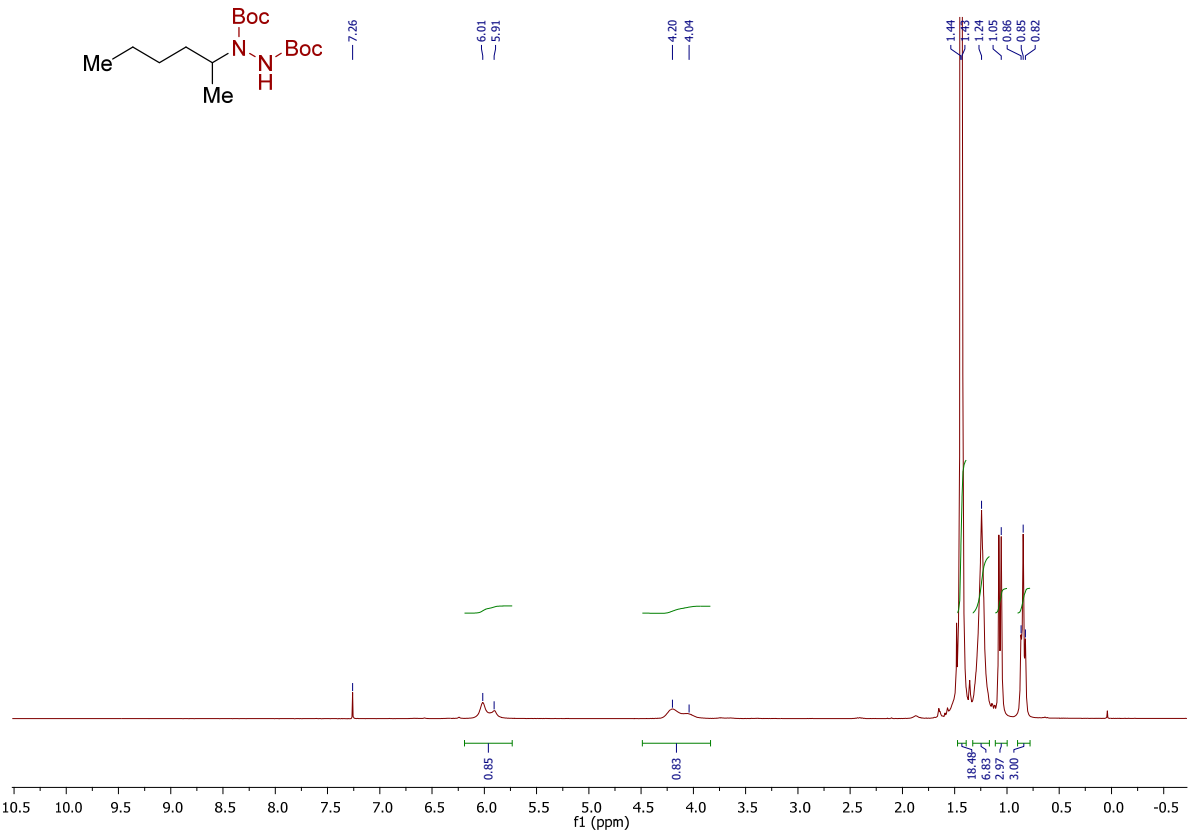

156.40
155.84
154.78
154.48
80.80
80.67
77.48
77.16
76.84
56.12
30.19
28.31
28.25
25.62
25.47
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

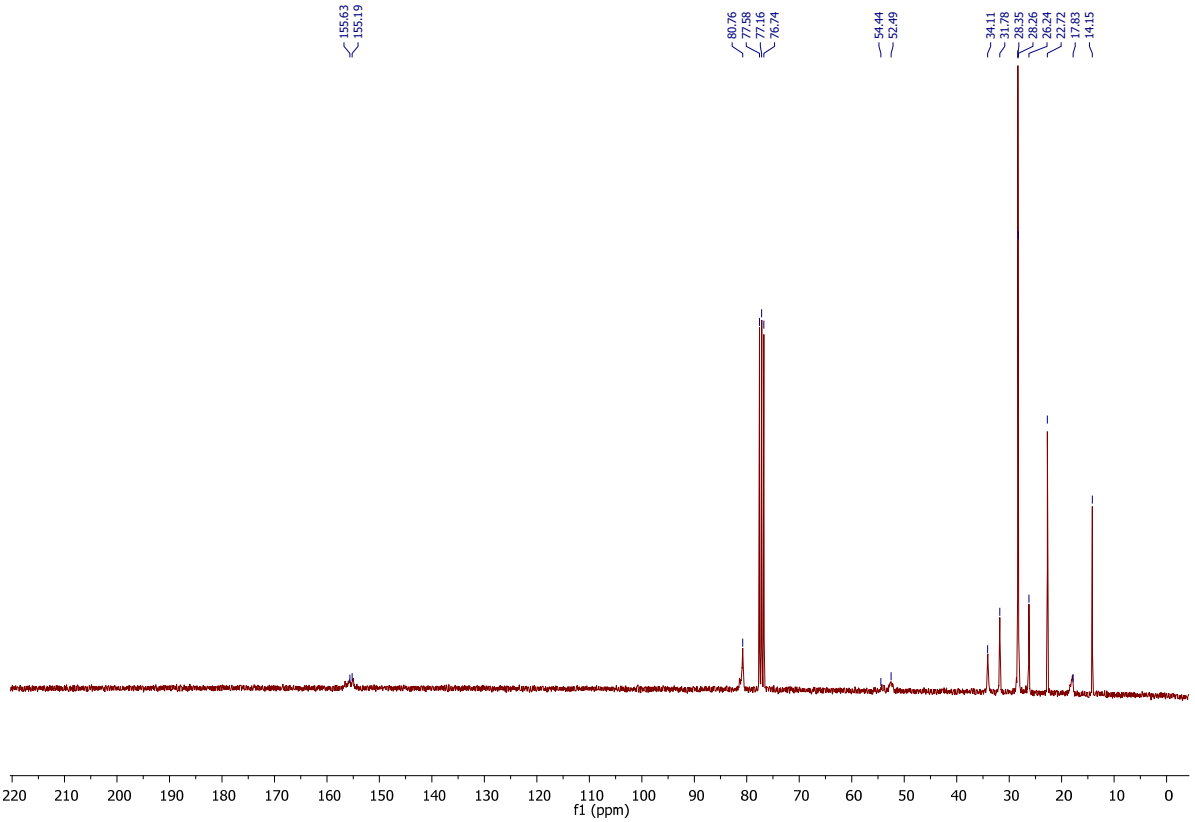

Boc
N
N
H
Boc
7.26
6.24
6.07
4.42
1.74
1.59
1.57
1.41
1.40
1.04
1.00
27.17
f1 (ppm)

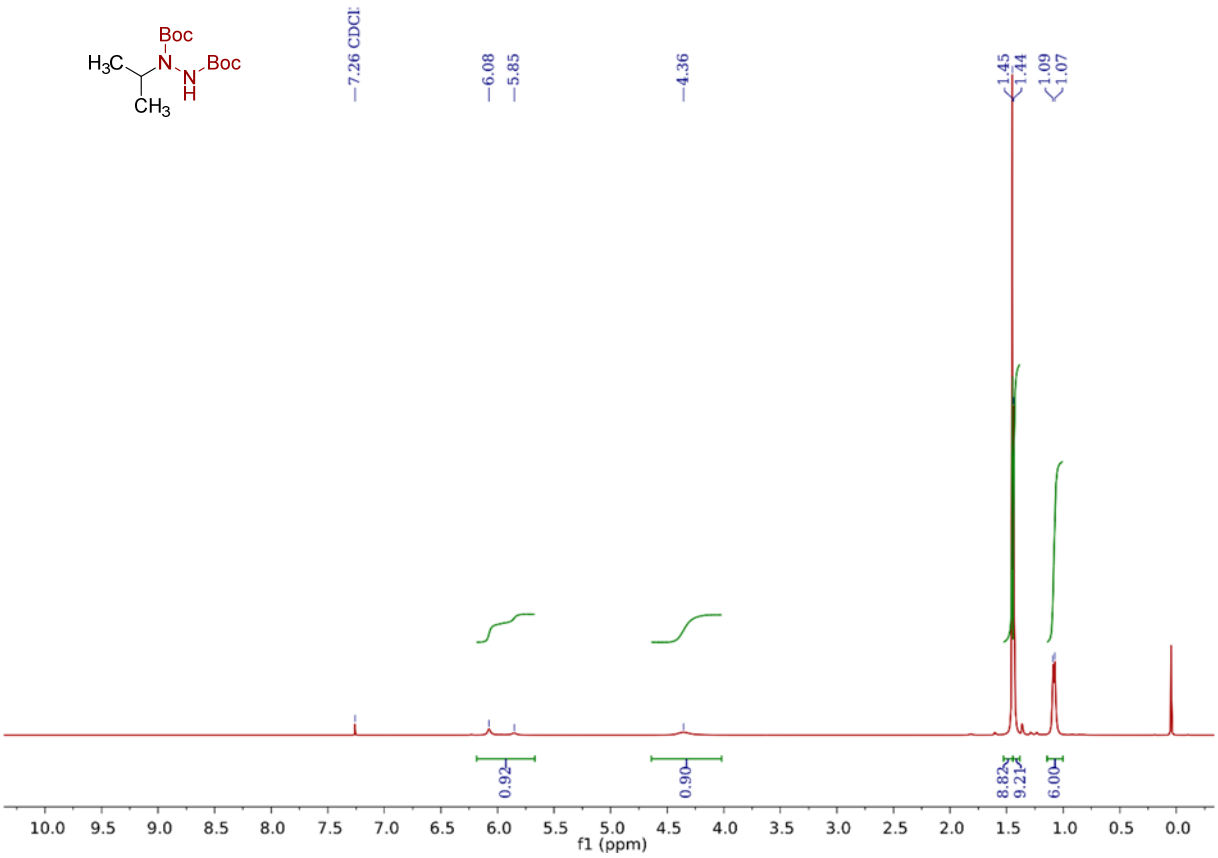

155.91
155.14
81.18
80.82
77.48
77.16
76.84
58.45
28.95
28.30
28.21
23.72
f1 (ppm)

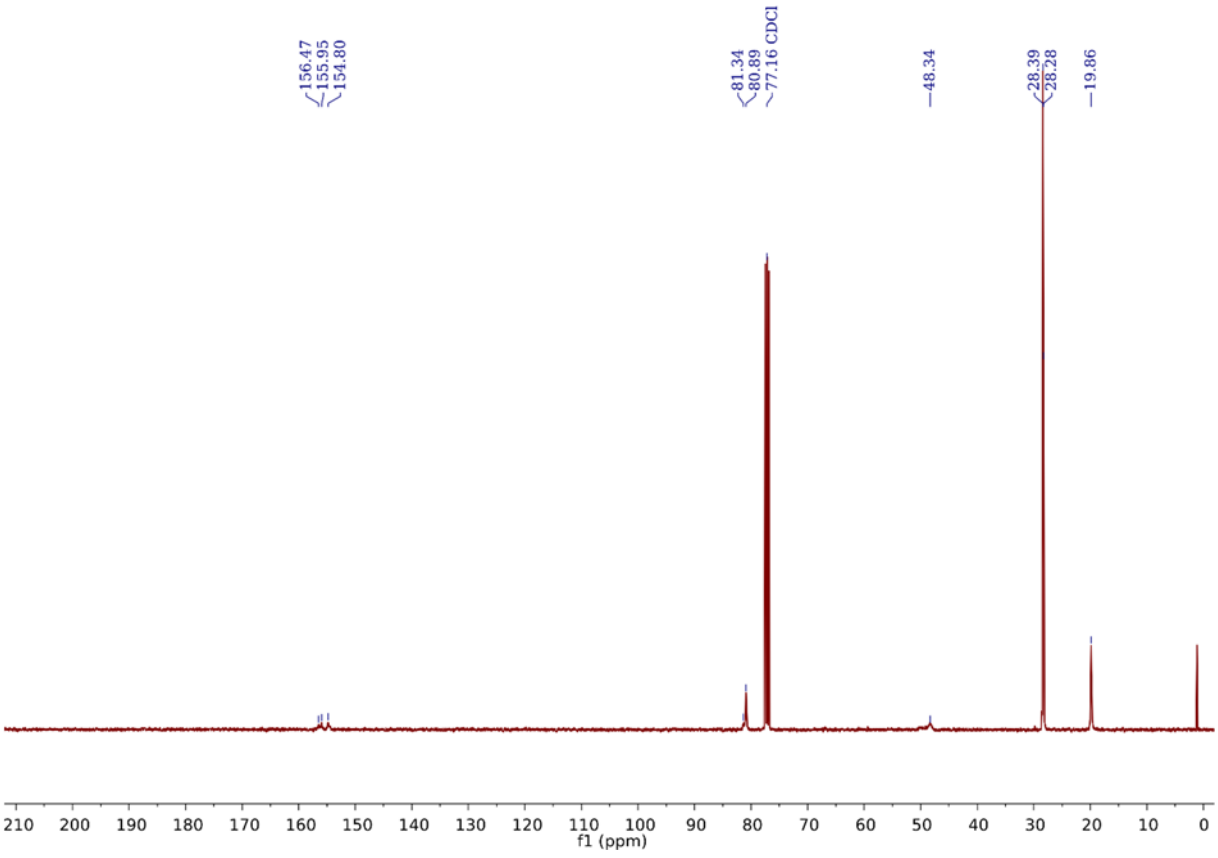

Boc
N
N
H
Boc
6.43
6.22
2.87
2.81
1.40
0.65
0.64
1.18
1.00
20.25
3.84
f1 (ppm)

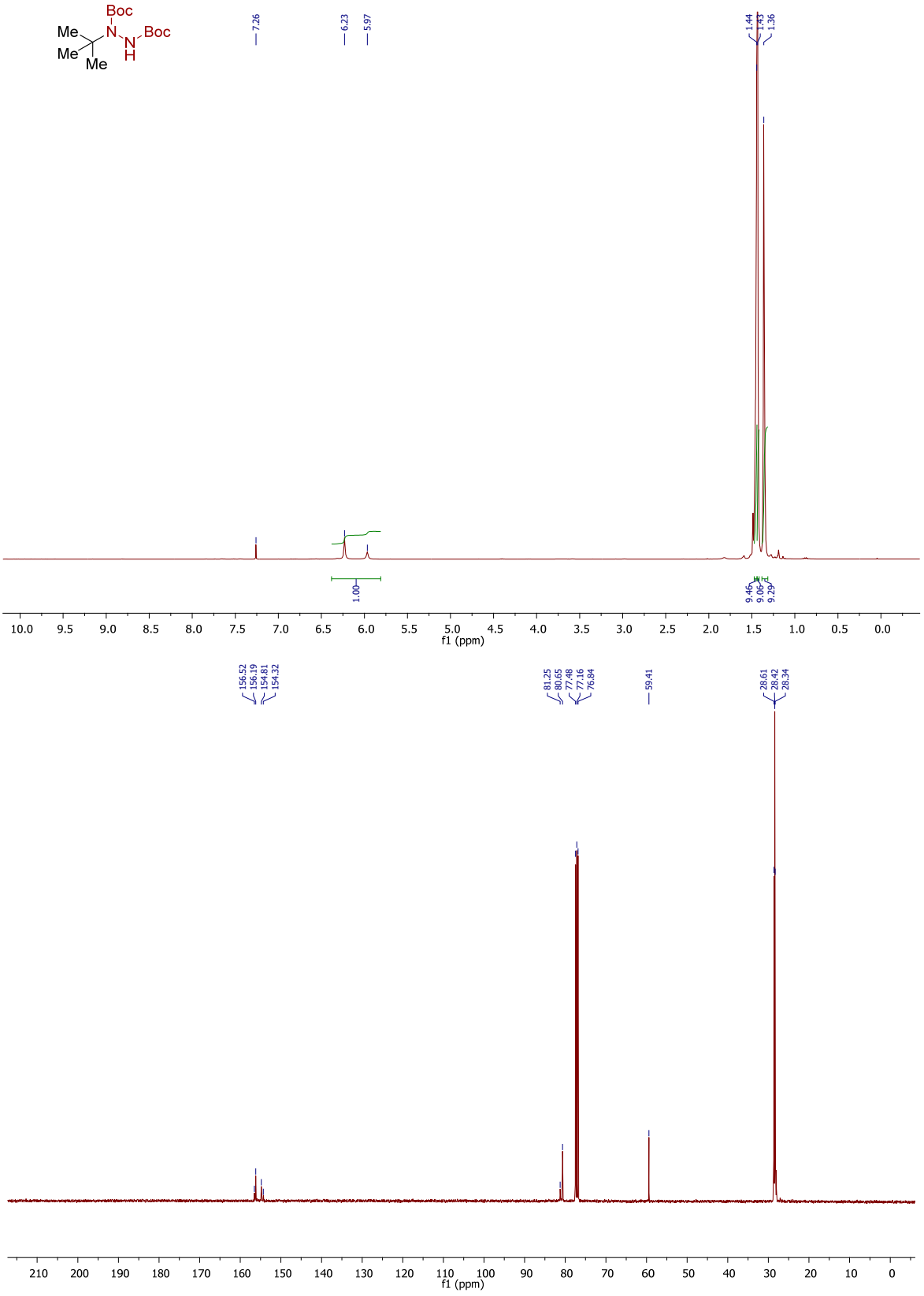

156.12
155.54
81.12
80.98
31.82
28.19
27.92
7.26
f1 (ppm)

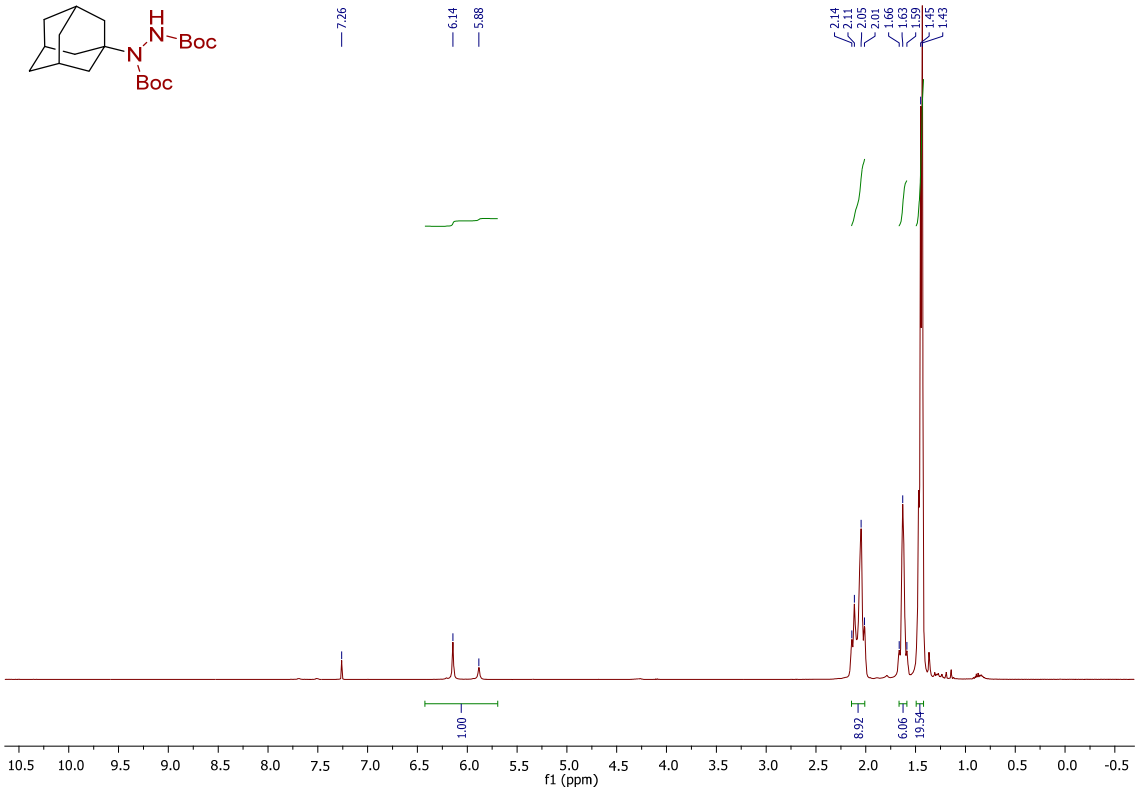

Boc
N
N
H
Boc
Me
Me
7.26
6.01
5.91
4.20
4.04
1.44
1.43
1.24
1.05
0.86
0.85
0.82
0.85
0.83
18.48
6.83
2.97
3.00
f1 (ppm)

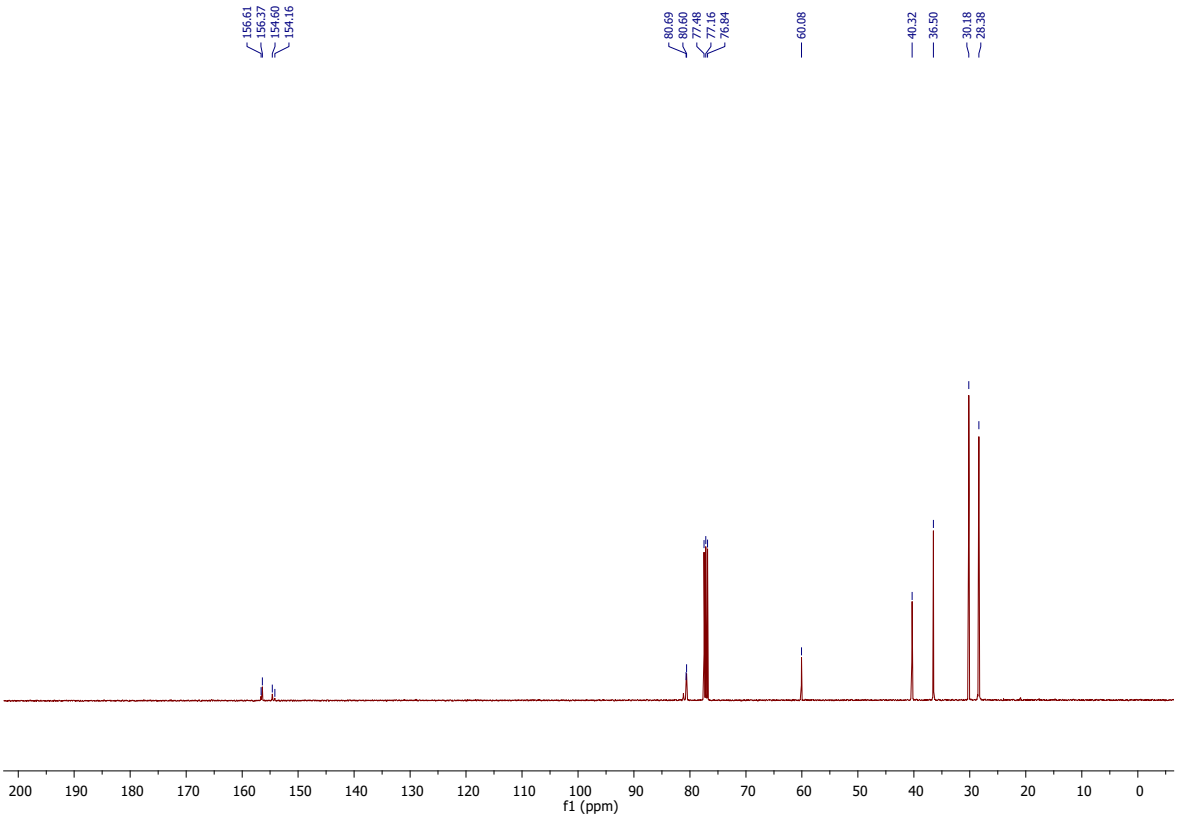

155.63
155.19
80.76
77.58
77.16
76.74
54.44
52.49
34.11
31.78
28.35
28.26
26.24
22.72
17.83
14.15
f1 (ppm)

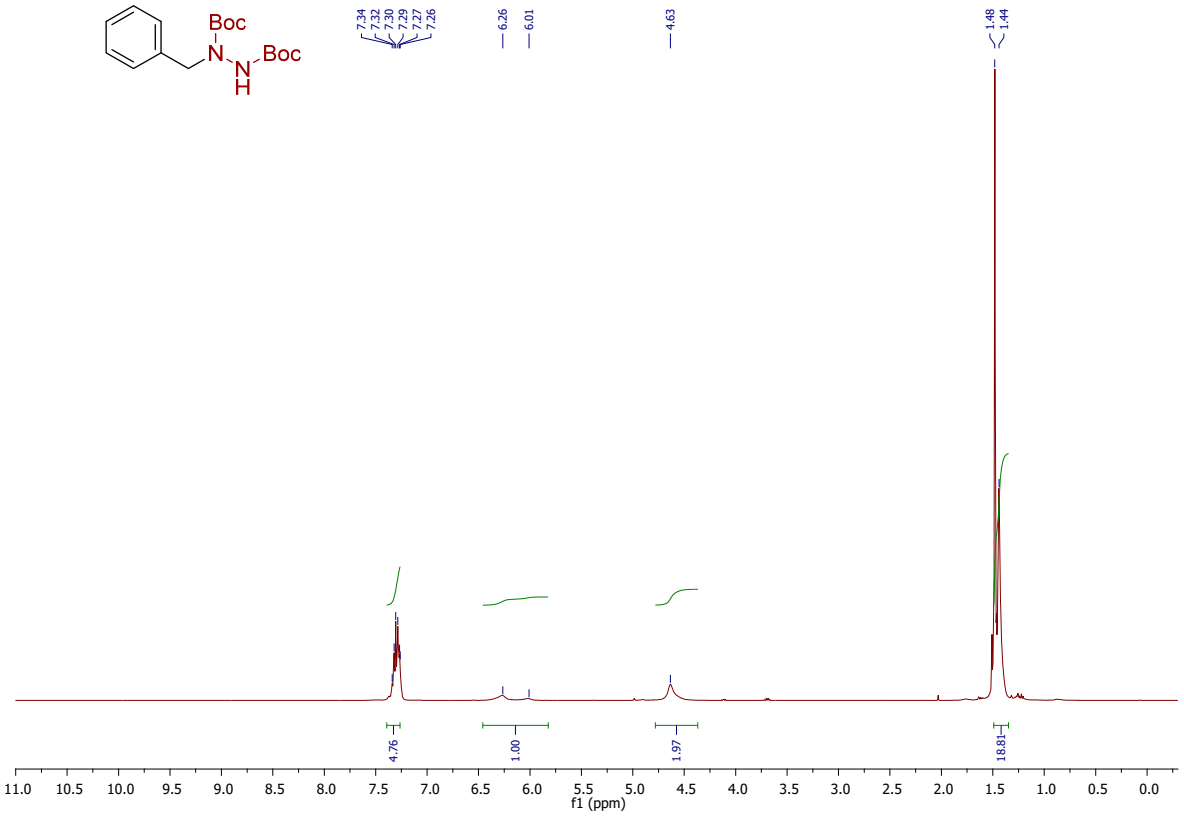

Boc
H3C
N
N
Boc
H
CH3
7.26 CDCl
6.08
5.85
4.36
1.45
1.44
1.09
1.07
0.92
0.90
8.82
9.21
6.00
f1 (ppm)

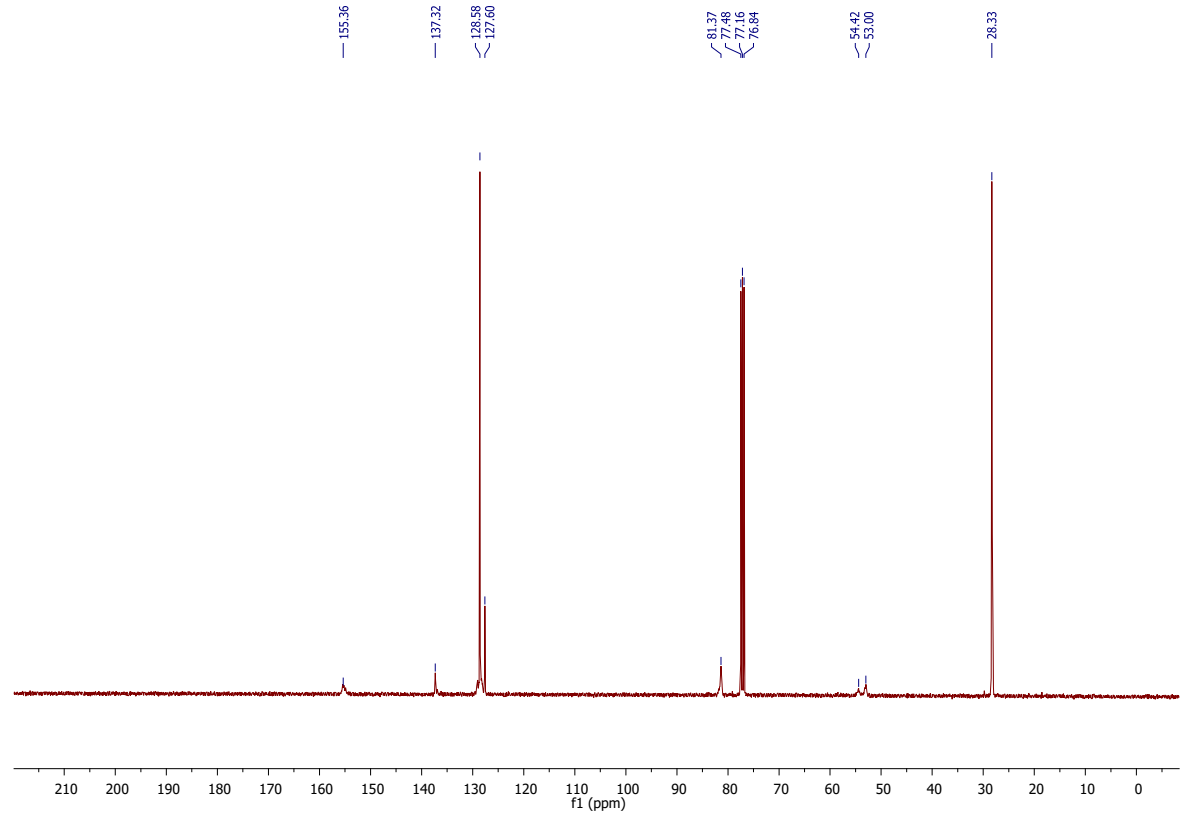

156.47
155.95
154.80
81.34
80.89
77.16 CDCl
48.34
28.39
28.28
19.86
f1 (ppm)

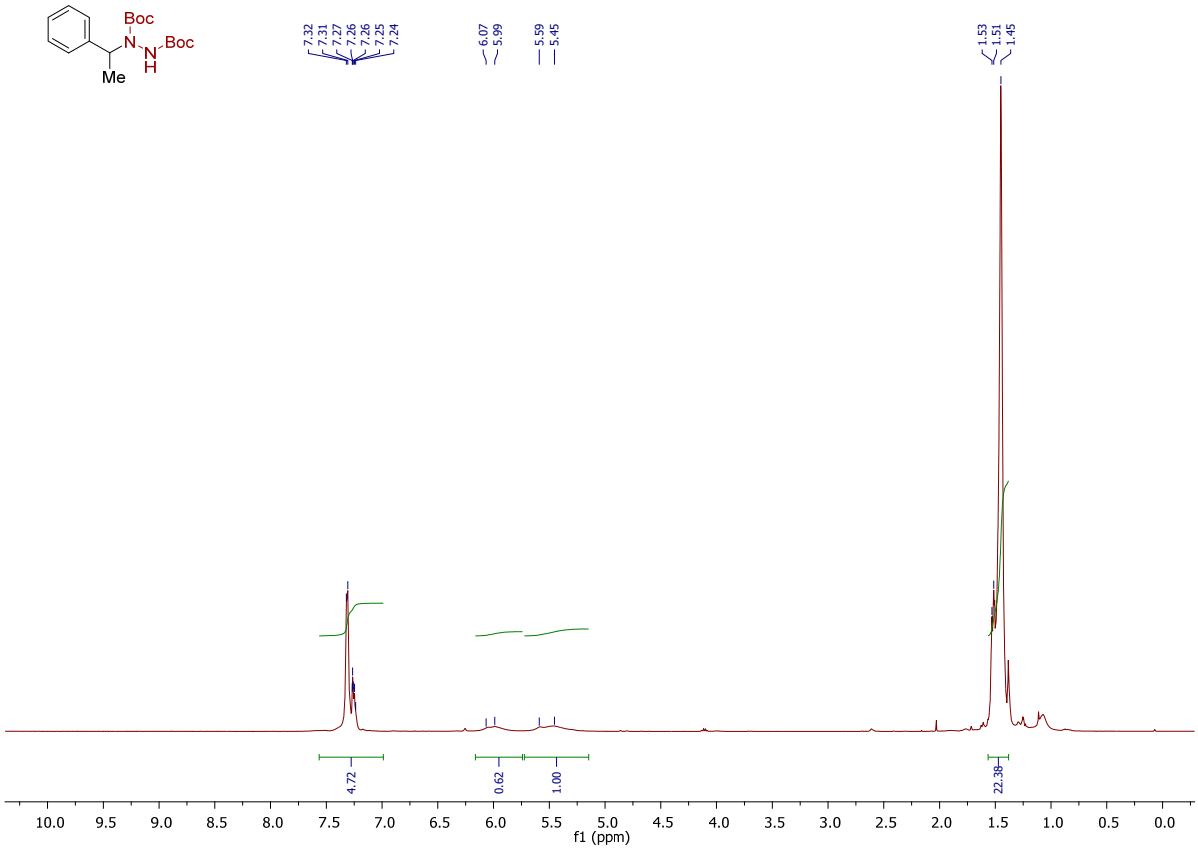

Boc
Me
N
Boc
Me
N
H
Me
7.26
6.23
5.97
1.44
1.43
1.36
1.00
9.46
9.06
9.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
156.52
156.19
154.81
154.32
81.25
80.65
77.48
77.16
76.84
59.41
28.61
28.42
28.34
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

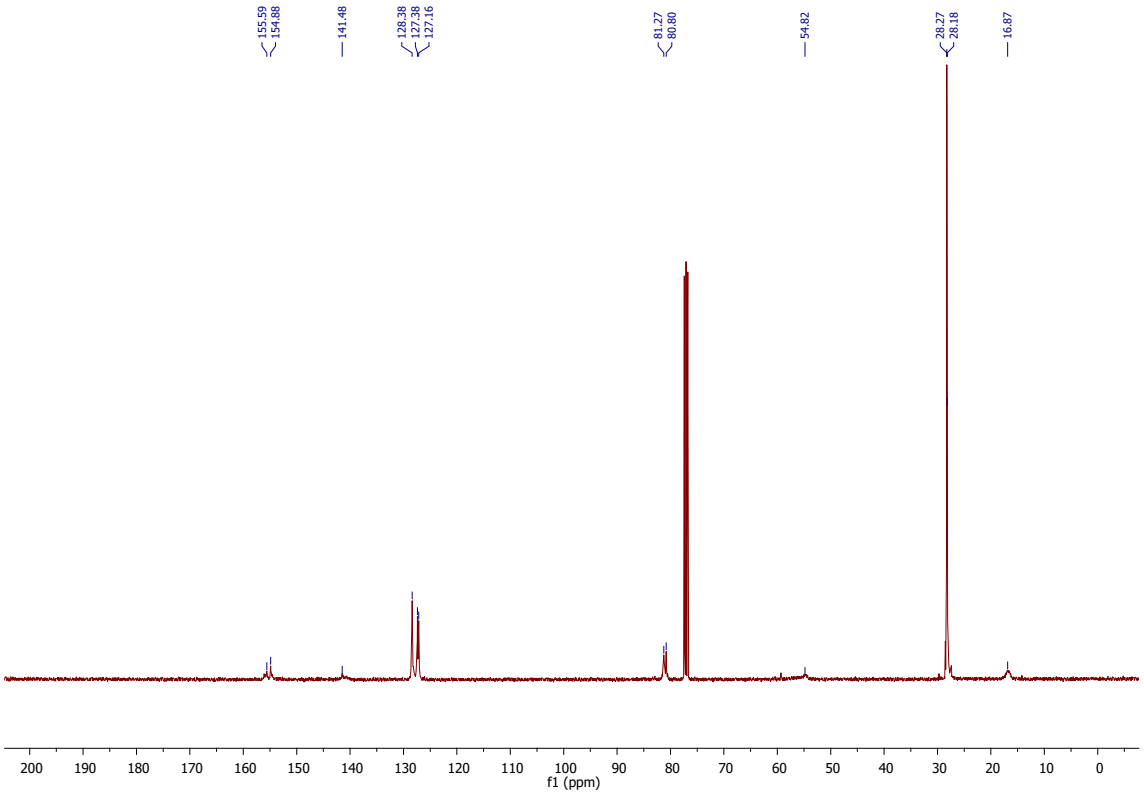

H
N
Boc
N
Boc
7.26
6.14
5.88
2.14
2.11
2.05
2.01
1.66
1.63
1.59
1.45
1.43
1.00
8.92
6.06
19.54
f1 (ppm)

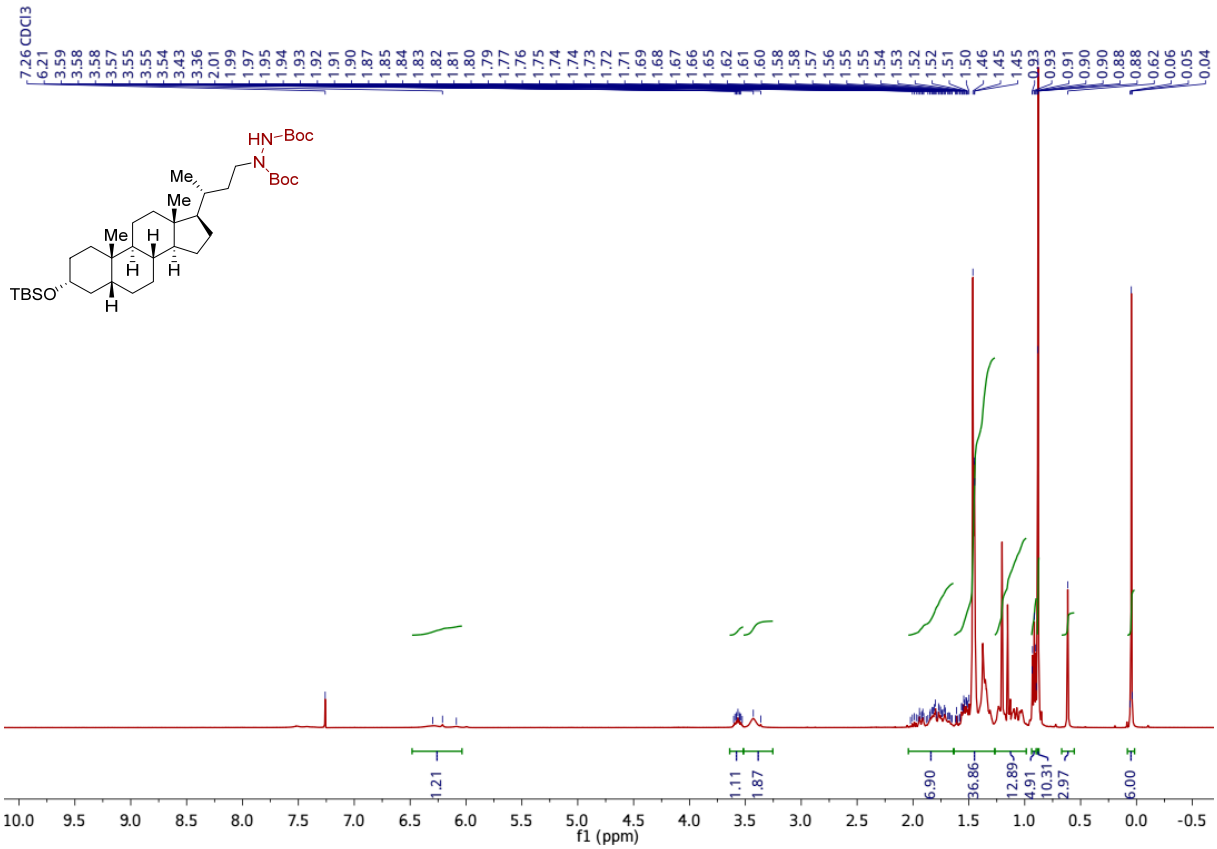

156.61
156.37
154.60
154.16
80.69
80.60
77.48
77.16
76.84
60.08
40.32
36.50
30.18
28.38
f1 (ppm)

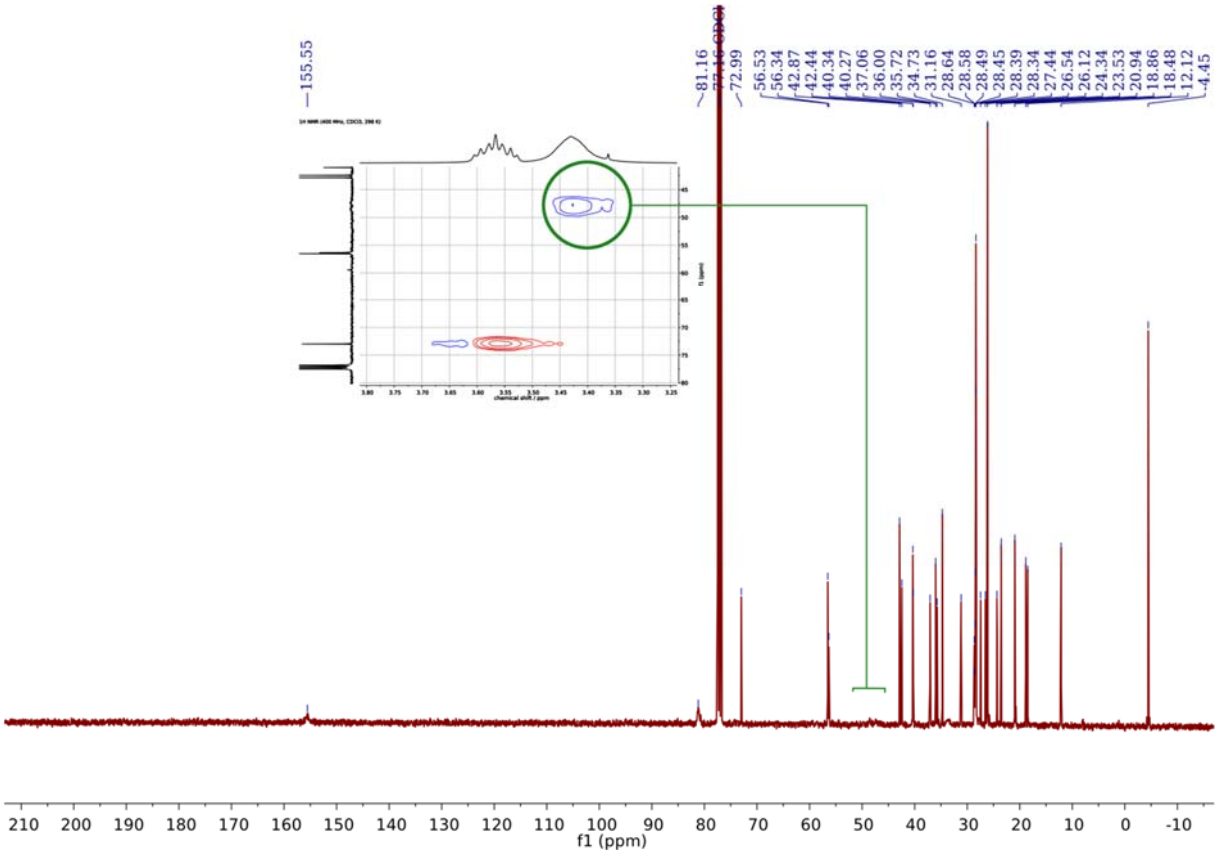

Boc
N
N
H
Boc
7.34
7.32
7.30
7.29
7.27
7.26
6.26
6.01
4.63
1.48
1.44
4.76
1.00
1.97
18.81
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

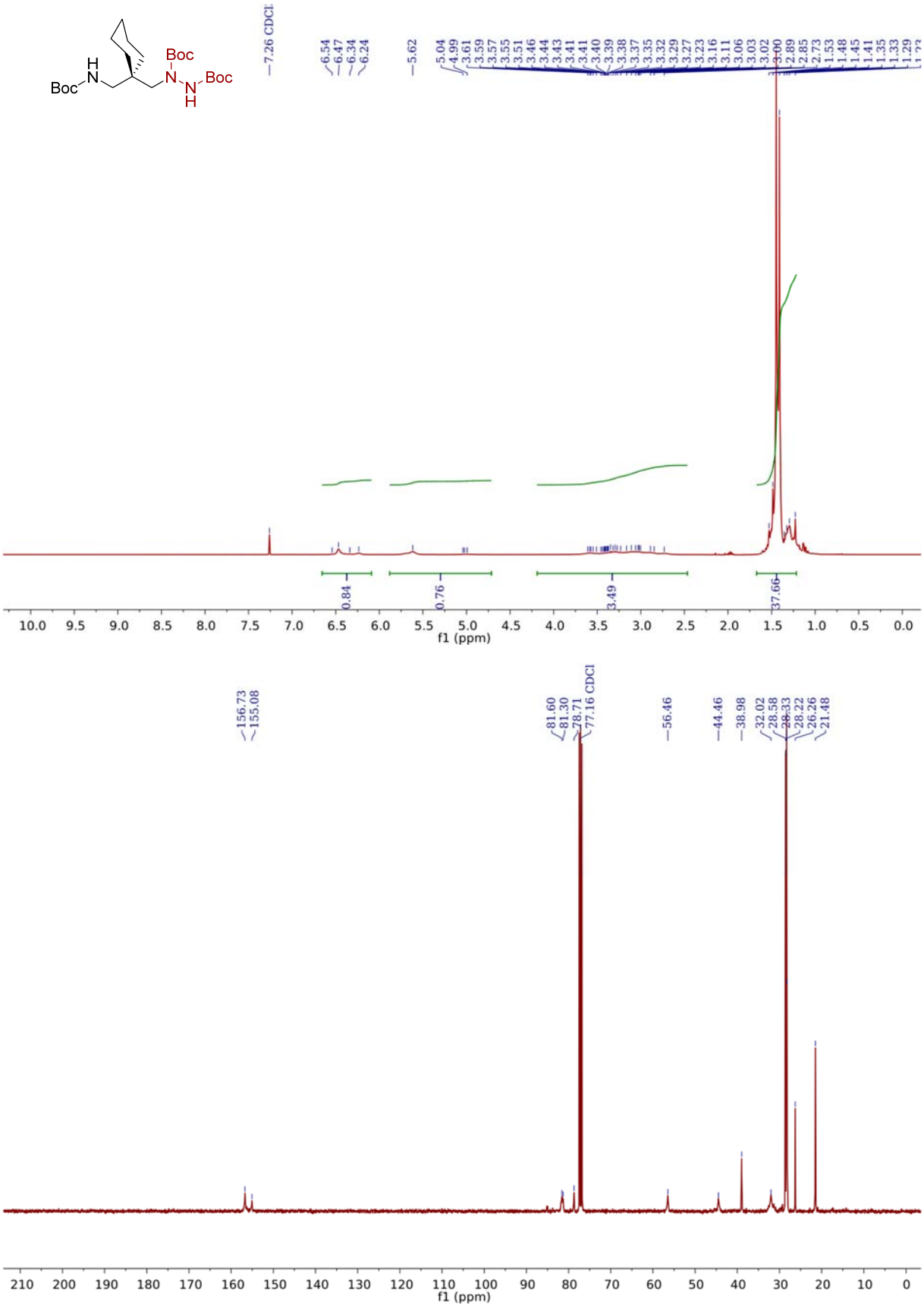

155.36
137.32
128.58
127.60
81.37
77.48
77.16
76.84
54.42
53.00
28.33
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

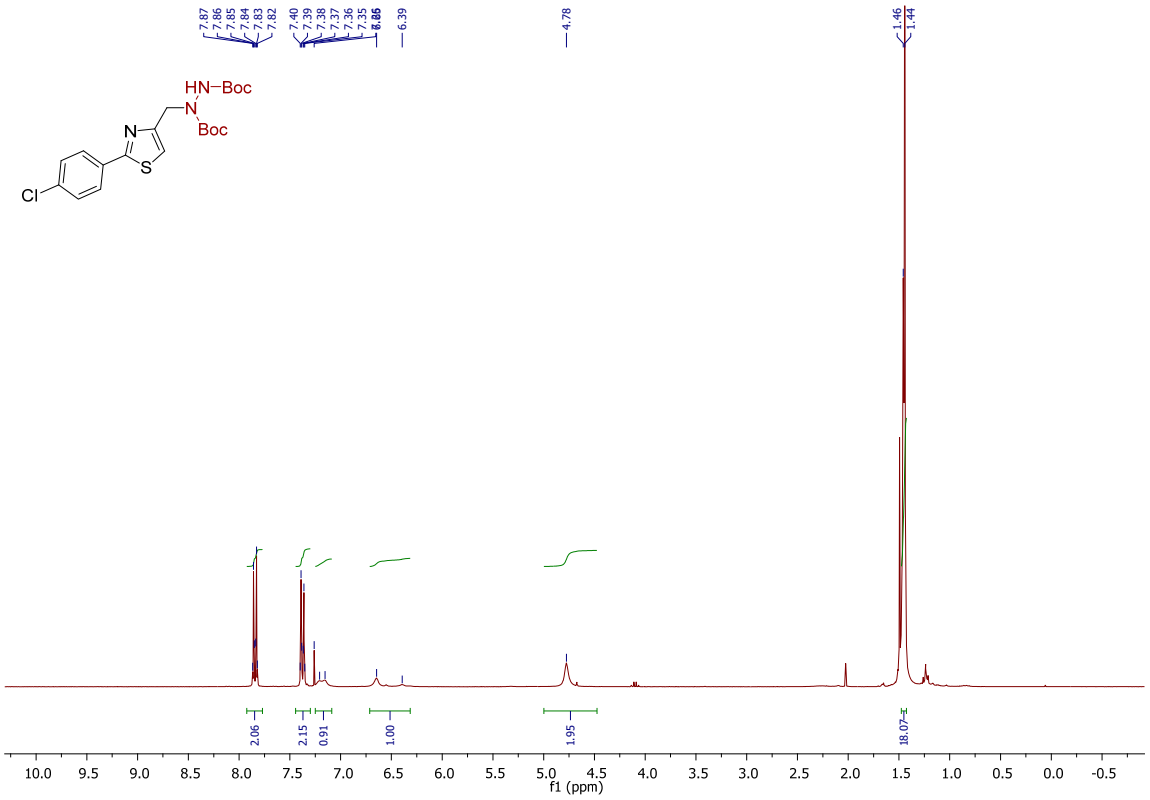

Boc
N
N
Boc
H
Me
7.32
7.31
7.27
7.26
7.26
7.25
7.24
6.07
5.99
5.59
5.45
1.53
1.51
1.45
4.72
0.62
1.00
22.38
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

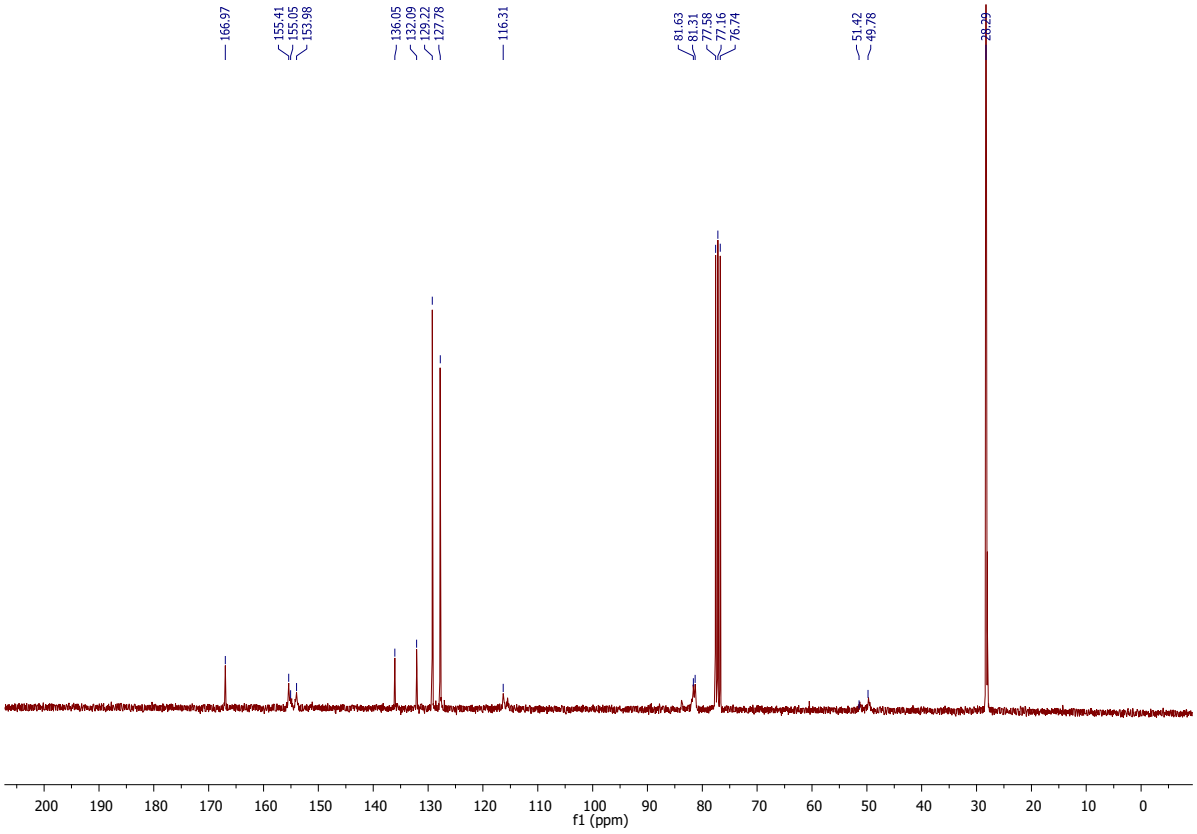

155.59
154.88
141.48
128.38
127.38
127.16
81.27
80.80
54.82
28.27
28.18
16.87
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

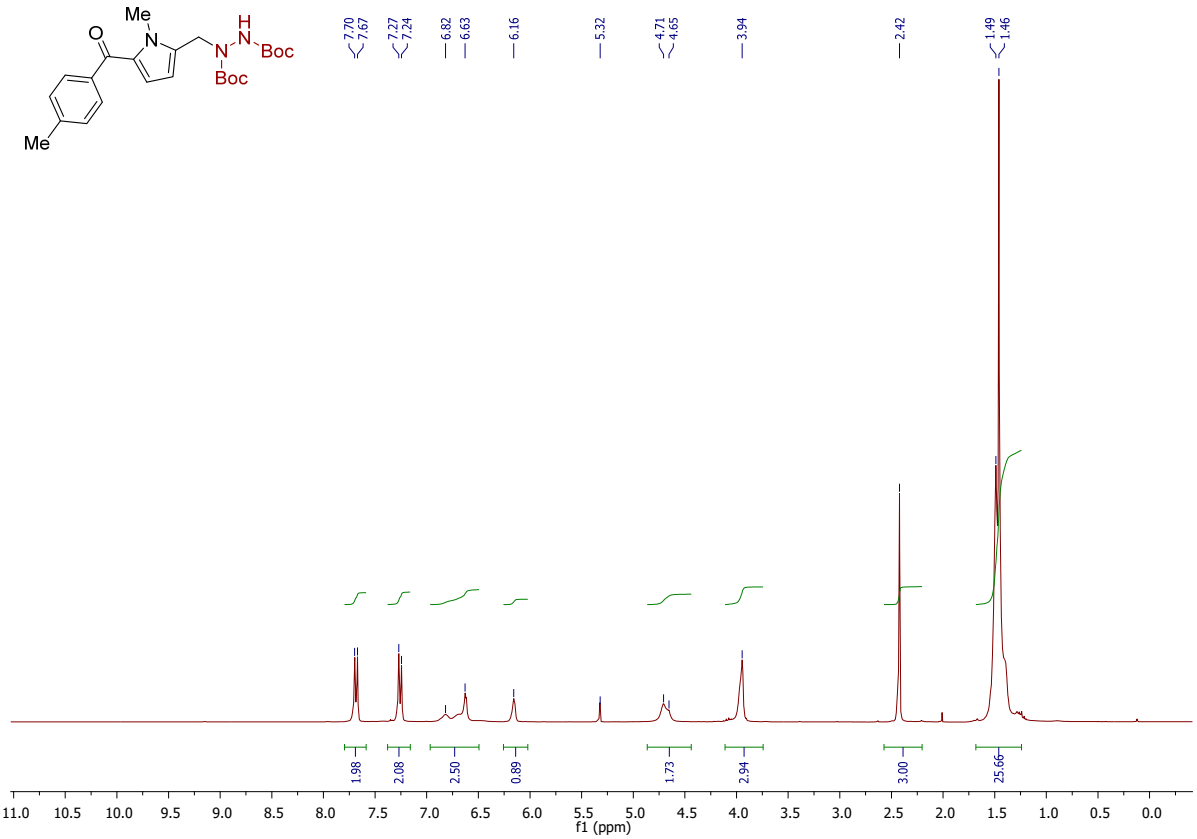

HN–Boc
N
Boc
Me
Me
Me
H
H
H
H
TBSO
f1 (ppm)

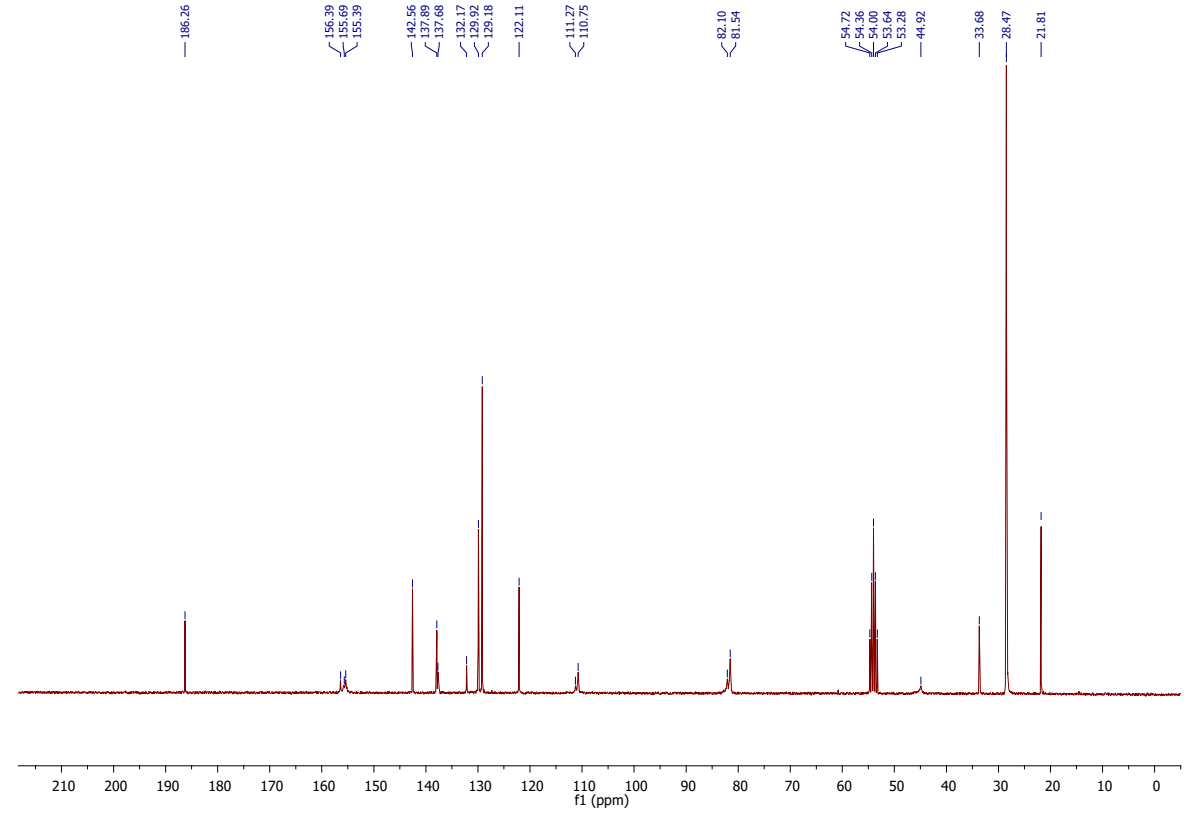

f1 (ppm)

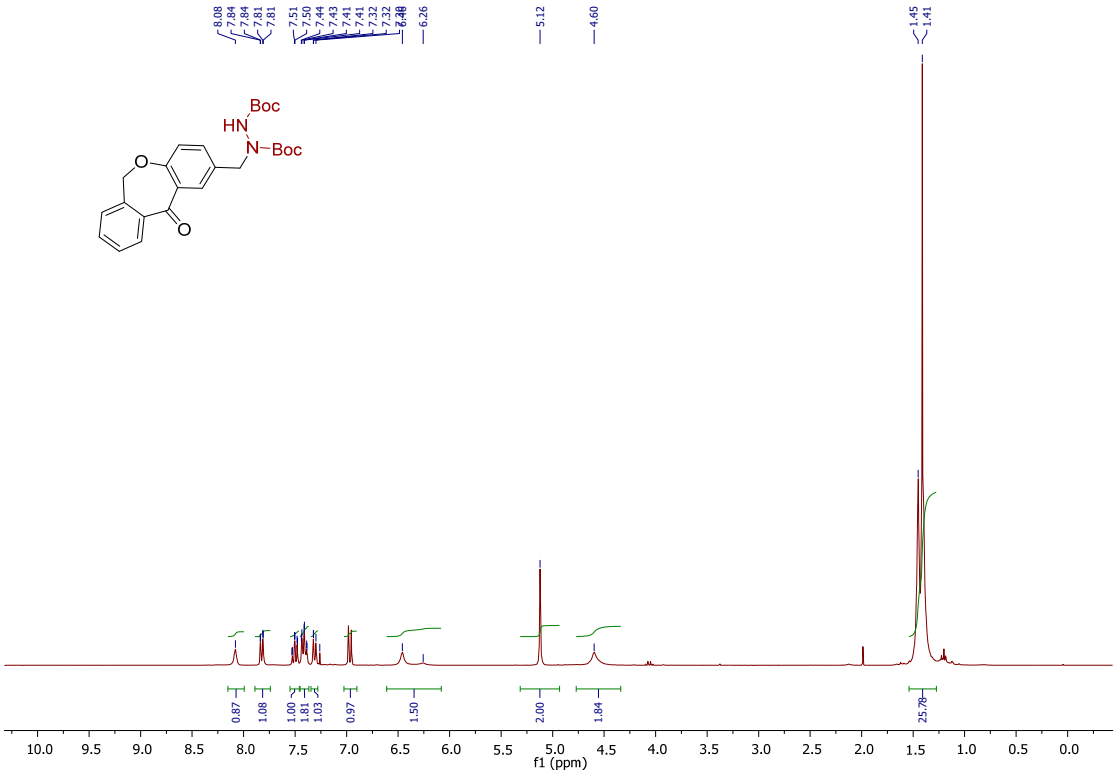

Boc
N
H
Boc
N
N
H
Boc
7.26 CDCl
6.54
6.47
6.34
6.24
5.62
5.04
4.99
3.61
3.59
3.57
3.55
3.51
3.46
3.44
3.43
3.41
3.40
3.39
3.38
3.37
3.35
3.32
3.29
3.27
3.23
3.16
3.11
3.06
3.03
3.02
3.00
2.89
2.85
2.73
1.53
1.48
1.45
1.41
1.35
1.33
1.29
0.84
0.76
3.49
37.66
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
156.73
155.08
81.60
81.30
78.71
77.16 CDCl
56.46
44.46
38.98
32.02
28.58
28.33
28.22
26.26
21.48
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

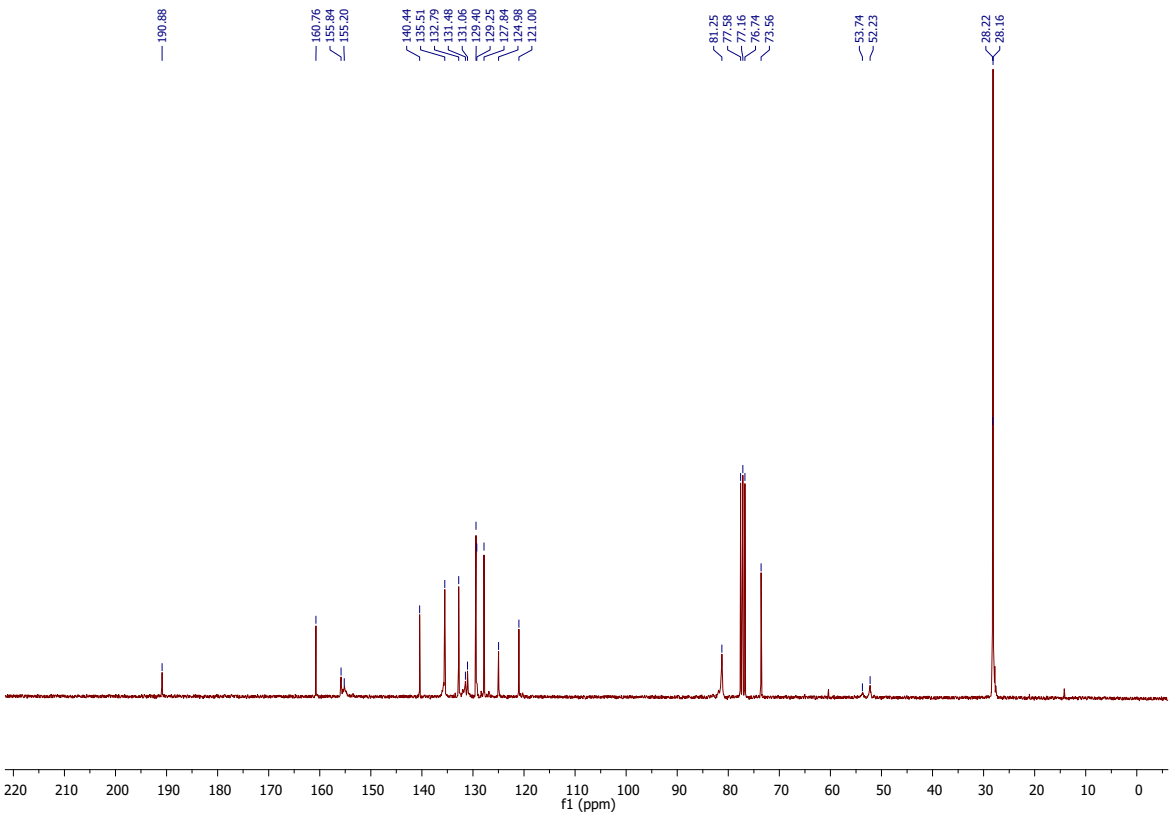

7.87
7.86
7.85
7.84
7.83
7.82
7.40
7.39
7.38
7.37
7.36
7.35
6.39
4.78
1.46
1.44
HN–Boc
N
Boc
N
S
Cl
2.06
2.15
0.91
1.00
1.95
18.07
f1 (ppm)

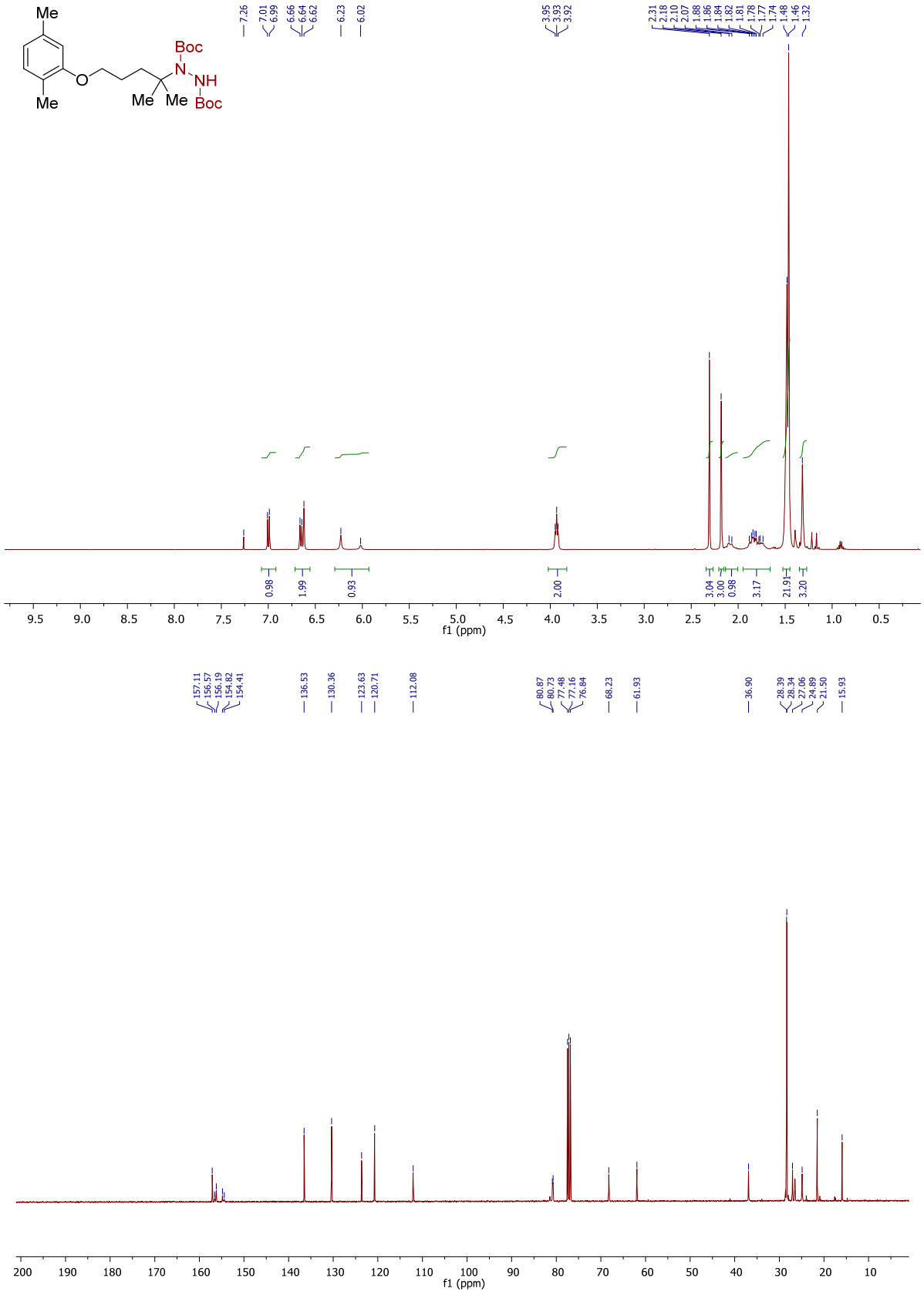

166.97
155.41
155.05
153.98
136.05
132.09
129.22
127.78
116.31
81.63
81.31
77.58
77.16
76.74
51.42
49.78
28.29
f1 (ppm)

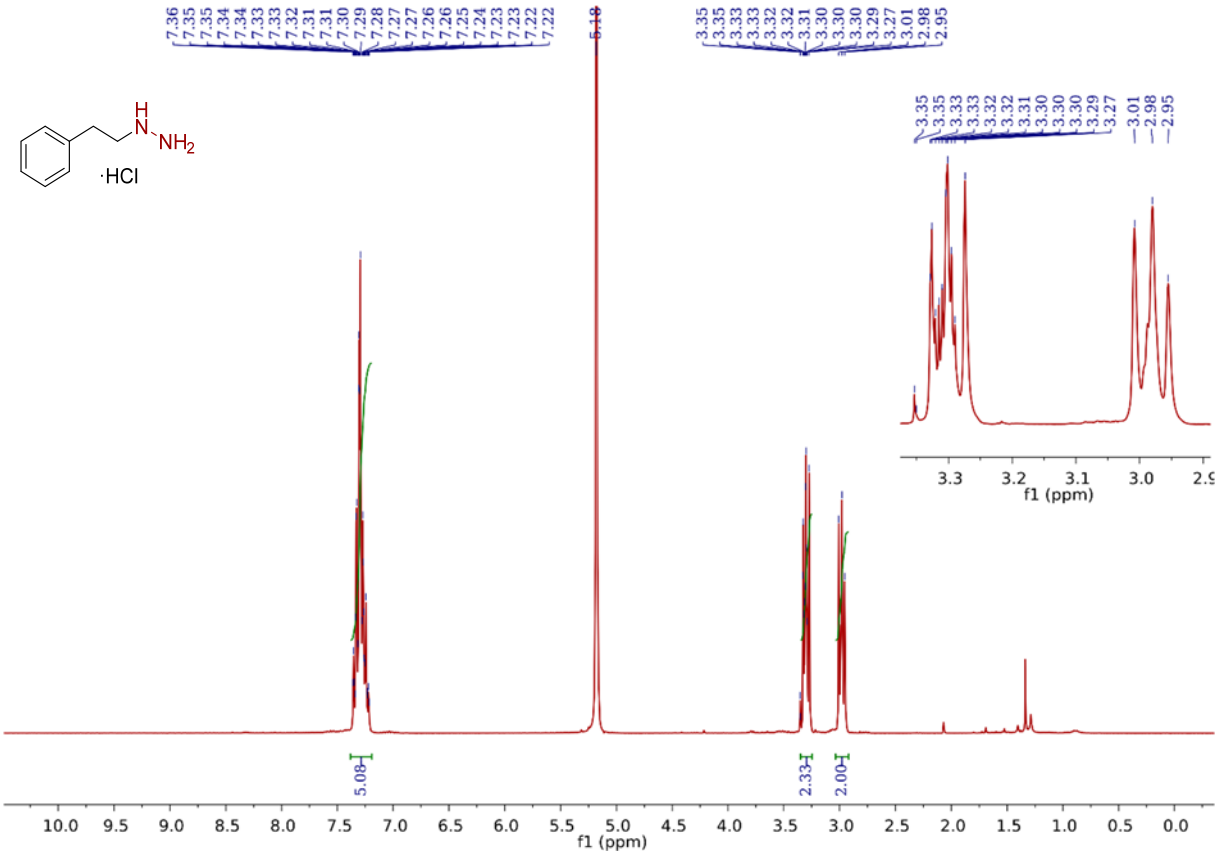

Me
O
N
H
N
Boc
N
Boc
Me
7.70
7.67
7.27
7.24
6.82
6.63
6.16
5.32
4.71
4.65
3.94
2.42
1.49
1.46
1.98
2.08
2.50
0.89
1.73
2.94
3.00
25.66
f1 (ppm)

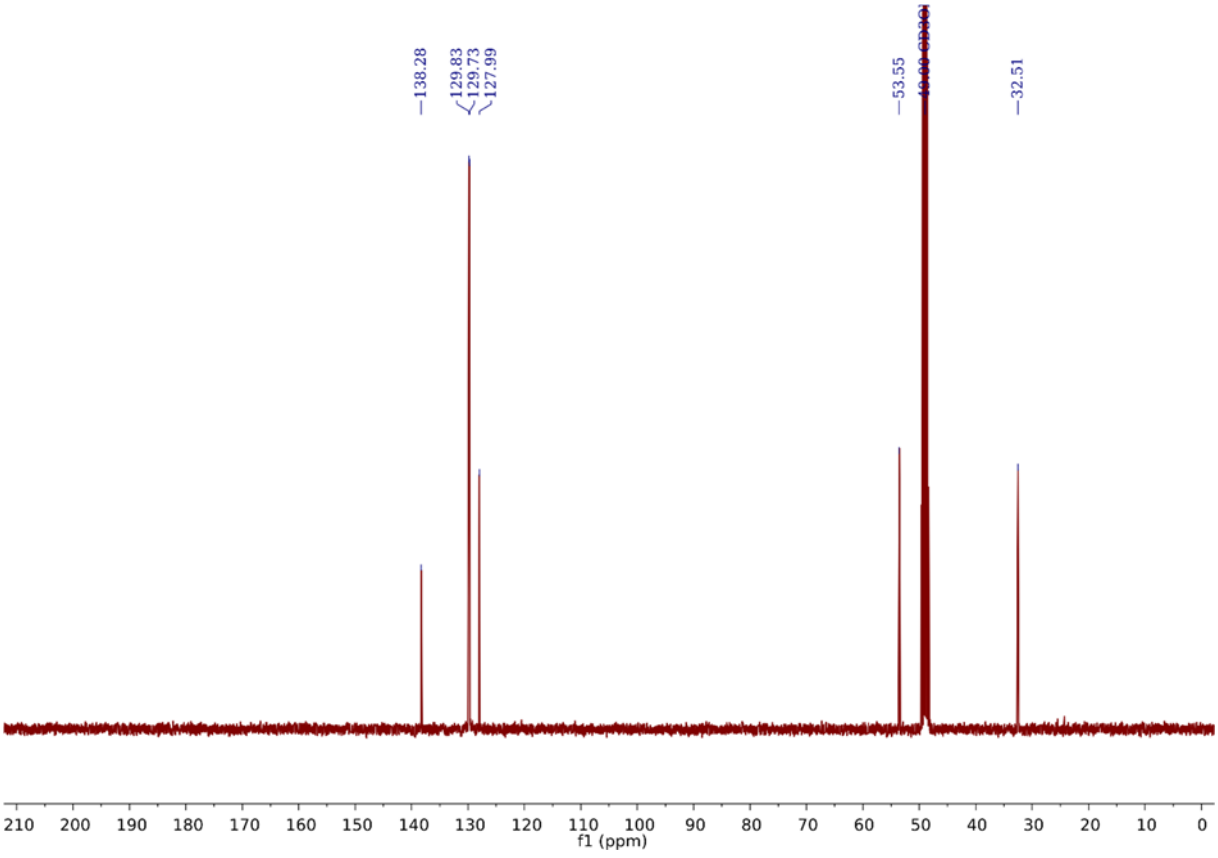

186.26
156.39
155.69
155.39
142.56
137.89
137.68
132.17
129.92
129.18
122.11
111.27
110.75
82.10
81.54
54.72
54.36
54.00
53.64
53.28
44.92
33.68
28.47
21.81
f1 (ppm)

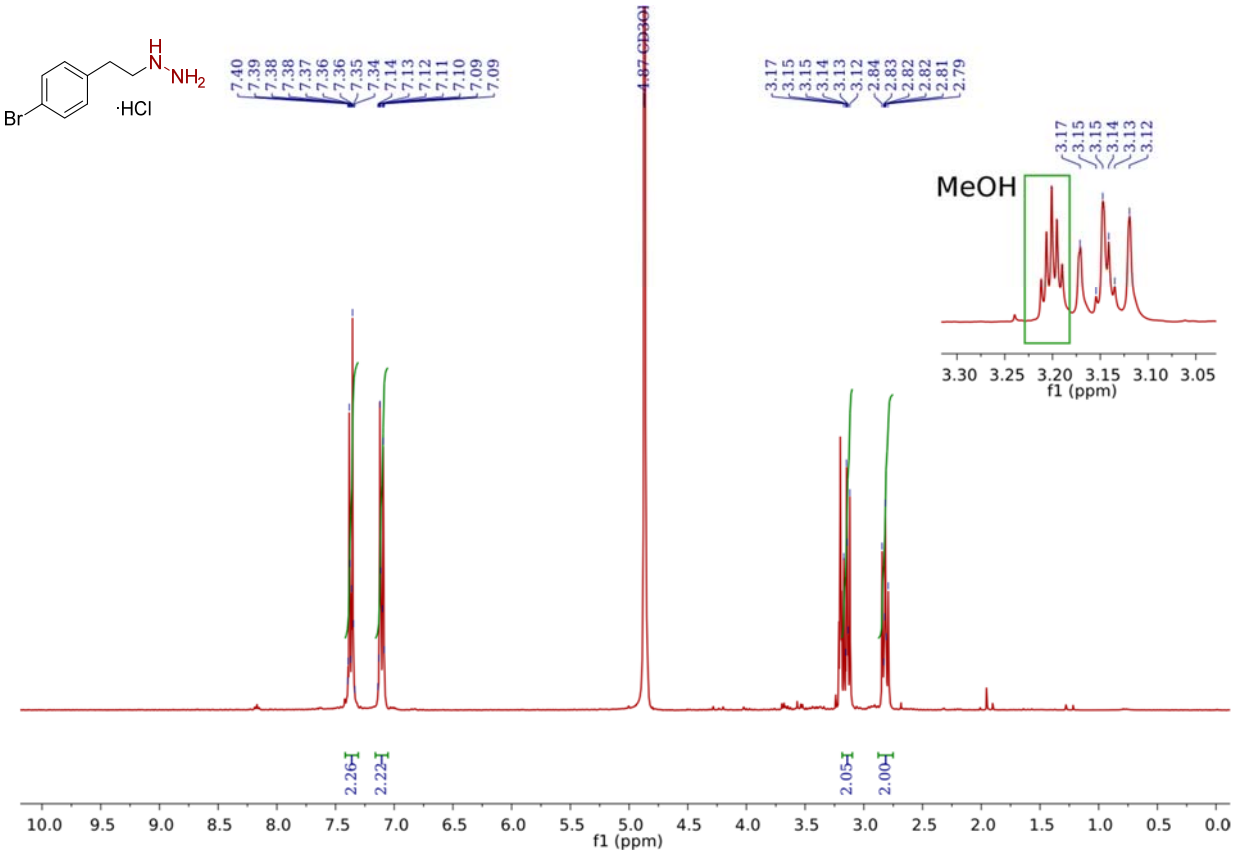

8.08
7.84
7.84
7.81
7.81
7.51
7.50
7.44
7.43
7.41
7.41
7.32
7.32
6.26
5.12
4.60
1.45
1.41
Boc
HN
N
Boc
O
O
0.87
1.08
1.00
1.81
1.03
0.97
1.50
2.00
1.84
25.78
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

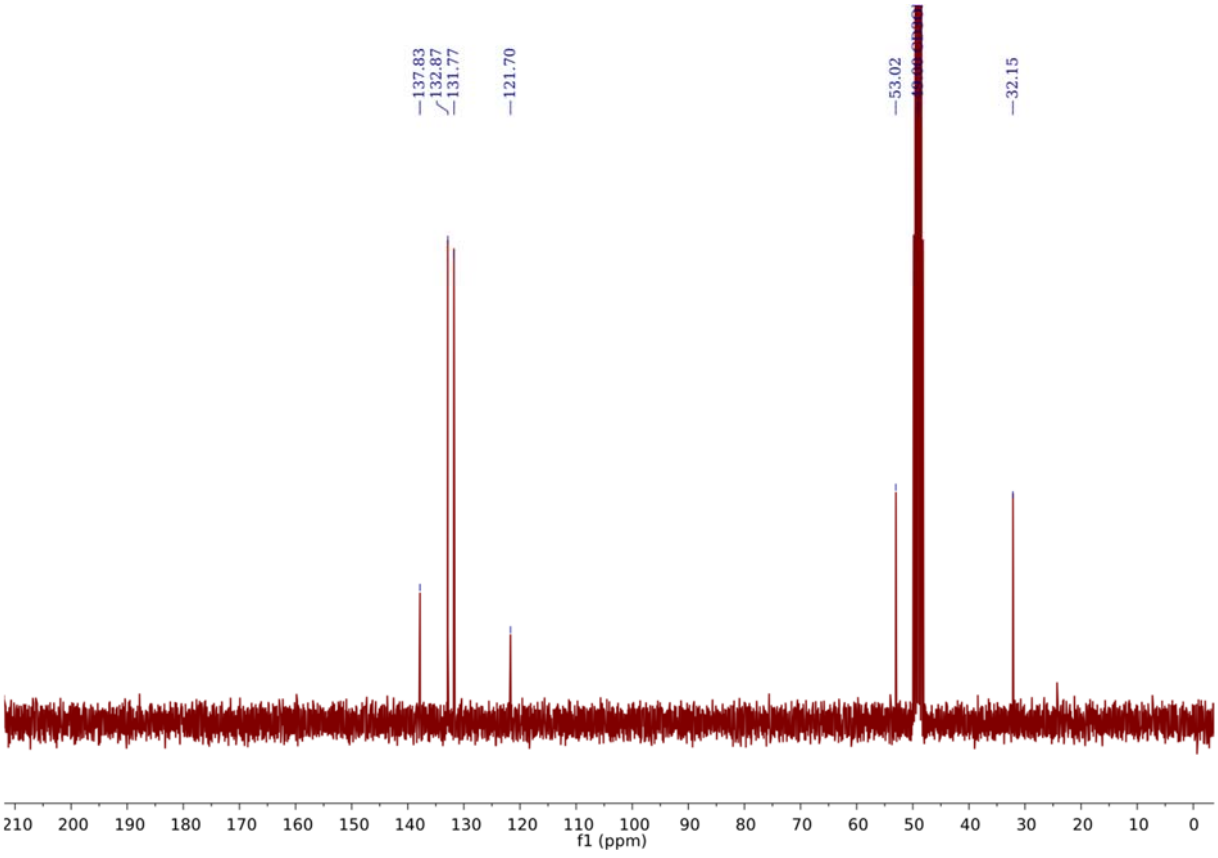

190.88
160.76
155.84
155.20
140.44
135.51
132.79
131.48
131.06
129.40
129.25
127.84
124.98
121.00
81.25
77.58
77.16
76.74
73.56
53.74
52.23
28.22
28.16
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

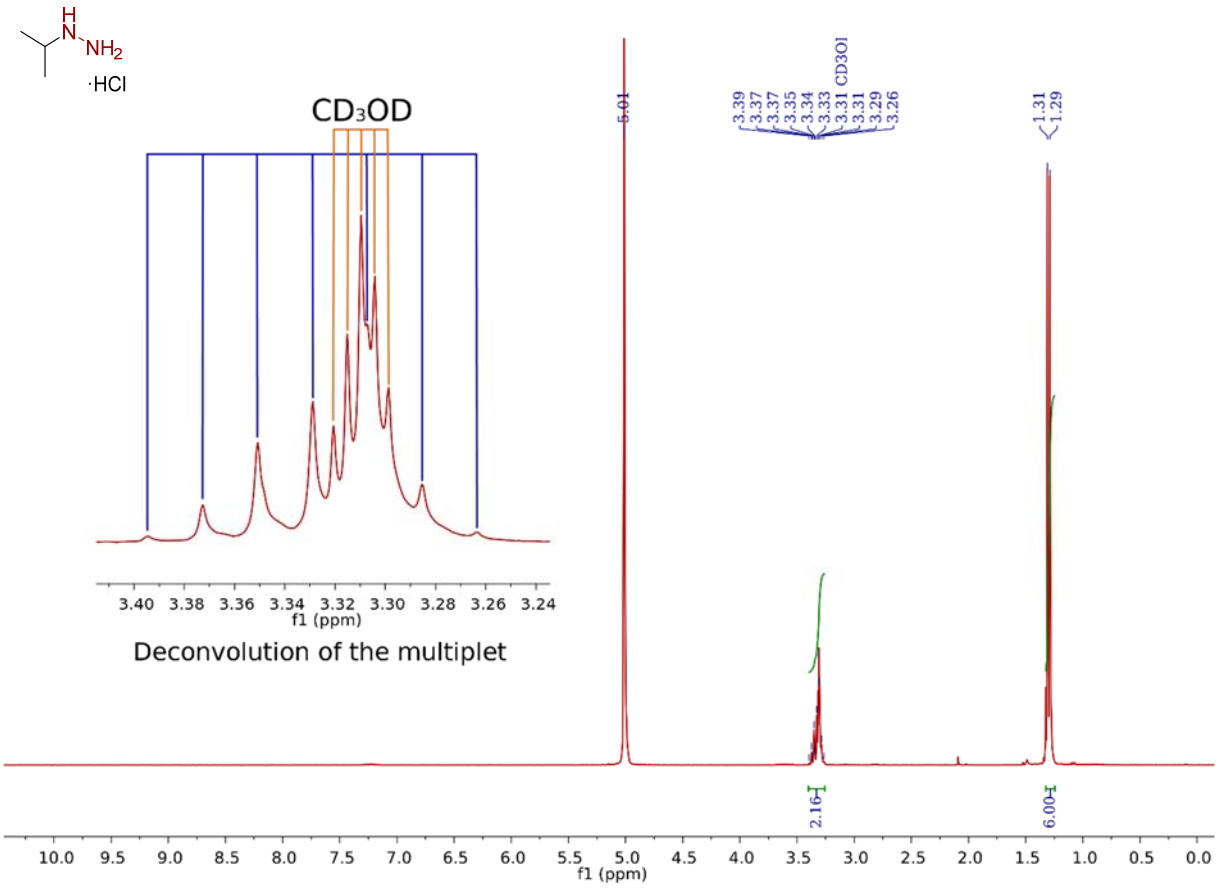

Me
Me
O
Boc
N
NH
Boc
Me
Me
7.26
7.01
6.99
6.66
6.64
6.62
6.23
6.02
3.95
3.93
3.92
2.31
2.18
2.10
2.07
1.88
1.86
1.84
1.82
1.81
1.78
1.77
1.74
1.48
1.46
1.32
0.98
1.99
0.93
2.00
3.04
3.00
0.98
3.17
21.91
3.20
f1 (ppm)
157.11
156.57
156.19
154.82
154.41
136.53
130.36
123.63
120.71
112.08
80.87
80.73
77.48
77.16
76.84
68.23
61.93
36.90
28.39
28.34
27.06
24.89
21.50
15.93
f1 (ppm)

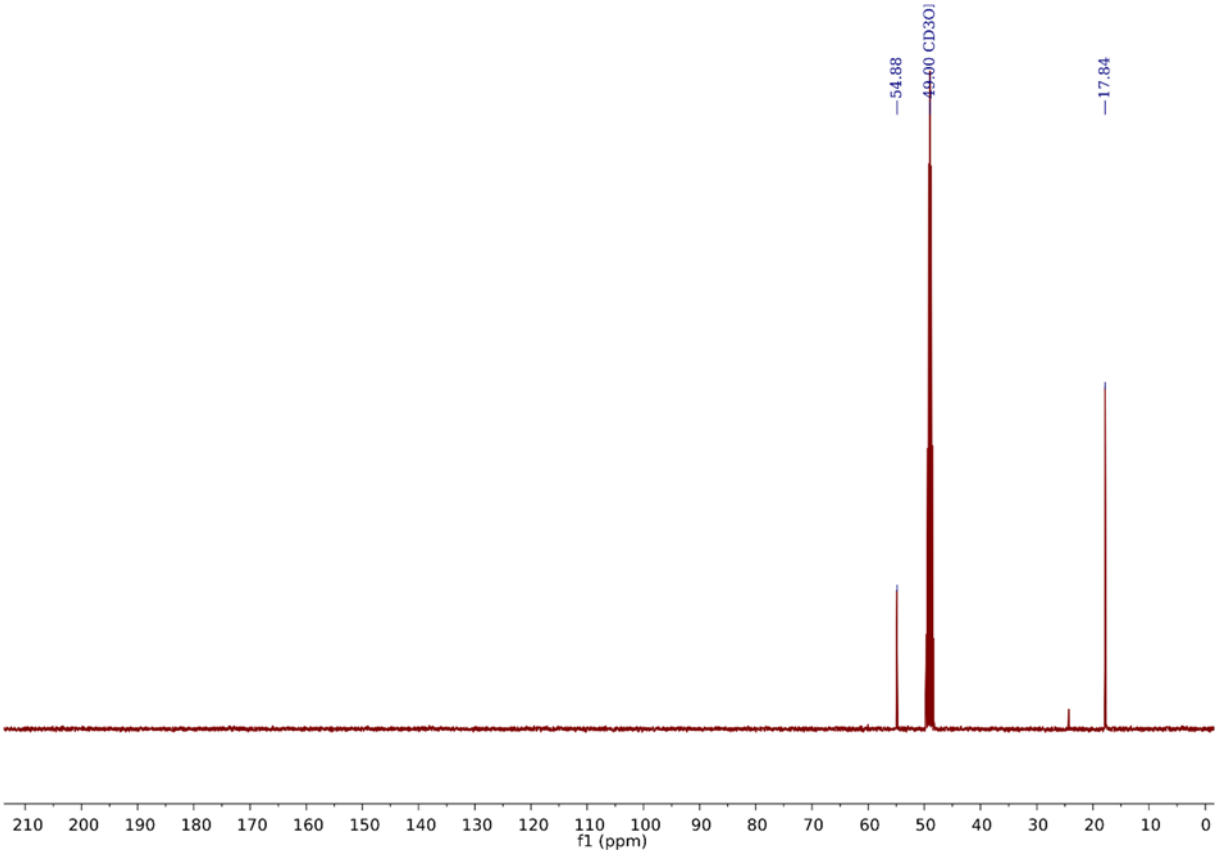

7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.29 7.28 7.27 7.27 7.26 7.26 7.25 7.24 7.23 7.23 7.22 7.22
5.18
3.35 3.35 3.33 3.33 3.32 3.32 3.31 3.30 3.30 3.30 3.29 3.27 3.01 2.98 2.95
H
N
NH2
·HCl
5.08
2.33
2.00
f1 (ppm)

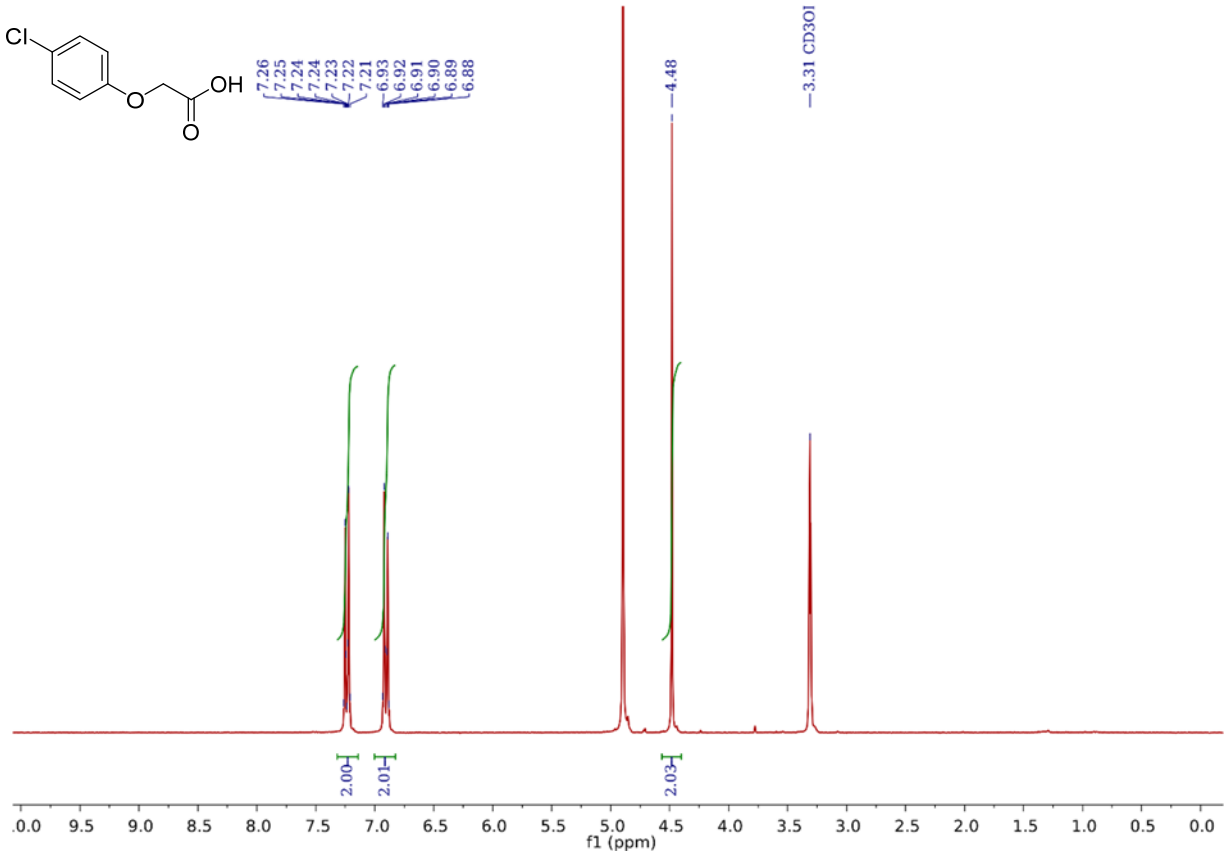

138.28
129.83
129.73
127.99
53.55
40.00 CDOD
32.51
f1 (ppm)

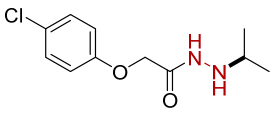

Br
·HCl
MeOH
f1 (ppm)


f1 (ppm)


CD3OD
Deconvolution of the multiplet
f1 (ppm)
5.01
3.39
3.37
3.37
3.35
3.34
3.33
3.31 CD3OI
3.31
3.29
3.26
1.31
1.29
2.16
6.00


54.88
49.00 CD3OI
17.84
f1 (ppm)


Cl
O
OH
O
7.26
7.25
7.24
7.24
7.23
7.22
7.21
6.93
6.92
6.91
6.90
6.89
6.88
4.48
3.31 CD3OI
2.00
2.01
2.03
.0.0 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
f1 (ppm)

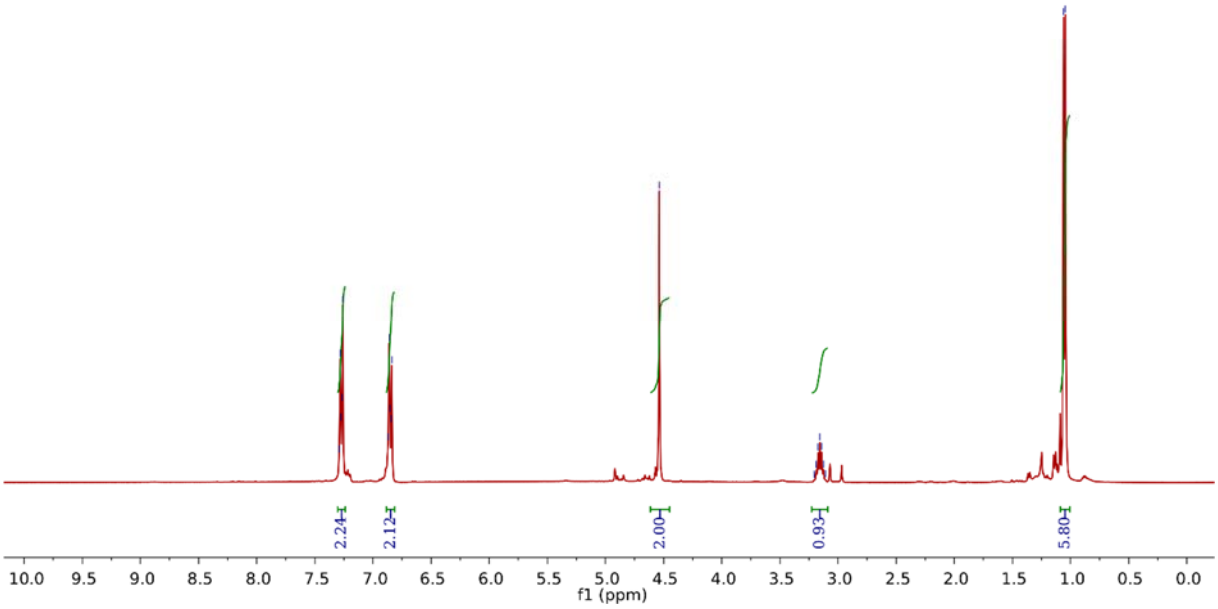


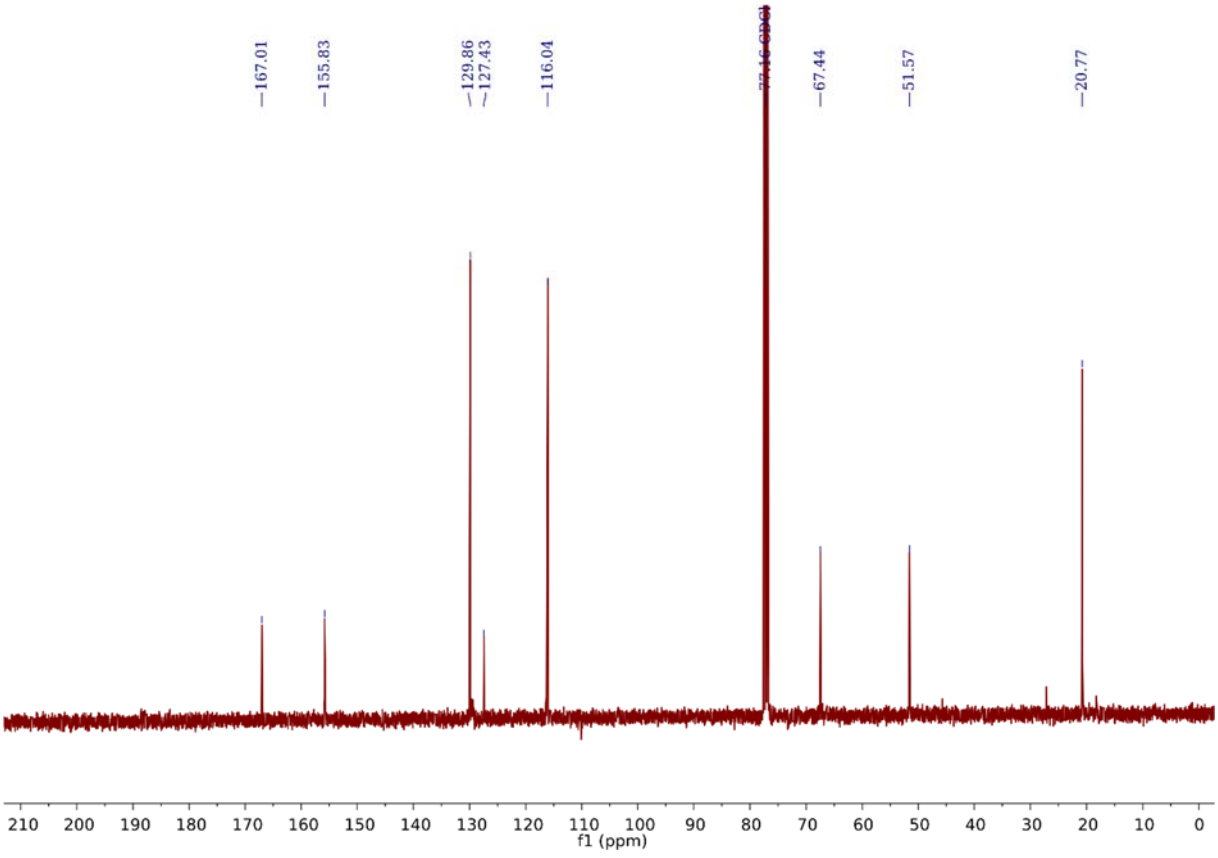

7.29
7.28
7.28
7.26
7.26
6.87
6.86
6.85
6.84
6.84

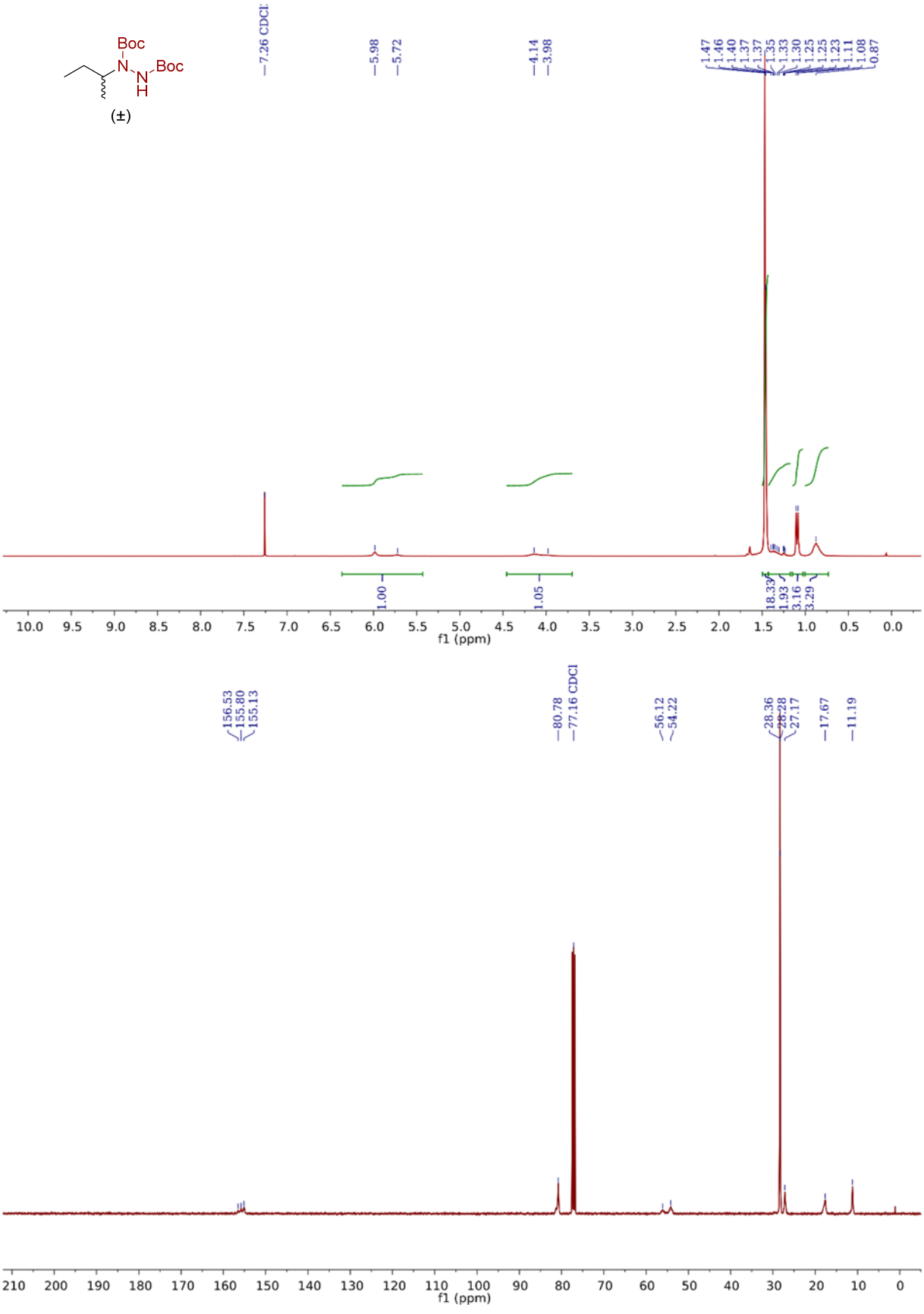
4.54

3.20
3.19
3.17
3.16
3.14
3.12
3.11

1.06
1.05




Boc
N
N
H
Boc
(±)
7.26 CDCl
5.98
5.72
4.14
3.98
1.47
1.46
1.40
1.37
1.37
1.35
1.33
1.30
1.25
1.25
1.23
1.11
1.08
0.87
1.00
1.05
18.33
1.93
3.16
3.29
f1 (ppm)
156.53
155.80
155.13
80.78
77.16 CDCl
56.12
54.22
28.36
28.28
27.17
17.67
11.19
f1 (ppm)