Ag(I)/TiO_2-Photocatalyzed N-Methylation of Amino Acids with Methanol

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Dedicated to Professor Akihiko Kudo on the occasion of his 60th birthday

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Abstract: Silver(I)-loaded titanium dioxide ($AgNO_3/TiO_2$) catalyzes the direct N-methylation of amino acids with methanol under irradiation with UV light. This method produces a variety of *N*-methyl and *N,N*-dimethyl amino acids with retention of their optical purity.

N-Methylated amino acids are important structural features in non-ribosomal peptides.[1,2] *N,N*-Dimethyl amino acids derived from valine, leucine, isoleucine, and phenylalanine are residues commonly encountered in bioactive natural products. Representative examples include dolastatin 10[3,4] and coibamide A,[5,6] both of which are natural products with potent antitumor activity (Figure 1). Moreover, *N,N*-dimethyl amino acids serve as isobaric tags for proteomics research.[7,8]

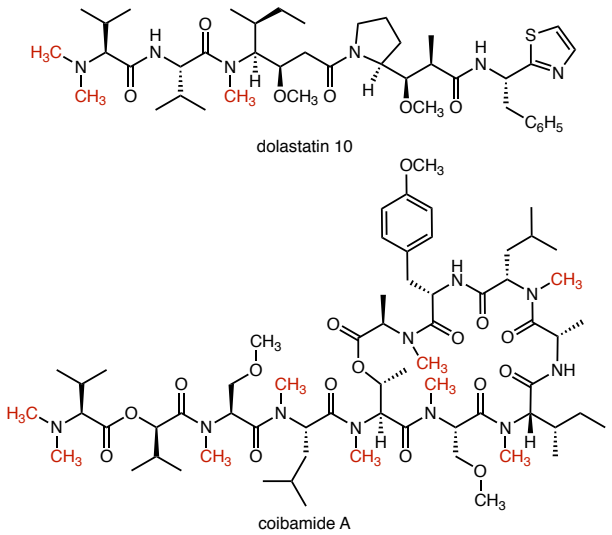
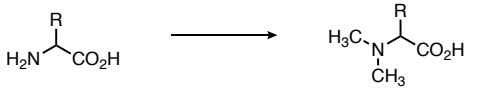


Figure 1. Representative, naturally occurring *N*-methyl amino acids.

Direct N-methylation of primary or secondary amino acids is a powerful tool for the synthesis of N-methylated amino acids.[9] Classical methods include the direct N-methylation of amino acids with alkyl halides (CH_3I/Ag_2O),[10] and the reductive amination with formaldehyde and sodium borohydrides[11] (Scheme 1A). However, these methods are limited, mostly due to the relatively low stability of the starting materials, and the formation of stoichiometric salt by-products that are inseparable from the charged amino acid products. The N-methylation of amino acids with methanol represents an attractive alternative process, considering that only the desired *N*-methyl amino acids and water are generated. In 2010, Huang reported the direct N-methylation of hydrophobic amino acids such as proline, leucine, and phenylalanine with methanol under an H_2 atmosphere at room temperature using palladium on charcoal (Pd/C) as a catalyst (Scheme 1B).[12] The reductive methylation of amino acids with formaldehyde and H_2 over Pd/C is also possible.[6,13,14]



A Conventional method (reliable but generates salt waste)

direct: CH_3I, Ag_2O; NaOH, ethanol
reductive: HCHO, $NaBH_4$, CF_3CH_2OH, reflux, 24 h

B Catalytic (clean but requires hazardrous reagents)

direct: CH_3OH, H_2, Pd/C, rt, 76 h
reductive: HCHO, H_2, Pd/C, H_2O, rt, 5 d; reflux, 10 min

C Photocatalytic (this work) (clean and safe)

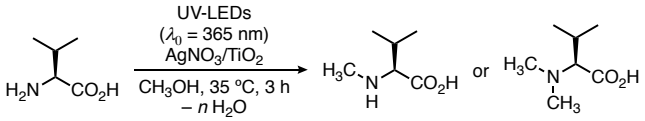
direct: CH_3OH, $AgNO_3/TiO_2$, $h\nu$, rt, 15 h

Scheme 1. N-Methylation of amino acids.

In the context of our program on the photocatalytic conversion of alcohols with metal-loaded titanium dioxide for N-alkylation of amines with alcohols,[15–17] dehydrogenation of primary alcohols,[18] and hydrogenolysis of allyl alcohols,[19,20] we have reported that L-proline can be N-methylated with methanol using a silver-loaded titanium dioxide (Ag/TiO_2) photocatalyst.[15] This was accomplished under irradiation with near UV-light and retention of the chirality at the α-position.[15] Based on this previous preliminary result, we report herein a versatile method for the direct N-methylation of amino acids with methanol at room temperature using an $AgNO_3$-loaded TiO_2 ($AgNO_3/TiO_2$) photocatalyst (Scheme 1C). It should be

noted here that this method does not require any hazardous stoichiometric reducing reagents such as $NaBH_4$ or H_2.

Table 1. Photocatalytic Methylation of L-Valine (**1**).[a]



1 (L-Val) **2** **3**

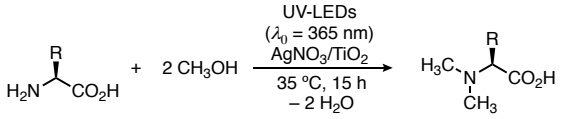
entry	changes in conditions	yield (%)[b] **2**	yield (%)[b] **3**
1	none	45	36
2	15 h	<1	98 [88][c]
3	CH_3OH/H_2O (1:1, 10 mL)	23	2
4	none[d]	45	33
5	CH_3OH/H_2O (1:1, 10 mL)[d]	13	<1
6	with NaOAc[e]	49	42
7	with NaOAc, 6 h[e]	<1	98 [72][c]
8	with NaOAc, in the dark[e]	<1	<1
9	without $AgNO_3/TiO_2$, with NaOAc[e]	<1	<1

[a]Conditions: **1** (0.10 mmol), CH_3OH (10 mL, 240 mmol), $AgNO_3/TiO_2$ (10 mg, 5 mol% Ag), UV-LEDs (λ_0 = 365 nm, 32 W), Ar (1 atm), 35 °C (stirred at rt, warmed by exposure to UV irradiation), 3 h. [b]Determined by ^1H NMR using maleic acid as the internal standard. [c]Isolated yields in brackets. [d]With Ag/TiO_2 (10 mg, 5 mol% Ag) prepared from $AgNO_3/TiO_2$, NaOAc, and $NaBH_4$ in H_2O. [e]With NaOAc (0.23 mmol).

Initially, we investigated the N-methylation of L-valine (**1**) because this reaction produces *N*-methyl valine (**2**) and *N*,*N*-dimethyl valine (**3**), which are often found in bioactive natural products. For that purpose, silver was loaded on a TiO_2 surface by impregnating TiO_2 (Aeroxide® P25) with an aqueous solution of silver nitrate ($AgNO_3/TiO_2$). The desired methyl amino acids **2** and **3** were obtained after mixing $AgNO_3/TiO_2$ (10 mg, 5 mol% Ag) and **1** (0.10 mmol) in dehydrated CH_3OH (10 mL, 240 mmol), and exposing the stirred reaction mixture for 3 h to irradiation from UV-LEDs (λ_0 = 365 nm, 32 W). A ^1H NMR analysis (internal standard: maleic acid) of the thus obtained mixture revealed the formation of **2** and **3** in 45% and 36% yield, respectively (Table 1, entry 1). The conversion of **1** to **3** was completed after 15 h of continuous irradiation (entry 2). Significant side reactions did not occur upon over-irradiation (Table S1). Product **3** was isolated in the form of the 0.58 hydrate after removing the solid photocatalyst by filtration, concentrating the filtrate, and drying under reduced pressure (88% yield). The obtained $[\alpha]_D^{21}$ value (+36.8 °; *c* 2.1; ethanol) is consistent with literature values ($[\alpha]_D^{26}$ = +38.6 °; *c* 2.1; ethanol)[6], which confirms the retention of the chirality at the α-carbon atom (Table 2, entry 1).

The photocatalytic N-methylation of **1** decelerated in the presence of water (Table 1, entry 3). The performance of the current Ag(I)/TiO_2 system is broadly the same as the original Ag(0)/TiO_2 system,[15] for which the reduction of $AgNO_3/TiO_2$ with $NaBH_4$ in an aqueous NaOAc solution is conducted separately before the photon-promoted N-methylation starts (Table 1, entries 1 and 3 vs 4 and 5, respectively). The presence of NaOAc enhances the reactivity (entry 6). However, the removal of NaOAc from **3** requires preparative HPLC separation (entry 7). The current photocatalytic reaction does not proceed in the dark, nor in the absence of the photocatalyst (Table 1, entries 8 and 9).

Table 2. N,N-Dimethylation of Amino Acids.[a]

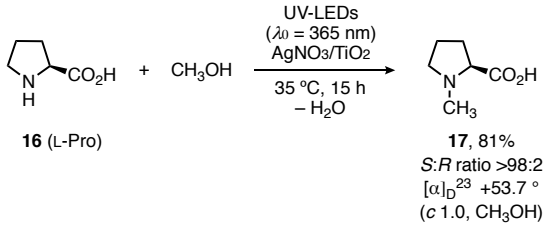


entry	reactant	product		yield,[b] *S*/*R* or dr $[\alpha]_D$
1	**1** (L-Val)		**3**	88% $[\alpha]_D^{21}$ +36.8 ° (*c* 2.1, ethanol)
2	**4** (Gly)		**5**	80%
3	**6** (L-Ala)		**7**	94%, *S*/*R* ratio >98:2[c] $[\alpha]_D^{23}$ –0.293 ° (*c* 0.3, CH_3OH)
4	**8** (L-Phe)		**9**	97% $[\alpha]_D^{21}$ +29.8 ° (*c* 1.0, CH_3OH)
5	**10** (L-Ile)		**11**	92%, dr >98:2[d] $[\alpha]_D^{23}$ +47.8 ° (*c*1.0, CH_3OH)
6	**12** (L-Leu)		**13**	82% $[\alpha]_D^{21}$ +47.6 ° (*c* 1.0, CH_3OH)
7	**14** (L-Met)		**15**	68% $[\alpha]_D^{23}$ +53.7 ° (*c* 1.0, CH_3OH)

[a]Conditions: **1** (0.10 mmol), CH_3OH (10 mL, 240 mmol), $AgNO_3/TiO_2$ (10 mg, 5 mol% Ag, 5 wt%), UV-LEDs (λ_0 = 365 nm, 32 W), Ar (1 atm), 35 °C, 15 h. [b]Isolated yield. [c]Determined by chiral GC/MS. [d]The diastereomeric ratio (dr) was determined by ^1H NMR spectroscopy.

Table 2 summarizes the results of the photocatalytic N-methylation of various amino acids under the optimized reaction conditions (Table 1, entry 2). The conversions and yields of each compound were determined by NMR analysis using 1,4-dioxane as an internal standard. Simple amino acids such as L-valine (**1**), glycine (**4**), L-alanine (**6**), L-phenylalanine (**8**), L-isoleucine (**10**), and L-leucine (**12**) were smoothly converted into the corresponding dimethyl amino acids without producing any side products (Table 2, entries 1–6).

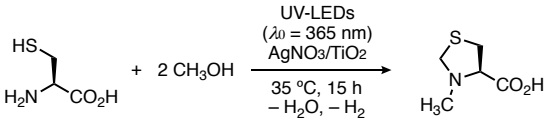
Retention of the stereochemistry at the α-carbon atoms in **7** and **11** was unambiguously confirmed by chiral GC/MS and NMR (diastereomeric ratio) analysis, respectively. In contrast to previously reported catalytic methods, the presence of a sulfur atom in L-methionine (**14**) was compatible (Table 2, entry 7). Unfortunately, irradiation of polar amino acids such as lysine, serine, threonine, arginine, tyrosine, asparagine, glutamine, aspartic acid, and glutamic acid (without protection of the corresponding side chains) under the standard conditions resulted in the formation of complex mixtures. As in the case of our previous work, the N-methylation of L-proline (**16**) proceeded smoothly to give **17** in 81% yield (*S*/*R* ratio >98:2, Scheme 2).



16 (L-Pro)

17, 81%
S:*R* ratio >98:2
$[\alpha]_D^{23}$ +53.7 °
(*c* 1.0, CH_3OH)

Scheme 2. N-Methylation of L-proline.



18 (L-Cys)

19, 68%
$[\alpha]_D^{24}$ –153.1 °
(*c* 1.0, CH_3OH)

Scheme 3. N-Methylation and N,S-acetalization of L-cysteine.

A trial on the dimethylation of L-cysteine (**18**) furnished mono-methylated *N*,*S*-acetal **19** in 68% yield (Scheme 3).[21] It should be noted here that **19** is a protected form of *N*-monomethyl cysteine, which is potentially usable in the Kent ligation (native chemical ligation).[22,23]

In summary, we found a straightforward system for the photocatalytic N-methylation and N,N-dimethylation of amino acids with methanol at ambient temperature using a silver(I)-loaded TiO_2 photocatalyst. Further applications of this method to natural amino acids with protected side chains currently under investigation.

Experimental Section

Preparation of the photocatalyst. Silver nitrate (78.7 mg, 0.46 mmol) was dissolved in deionized water (30.0 mL) in a 100-mL round bottom flask wrapped in aluminum foil. Subsequently, TiO_2 (950 mg) was added to the solution. The resulting suspension was rotated at 50 ºC for 30 min on a rotary evaporator, before the solvent was removed under reduced pressure (20 mmHg) to give $AgNO_3/TiO_2$. The preparative method and the characterization data for Ag/TiO_2 have previously been reported.[14]

Photocatalytic N-methylation of 1 to afford 3. $AgNO_3/TiO_2$ (10 mg, 5 mol% Ag), L-valine (**1**, 11.8 mg, 0.10 mmol), and dehydrated CH_3OH (10 mL) were added to a 30-mL Pyrex® test tube equipped with a magnetic stirring bar and a rubber septum. After sonication for 15 s, the resulting mixture was sparged with argon (cannula, 5 min) and stirred at rt for 15 h under exposure to UV light (UV-LEDs; λ_0 = 365 nm; 32 W). Then, the mixture was filtered through a membrane filter (pore size: 0.45 μm) and the solvent was evaporated. The residue was dissolved in D_2O and examined by NMR spectroscopy (Table 1), using maleic acid as an internal standard (98%). During isolation and characterization (Table 2), the residue was dried under reduced pressure (0.01 mmHg, 10 h) to give **3**·0.58H_2O (14.1 mg, 88% yield). Analytical data: white solid, Mp 123.4−127.8 ºC; ^{1}H NMR (600 MHz, D_2O, 1,4-dioxane) δ 0.96 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 2.31−2.39 (m, 1H), 2.89 (s, 6H), 3.41 (d, *J* = 6.0, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, D_2O) δ 16.4, 19.9, 26.6, 40.7, 43.7, 76.8, 172.3; elemental analysis calcd for [$C_7H_{15}NO_2$]: C, 53.98; H, 10.46; N, 8.99, found C, 53.98; H, 10.45; N, 8.64; $[\alpha]_D^{21}$ +36.8 ° (*c* 2.1, ethanol) [lit.[6] $[\alpha]_D^{26}$ +38.6° (*c* 2.1, ethanol)]; HRMS (ESI) calcd for [$C_7H_{14}NO_2^-$] ([M-H]$^-$) 144.1030, found 144.1053.

Supporting Information

Supplementary table; experimental procedures; spectral data (PDF)

^{1}H and ^{13}C NMR spectra; chromatographic charts (PDF)

Acknowledgments

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Keywords: amino acid • methylation • photocatalysis • silver • methanol

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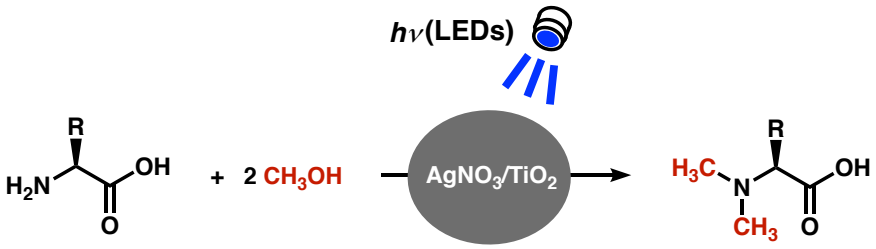

Silver-nitrate-loaded titanium dioxide ($AgNO_3/TiO_2$) promotes the direct N-methylation of amino acids with methanol under UV light irradiation. This method produces a variety of *N,N*-dimethyl amino acids under retention of their optical purity.

Twitter username: @hirosh_naka

Supporting Information for

Ag(I)/TiO_2-Photocatalyzed N-Methylation of Amino Acids with Methanol

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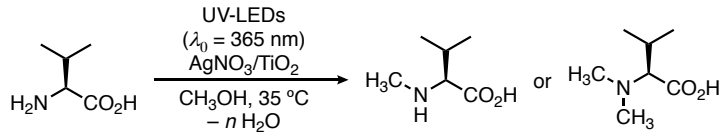
1. Supplementary Table

Table S1. Reaction Progress in the Photocatalytic Methylation of **1** [a].



1 (L-Val) **2** **3**

		molar ratio (%)[b]		
entry	time (h)	**1**	**2**	**3**
1	3	18	45	36
2	5	<1	27	72
3	7	<1	16	84
4	10	<1	3	97
5	13	<1	2	98
6	15	<1	<1	99
7	19	<1	1	99
8	25	<1	1	99

[a]Conditions are analogous to those in Table 1. [b]Determined by ^{1}H NMR.

2. General Comments

GC/MS analyses were performed on Agilent 7820A series network GC systems and Agilent 5977E series Mass Selective Detectors (EI). The following conditions were used unless otherwise noted: [column: CYCLOSIL-B capillary column (l = 30 m, d = 0.25 mm, film thickness = 0.25 μm), carrier gas: He (1.5 mL/min, at 27 psi)]. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a JEOL ECA-600 (600 MHz for ^{1}H, 150 MHz for ^{13}C{^{1}H}) at 27 °C. Chemical shifts are reported as δ in ppm and are referenced to 1,4-dioxane (δ 3.76 ppm for ^{1}H, internal reference) or tetramethylsilane (TMS, δ 0.68 ppm for ^{13}C{^{1}H}, external reference)]. The following abbreviations are used: s = singlet, d = doublet, dd = doublet of doublets, and m = multiplet. High-resolution mass spectra (HRMS) were obtained from micrOTOF-QII (ESI, Bruker). Low-resolution mass spectra (LRMS) were obtained from Agilent 5973 MSD (EI). Preparative reverse phase high performance liquid chromatography (PREP-HPLC) was conducted using JASCO preparative instruments equipped with UV-2077 plus detector, PU 2080 plus and 2087 plus pumps.

3. Materials

The following reagents were purchased from commercial suppliers and used as received unless otherwise noted.

Preparation of Photocatalyst

titanium(IV) dioxide (Aeroxide P25)	Sigma-Aldrich
silver(I) nitrate	Wako Chemicals
sodium acetate	Wako Chemicals
sodium borohydride	Tokyo Chemical Industry

Photocatalytic Reactions

L-valine (**1**)	Wako Chemicals
dehydrated methanol (CH_3OH)	KANTO Chemicals
deuterium oxide (D_2O, 99.8%)	KANTO Chemicals
DL-valine	Tokyo Chemical Industry
DL-phenylalanine	KANTO Chemicals
DL-proline	Tokyo Chemical Industry
DL-alanine	Tokyo Chemical Industry
N,*O*-bis(trimethylsilyl)acetamide (BSA)	Tokyo Chemical Industry
glycine (**4**)	Tokyo Chemical Industry
L-alanine (**6**)	Wako Chemicals
L-phenylalanine (**8**)	Sigma-Aldrich
L-isoleucine (**10**)	KANTO Chemicals
L-leucine (**12**)	Tokyo Chemical Industry
L-methionine (**14**)	Wako Chemicals
L-proline (**16**)	Sigma-Aldrich
L-cysteine (**18**)	Sigma-Aldrich
acetic acid	Wako Chemicals
1,4-dioxane	Wako Chemicals
maleic acid	Tokyo Chemical Industry
dehydrated toluene	KANTO Chemicals.
chloroform-*d* ($CDCl_3$, 99.8% + 0.05% v/v TMS)	Cambridge Isotope Laboratory Inc.
HCl (2 M in diethyl ether)	Sigma-Aldrich

4. Preparation of the Photocatalyst

Silver nitrate (78.7 mg, 0.46 mmol) was dissolved in deionized water (30.0 mL) in a 100-mL round bottom flask wrapped with aluminum foil. Subsequently, TiO_2 (950 mg) was added to the solution. The resulted suspension was rotated at 50 ºC for 30 min on a rotary evaporator, before the solvent was removed under vacuum (20 mmHg) to give $AgNO_3/TiO_2$. The preparative method and the characterization data for Ag/TiO_2 have previously been reported.[1]

5. Photocatalytic Reactions

General Procedure: $AgNO_3/TiO_2$ (10 mg, 5 mol% Ag), amino acid (0.10 mmol), and dehydrated CH_3OH (10 mL) were added to a 30-mL Pyrex test tube (IWAKI TE-32) equipped with a magnetic stirring bar and a rubber septum. After sonication for 15 s, the resulting mixture was sparged with argon (cannula, 5 min) and stirred at rt under exposure to UV light [λ_0 = 365 nm, 32 W UV-LEDs (2 × 16W LN-128UV2-365 model provided by CCS Inc.)] (mixture temperature = ~35 ºC) for indicated periods. The reaction mixture was filtered through a 0.45 μm membrane filter (Merck Millipore SLLHH13NK 0.45 μm pore size, hydrophilic PTFE membrane, 13 mm diameter) and the solvent was evaporated. The residue was analyzed by ^{1}H NMR in D_2O using maleic acid (0.1 M) as an internal standard (Table 1). During isolation and characterization (Table 2), the residue was dried under reduced pressure (0.01 mmHg, 10 h) using an oil pump to give products as hydrates. The degrees of hydrate were determined by NMR using 1,4-dioxane (8.8 mg, 100 μmol, 3.77 ppm, 8H) as an internal standard.

3: Substrate: L-valine (**1**, 11.8 mg, 0.10 mmol). The product was dried to give **3**•0.58H_2O (14.1 mg, 88% yield). Analytical data: white solid, Mp 123.4−127.8 ºC; ^{1}H NMR (600 MHz, D_2O, 1,4-dioxane) δ 0.96 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 2.31−2.39 (m, 1H), 2.89 (s, 6H), 3.41 (d, J = 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, D_2O) δ 16.4, 19.9, 26.6, 40.7, 43.7, 76.8, 172.3; elemental analysis calcd for [$C_7H_{15}NO_2$]: C, 53.98; H, 10.46; N, 8.99, found C, 53.98; H, 10.45; N, 8.64; $[\alpha]_D^{21}$ +36.8 ° (c 2.1, ethanol) [lit.[2] $[\alpha]_D^{26}$ +38.6° (c 2.1, ethanol)]; HRMS (ESI) calcd for [$C_7H_{14}NO_2^-$] ([M-H]$^-$) 144.1030, found 144.1053.

PREP-HPLC purification of 3: A crude mixture of **3** that contains NaOAc (after reaction using $AgNO_3/TiO_2$ and NaOAc for 6 h) was purified by PREP-HPLC [column: C18-20-4 (OD-S), H_2O/CH_3CN + 0.1% TFA = 9:1–2:3 (gradient), 10 mL/min] to give **3** (72% yield). Analytical data: ^{1}H NMR (600 MHz, D_2O) δ 0.95 (d, J = 9.0 Hz, 3H), 1.08 (d, J = 9.0 Hz, 3H), 2,40 (octet, J = 5.5 Hz, 1H), 2.89 (d, J =10.3 Hz, 6H), 3.63 (d, J = 4.9 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, D_2O) δ 15.5, 19.1, 26.1, 40.2, 43.2, 74.6, 170.6.

5: Substrate: glycine (**4**, 7.5 mg, 0.10 mmol). The product was dried to afford **5**•2.6H_2O (12.2 mg, 80% yield). Analytical data: pale yellow oil; ^{1}H NMR (600 MHz, D_2O, 1,4-dioxane) δ 2.93 (s, 6H), 3.72 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, D_2O) δ 44.2, 60.5, 170.9; HRMS (ESI) calcd for [$C_4H_8NO_2^-$] ([M-H]$^-$) 102.0561, found 102.0566.

7: Substrate: L-alanine (**6**, 9.0 mg, 0.10 mmol). The product was dried to afford **7**•0.22H_2O (11.5 mg, 94% yield). Analytical data: white solid; ^{1}H NMR (600 MHz, D_2O,

1,4-dioxane) δ 1.49 (d, J = 7.2 Hz, 3H), 2.86 (s, 6H), 3.72 (dd, J = 14.4, 6.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, D_2O) δ 12.6, 39.5, 43.3, 66.6, 174.6; HRMS (ESI) calcd for [$C_5H_{10}NO_2^-$] ([M-H]$^-$) 116.0717, found 116.0738; $[\alpha]_D^{23}$ −0.293 ° (c 0.3, CH_3OH); chiral GC/MS (Agilent Cyclosil-B, chromatographic elution: isothermal at 50 °C for 1.0 min, 50−70 °C at a rate of 0.1 °C min^{-1}, isothermal at 70 °C for 0 min, 70−230 °C at a rate of 20 °C min^{-1}, isothermal at 230 °C for 4 min, after silylation with BSA [70°C, 150 min]): t_R 36.6 min (*S*), *S*:*R* ratio >98:2. A racemic sample was prepared using the same procedure (48% yield): t_R 36.7 min (*S*), t_R 37.2 min (*R*).

9: Substrate: L-phenylalanine (**8**, 16.5 mg, 0.10 mmol). The product was dried to afford **9**•0.24H_2O (18.8 mg, 97% yield). Analytical data: white solid; ^{1}H NMR (600 MHz, D_2O, 1,4-dioxane) δ 2.93 (s, 6H), 3.12 (dd, J = 13.8, 9.6 Hz, 1H), 3.34 (dd, J = 15.0, 7.2 Hz, 1H), 3.84 (dd, J = 9.6, 6.6 Hz, 1H), 7.32–7.41 (m, 5H); $^{13}C\{^{1}H\}$ NMR (150 MHz, D_2O) δ 34.7, 41.8, 43.5, 72.8, 128.1, 129.6, 129.8, 135.9, 172.9; HRMS (ESI) calcd for [$C_{11}H_{14}NO_2^-$] ([M-H]$^-$) 192.1030, found 192.1047; elemental analysis calcd for [$C_{11}H_{15}NO_2$]: C, 66.84; H, 7.89; N, 7.08, found C, 66.84; H, 7.96; N, 6.99; $[\alpha]_D^{21}$ +29.8 ° (c 1.0, CH_3OH).

11: Substrate: L-isoleucine (**10**, 13.1 mg, 0.10 mmol). The product was dried to afford **11**•1.0H_2O (16.4 mg, 92% yield). Analytical data: white solid; ^{1}H NMR (600 MHz, D_2O, 1,4-dioxane) δ 0.93–0.98 (m, 6H), 1.29–1.36 (m, 1H), 1.49–1.56 (m, 1H), 2.03–2.10 (m, 1H), 2.88 (s, 6H), 3.50 (d, J = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, D_2O) δ 11.9, 13.7, 27.3, 33.4, 40.4, 44.2, 75.4, 172.2; HRMS (ESI) calcd for [$C_8H_{16}NO_2^-$] ([M-H]$^-$) 158.1187, found 158.1198; $[\alpha]_D^{23}$ +47.8 ° (c1.0, CH_3OH).

13: Substrate: L-leucine (**12**, 13.1 mg, 0.10 mmol). The product was dried to afford **13**•2.8H_2O (17.0 mg, 82% yield). Analytical data: white solid; ^{1}H NMR (600 MHz, D_2O, TMS) δ0.95–0.97 (m, 6H), 1.63–1.75 (m , 3H), 2.88 (s , 6H), 3.55–3.57 (m, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, D_2O) δ 21.2, 23.4, 25.7, 37.4, 40.8, 43.0, 70.9, 174.2; HRMS (ESI) calcd for [$C_8H_{16}NO_2^-$] ([M-H]$^-$) 158.1187, found 158.1215; $[\alpha]_D^{21}$ +47.6 ° (c 1.0, CH_3OH) [lit.[3] $[\alpha]_D^{26}$ +35.1° (c 1.0, CH_3OH)].

15: Substrate: L-methionine (**14**, 14.9 mg, 0.10 mmol). The product was dried to afford **15**•2.3H_2O (17.7 mg, 81% yield). Analytical data: pale yellow solid; ^{1}H NMR (600 MHz, D_2O, 1,4-dioxane) δ 2.11–2.23 (m, 5H), 2.53–2.60 (m, 1H), 2.62–2.67 (m, 1H), 2.90 (s, 6H), 3.69 (dd, J = 9.0, 4.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, D_2O, TMS) δ 14.8, 27.8, 29.8, 40.6, 43.6, 70.5, 173.1; HRMS (ESI) calcd for [$C_7H_{14}NO_2S^-$] ([M-H]$^-$) 176.0751, found 175.0750; $[\alpha]_D^{23}$ +53.7 ° (c 1.0, CH_3OH).

17: Substrate: L-proline (**16**, 11.5 mg, 0.10 mmol). The product was dried to afford **17**•1.9H_2O (14.0 mg, 79% yield). Analytical data: pale yellow solid; ^{1}H NMR (600 MHz, D_2O, 1,4-dioxane) δ 1.96–2.02 (m, 1H), 2.06–2.12 (m, 1H), 2.13–2.19 (m, 1H), 2.47–2.54 (m, 1H), 2.94 (s, 3H), 3.14–3.18 (m, 1H), 3.70−3.80 (m, 1H), 3.80−3.91 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, D_2O) δ 23.5, 29.4, 41.4, 57.0, 71.3, 174.3; HRMS (ESI) calcd for [$C_6H_{10}NO_2^-$] ([M-H]$^-$) 128.0717, found 128.0742; $[\alpha]_D^{21}$ −92.2 ° (*c* 1.5, CH_3OH) [lit.[1] $[\alpha]_D^{23}$ −78° (*c* 1.5, CH_3OH)]; chiral GC/MS (Agilent Cyclosil-B, chromatographic elution: isothermal at 50 °C for 1.0 min, 50−70 °C at a rate of 0.2 °C min^{-1}, isothermal at 70 °C for 0 min, 70−230 °C at a rate of 20 °C min^{-1}, isothermal at 230 °C for 4 min, after silylation with BSA [70°C, 150 min]): t_R 87.6 min (*S*), *S*:*R* ratio >98:2. A racemic sample was prepared using the same procedure (54% yield): t_R 89.2 min (*S*), t_R 87.7 min (*R*).

19: Substrate: L-cysteine (**18**, 12.1 mg, 0.10 mmol). The product was dried to afford **19**•3.7H_2O (14.6 mg, 68% yield). Analytical data: pale yellow solid ; ^{1}H NMR (600 MHz, D_2O, 1,4-dioxane) δ 3.05 (s, 3H), 3.40 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.59 (dd, *J* = 11.4, 8.4 Hz, 1H), 4.20 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.27 (d, *J* = 10.2 Hz, 1H), 4.68 (d, *J* = 10.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, D_2O) δ 33.3, 41.4, 58.8, 72.9, 172.0; HRMS (ESI) calcd for [$C_5H_8NO_2S^-$] ([M-H]$^-$) 146.0281, found 146.0287; $[\alpha]_D^{24}$ −153.1 ° (*c* 1.0, CH_3OH).

6. References

[1] Tsarev, V, N.; Morioka, Y.; Caner, J.; Wang, Q.; Ushimaru, R.; Kudo, A.; Naka, H.; Saito, S. N-Methylation of Amines with Methanol at Room Temperature. *Org. Lett.* **2015**, *17*, 2530–2533.

[2] Yao, G.; Pan, Z.; Wu, C.; Wang, W.; Fang, L.; Su, W. Efficient Synthesis and Stereochemical Revision of Coibamide A. *J. Am. Chem. Soc*. **2015**, *137*, 13488–13491.

[3] Barcelo, V, S.; Bienz, S. Synthesis of Highly Substituted 3-Pyrrolin-2-ones from *N,N*–Disubstituted α-Amino Acids. *J. Org. Chem.* **2018**, *83*, 2734–2743.

Supporting Information (NMR and Chromatographic Charts) for

Ag(I)/TiO_2-Photocatalyzed N-Methylation of Amino Acids with Methanol

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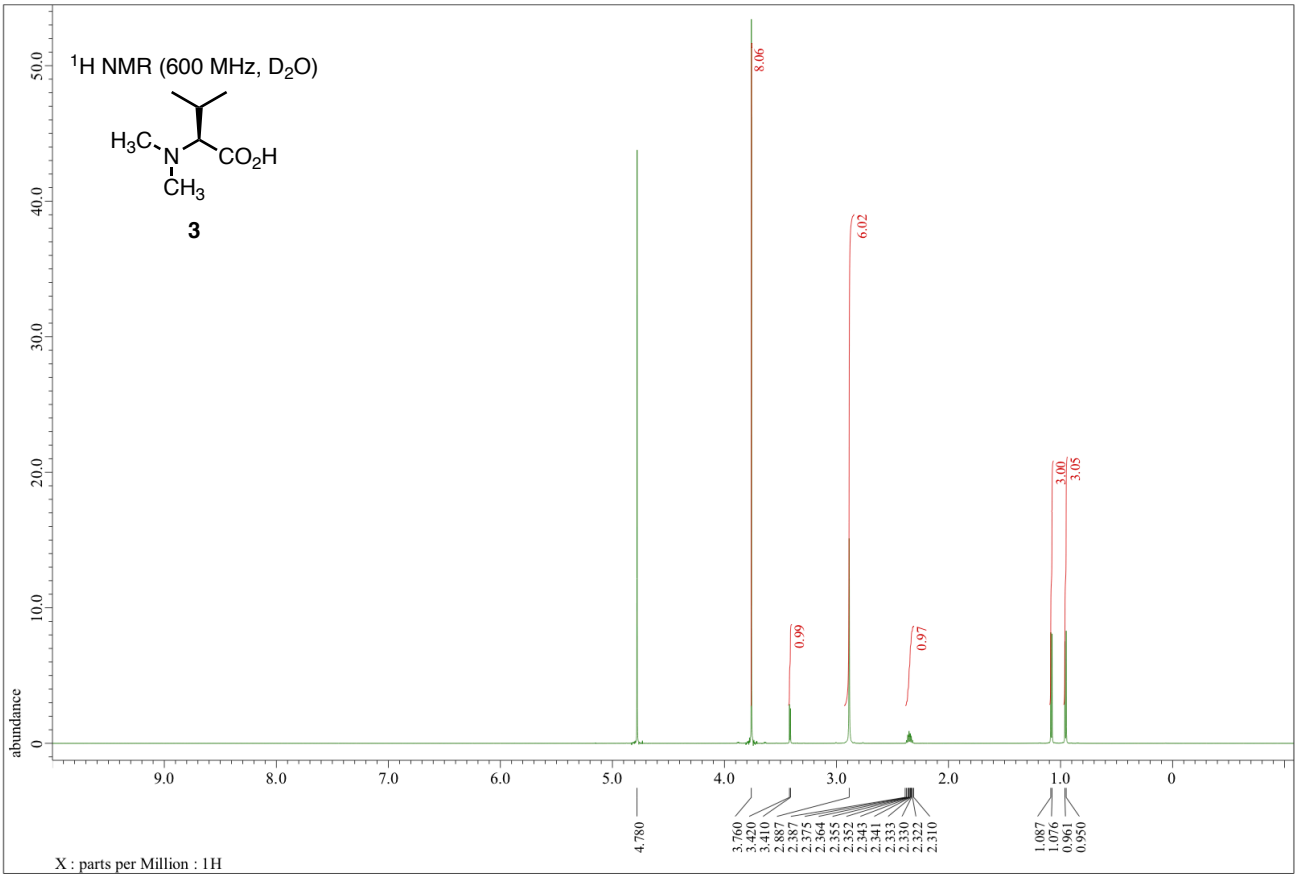
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N
CO_2H
CH_3
3
abundance
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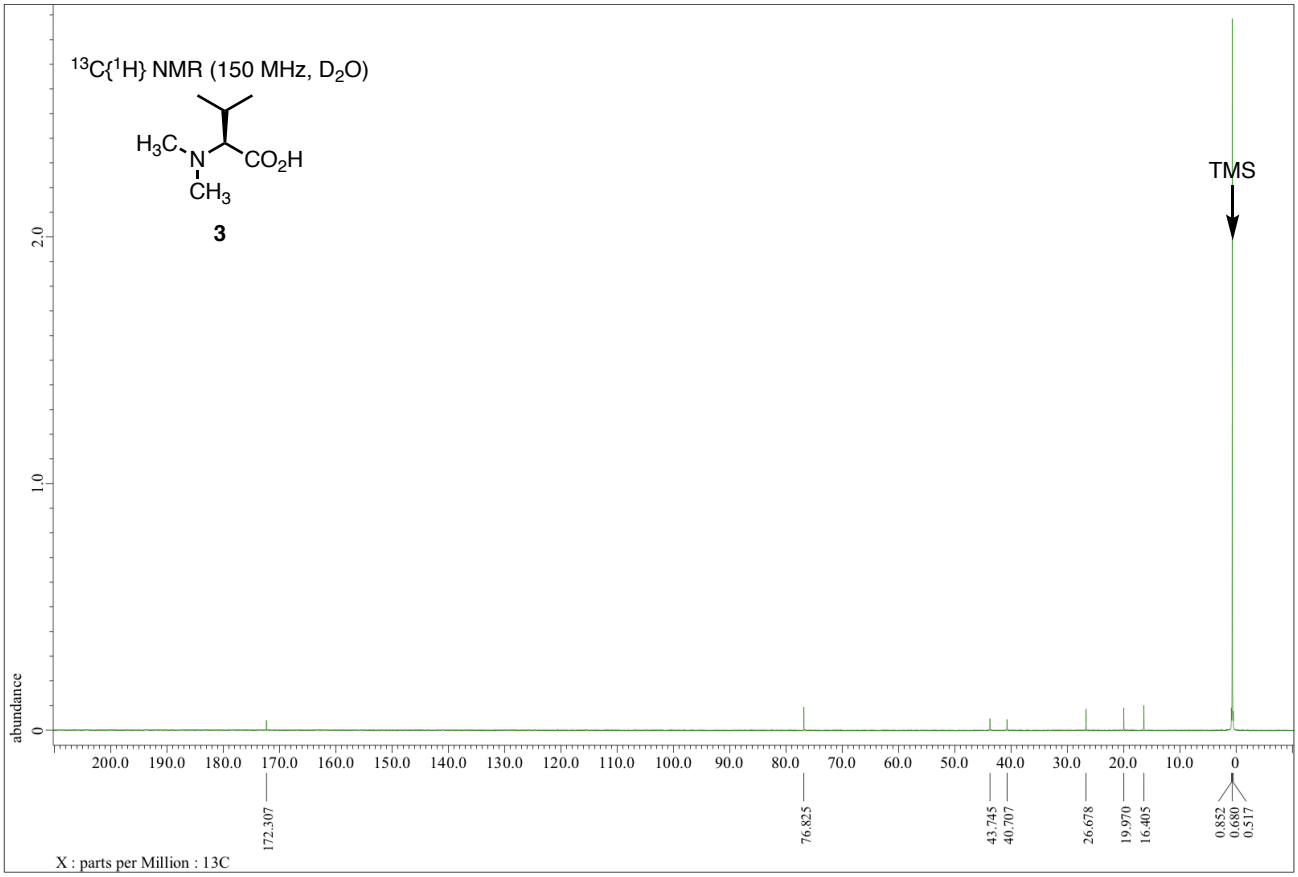
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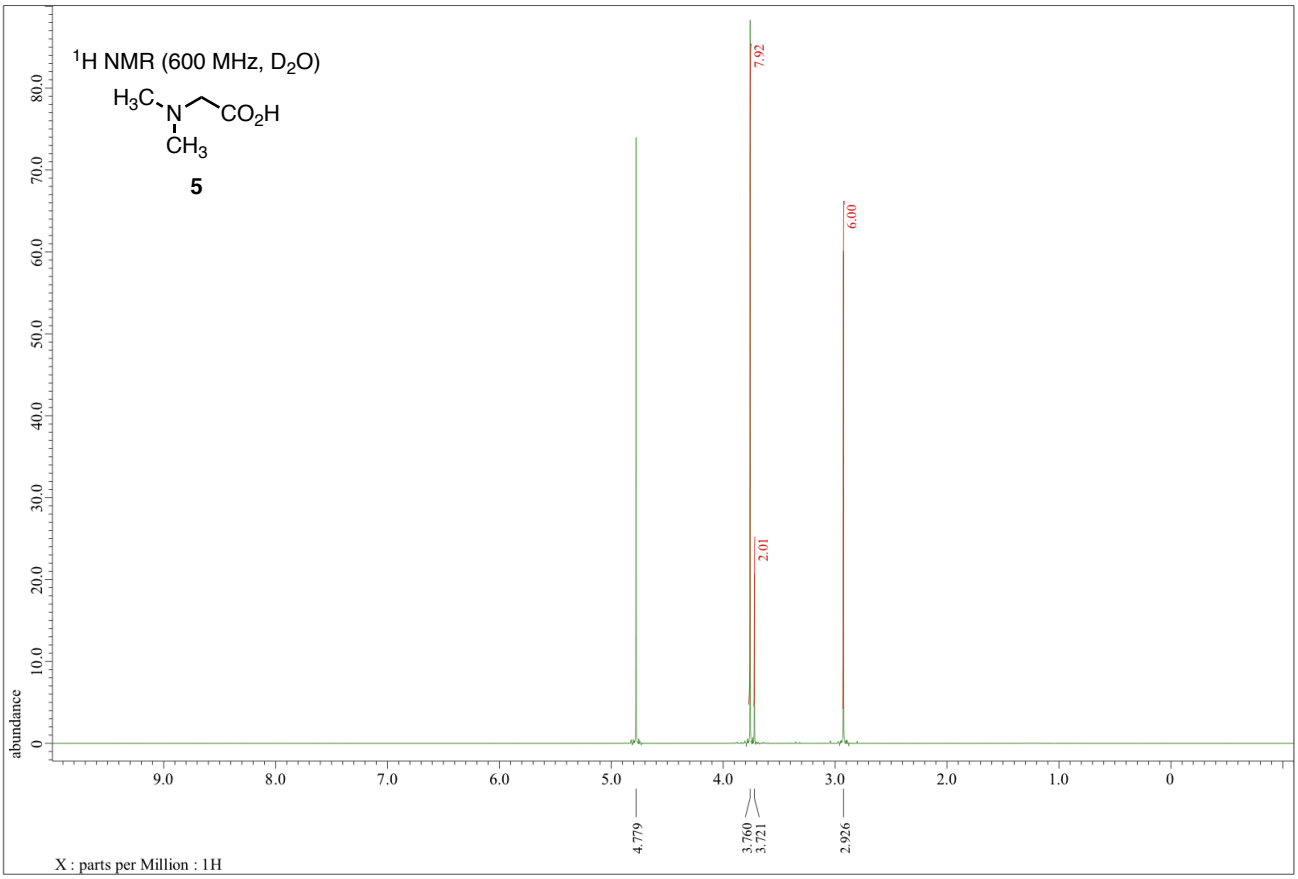
CO_2H
CH_3
3
TMS
abundance
X : parts per Million : 13C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6.00
2.01
abundance
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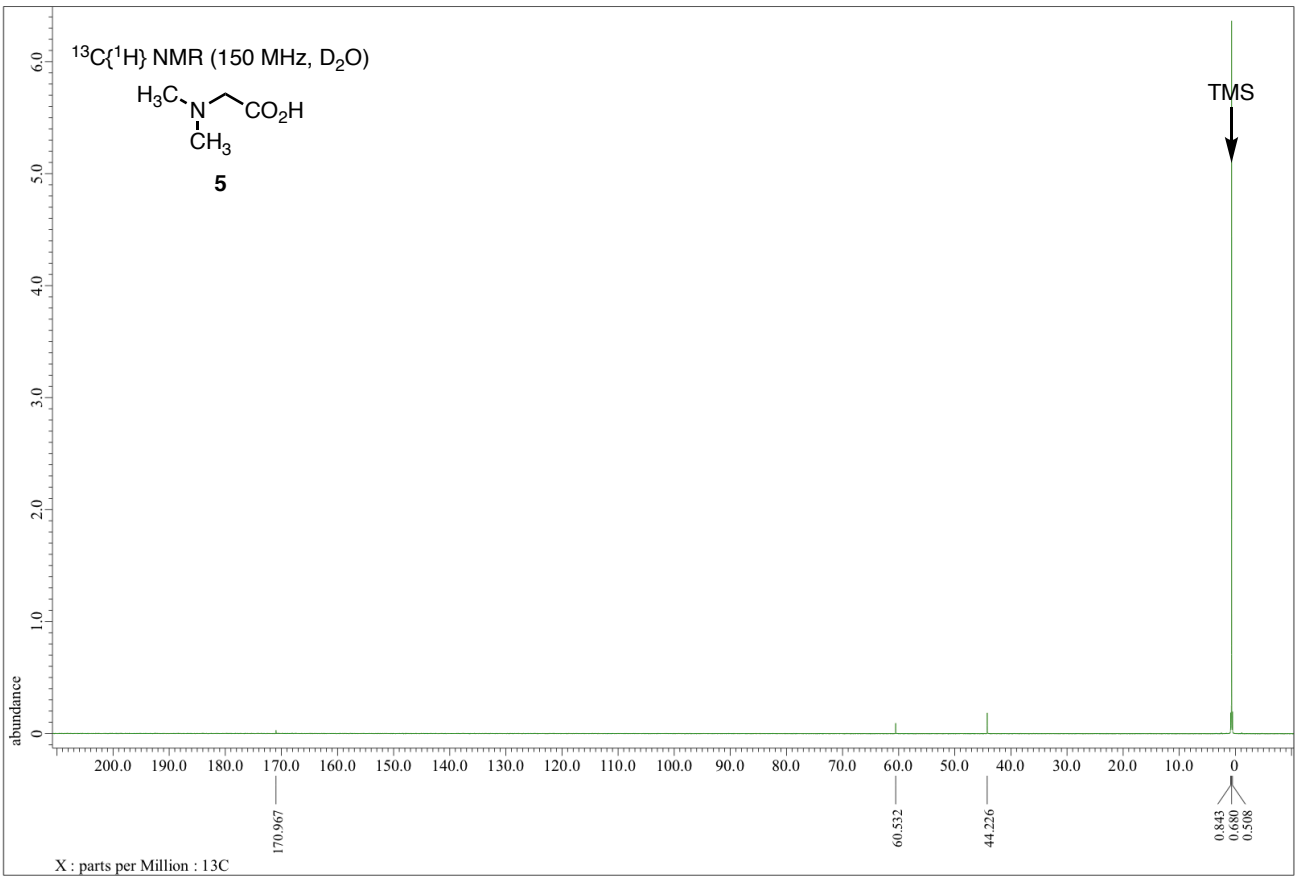
3.760
3.721
2.926
X : parts per Million : 1H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5
TMS
abundance
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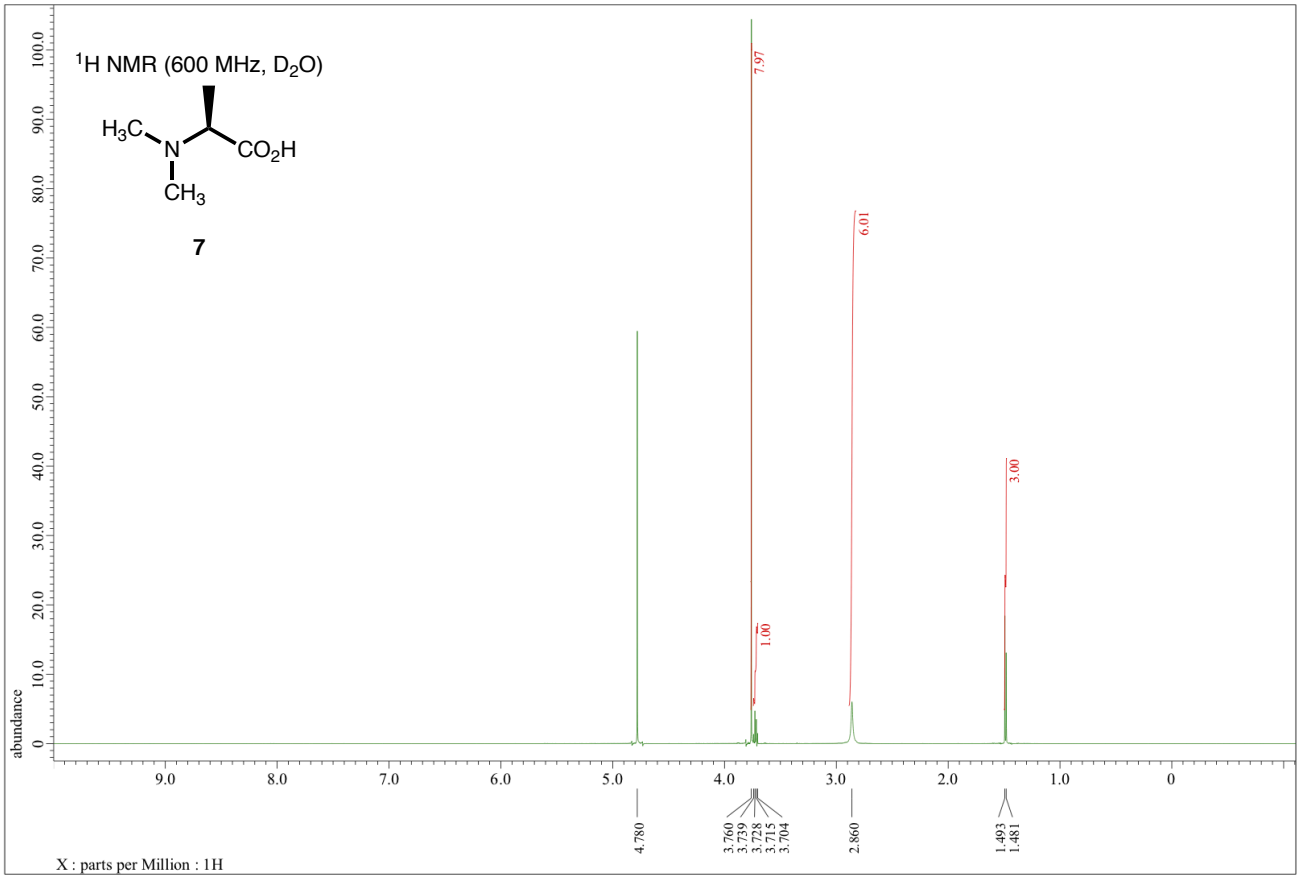
0.843
0.680
0.508
X : parts per Million : 13C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CO_2H
CH_3
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3.00
1.00
abundance
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
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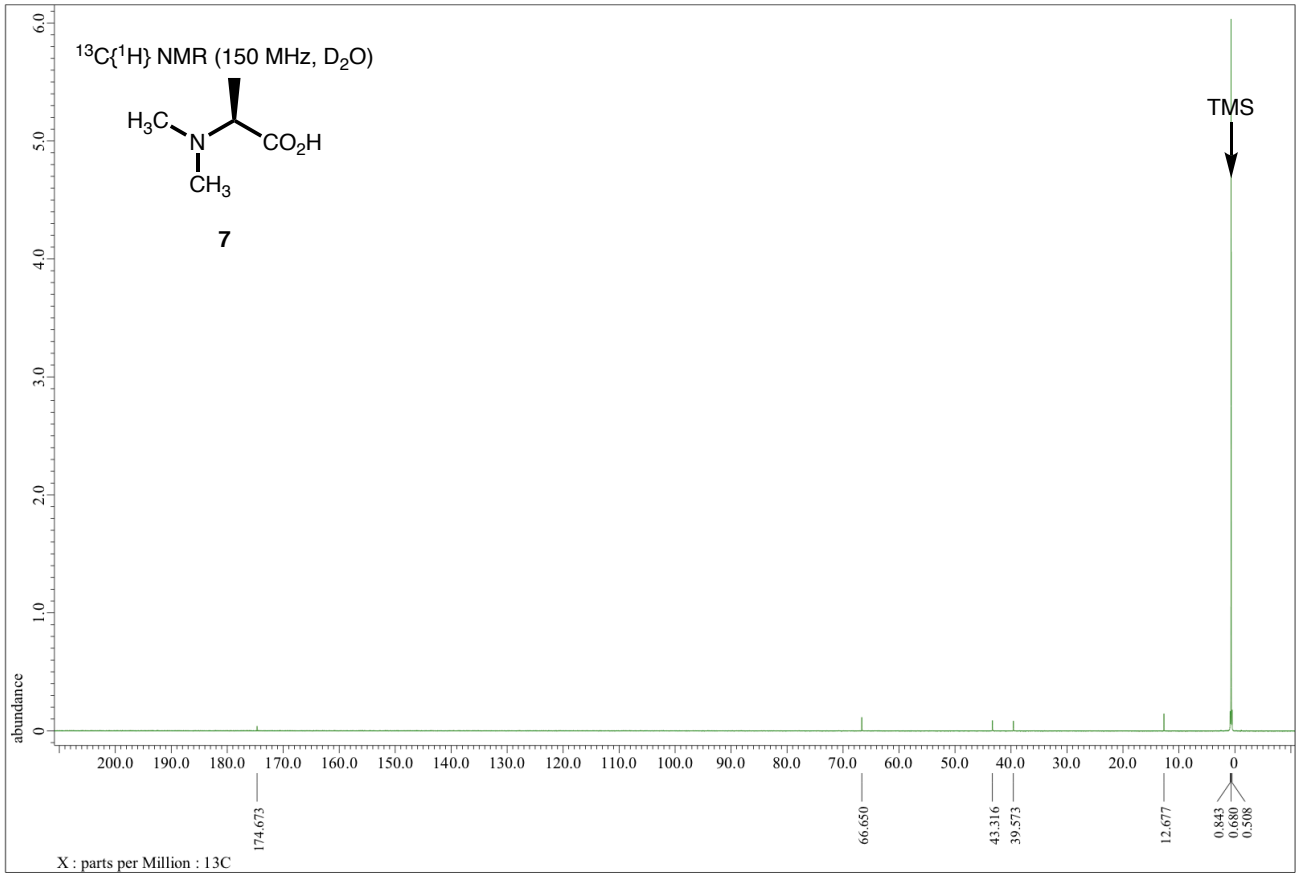
2.860
1.493
1.481
X : parts per Million : 1H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N
CO_2H
CH_3
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TMS
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180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
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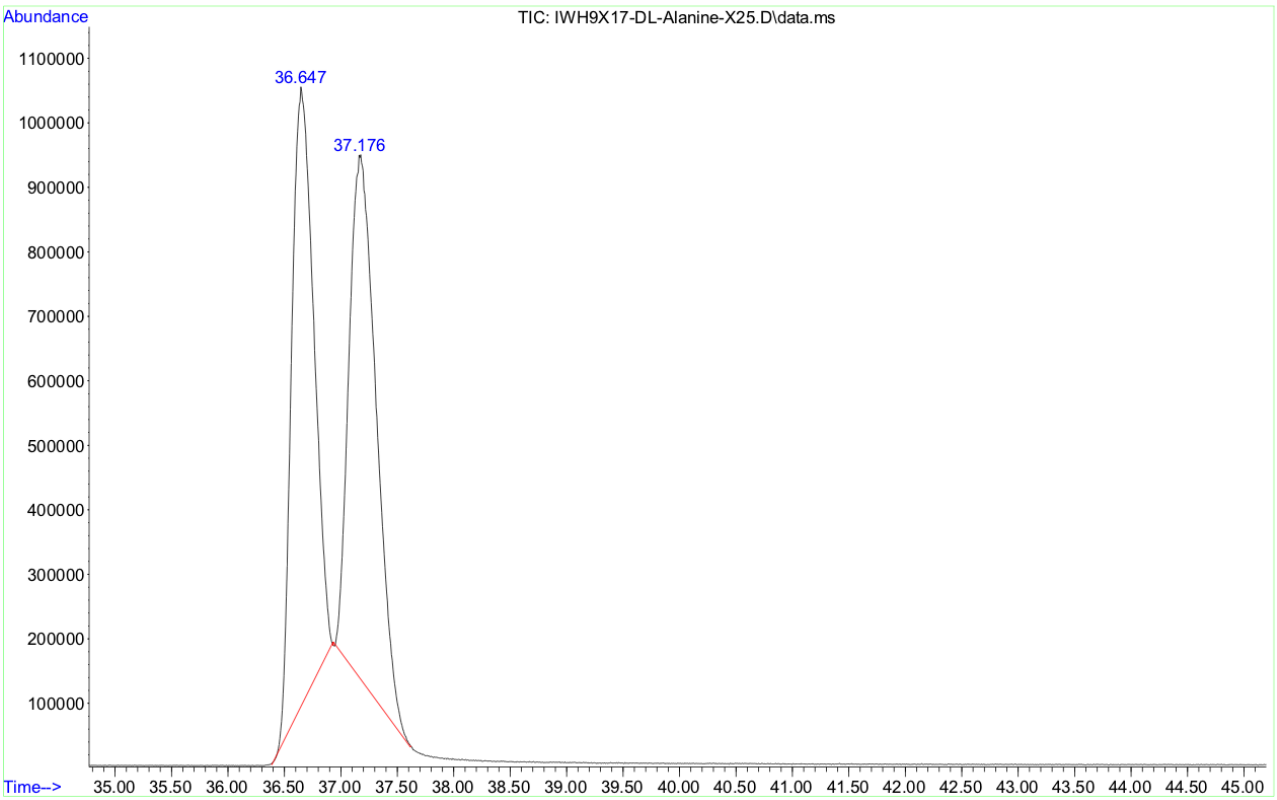
0.508
X : parts per Million : 13C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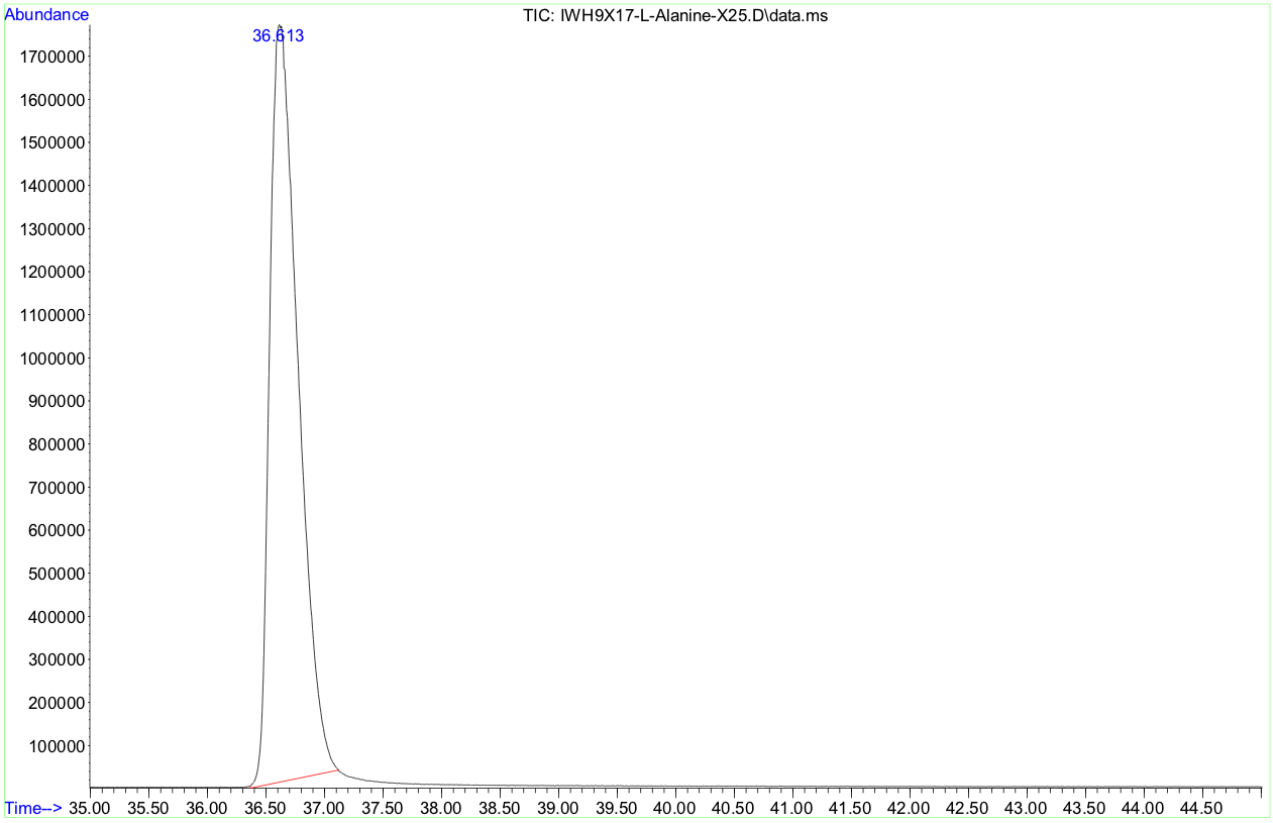
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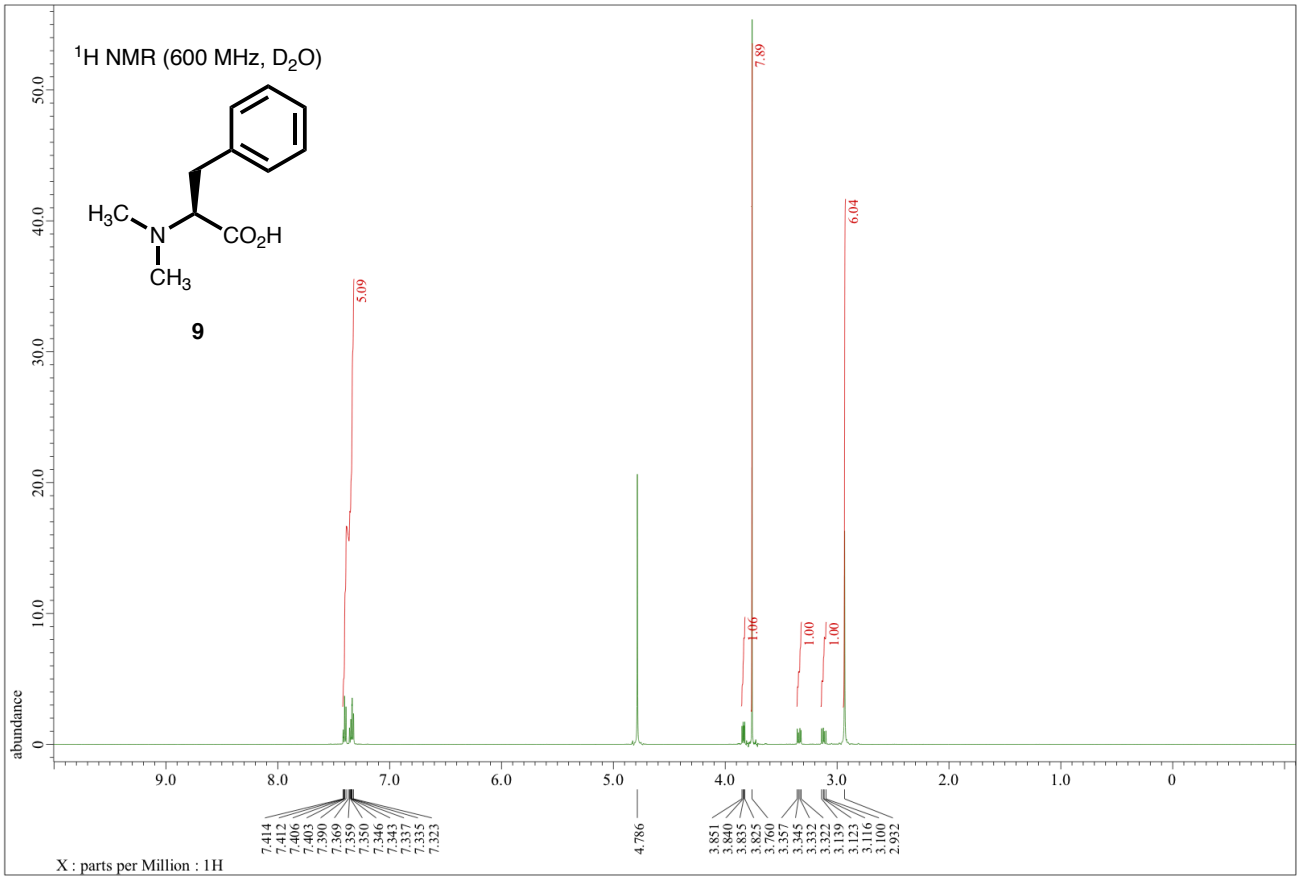
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H3C
N
CH3
CO2H
9
abundance
X : parts per Million : 1H
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6.04
5.09
1.06
1.00
1.00
4.786
7.414
7.412
7.406
7.403
7.390
7.369
7.359
7.350
7.346
7.343
7.337
7.335
7.323
3.851
3.840
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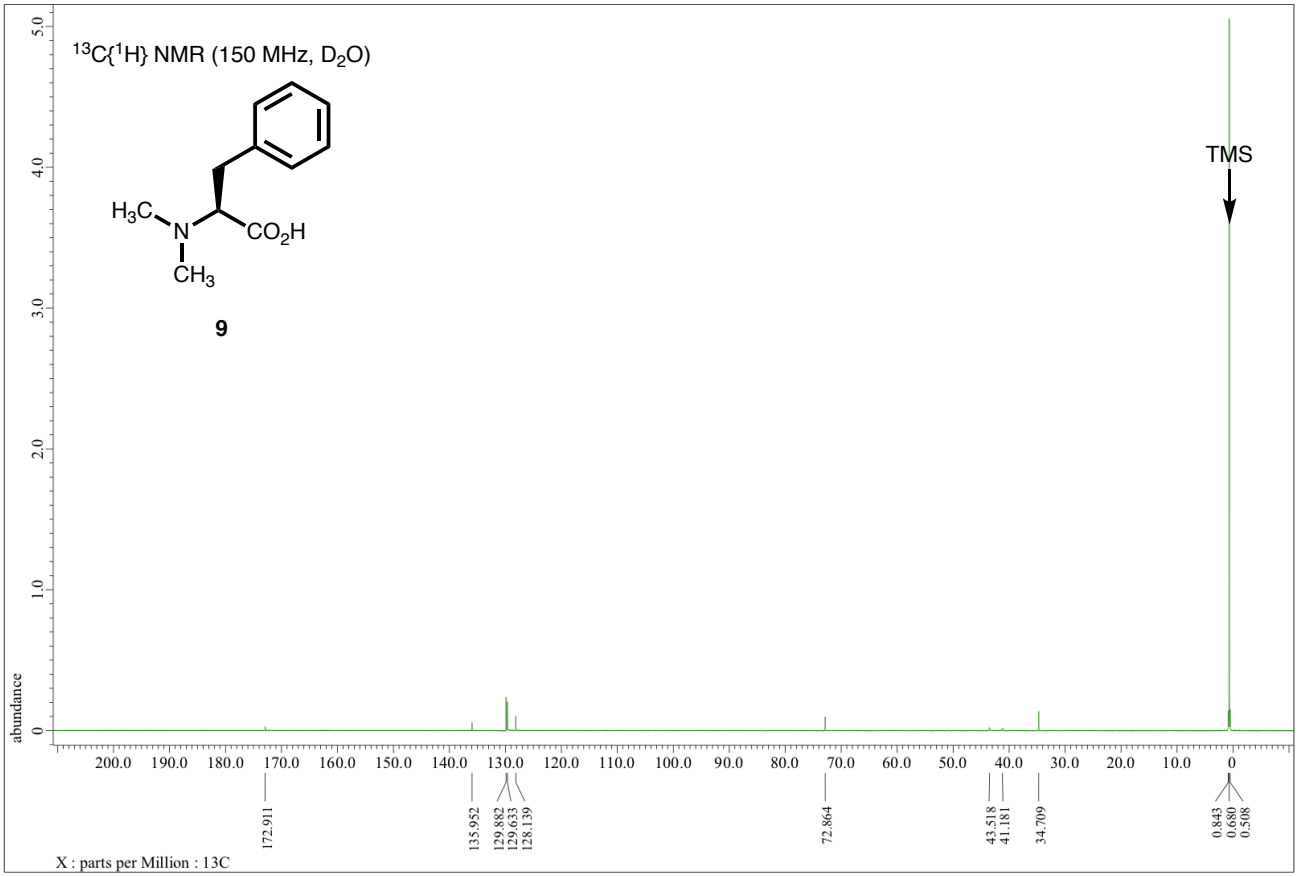
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H3C
N
CH3
CO2H
9
TMS
abundance
X : parts per Million : 13C
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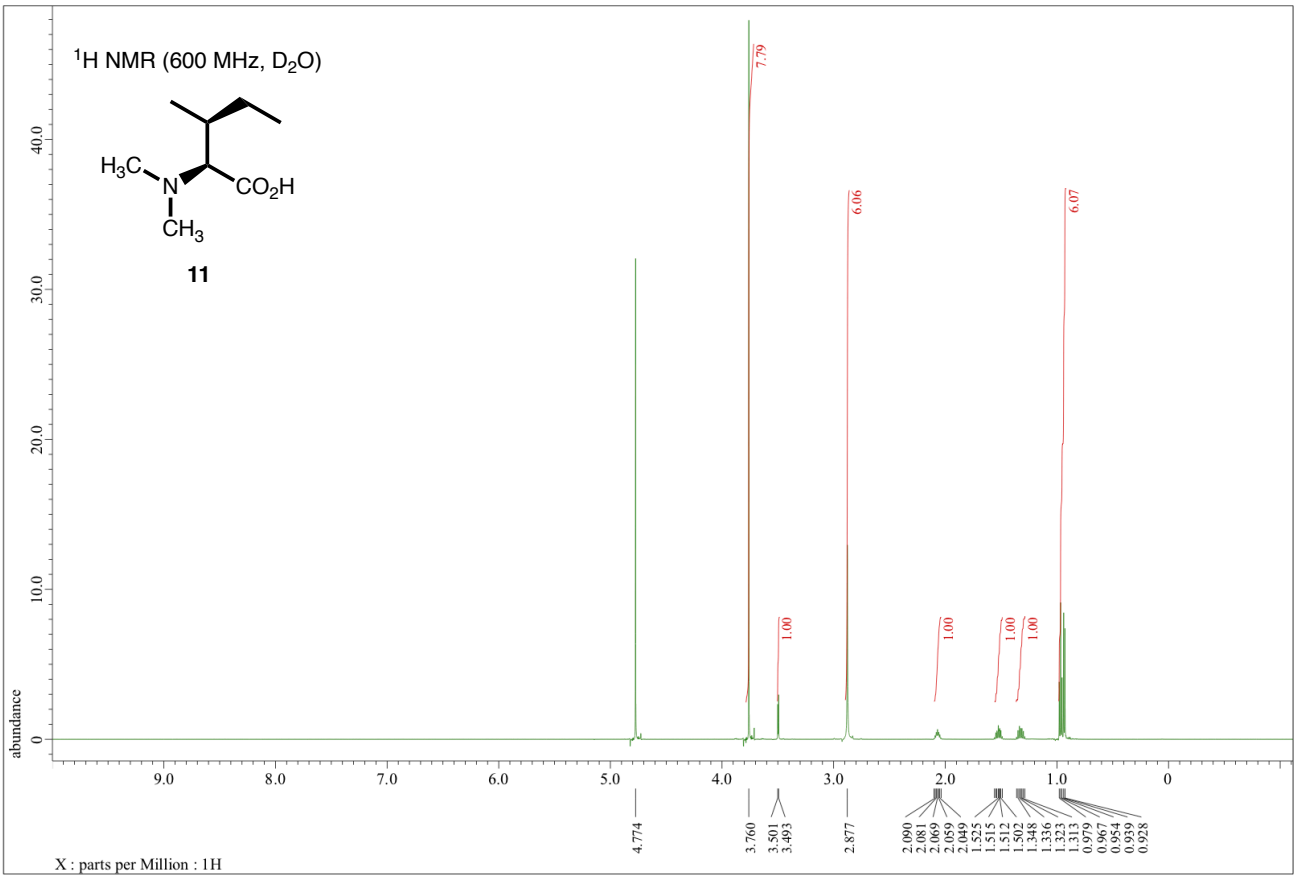
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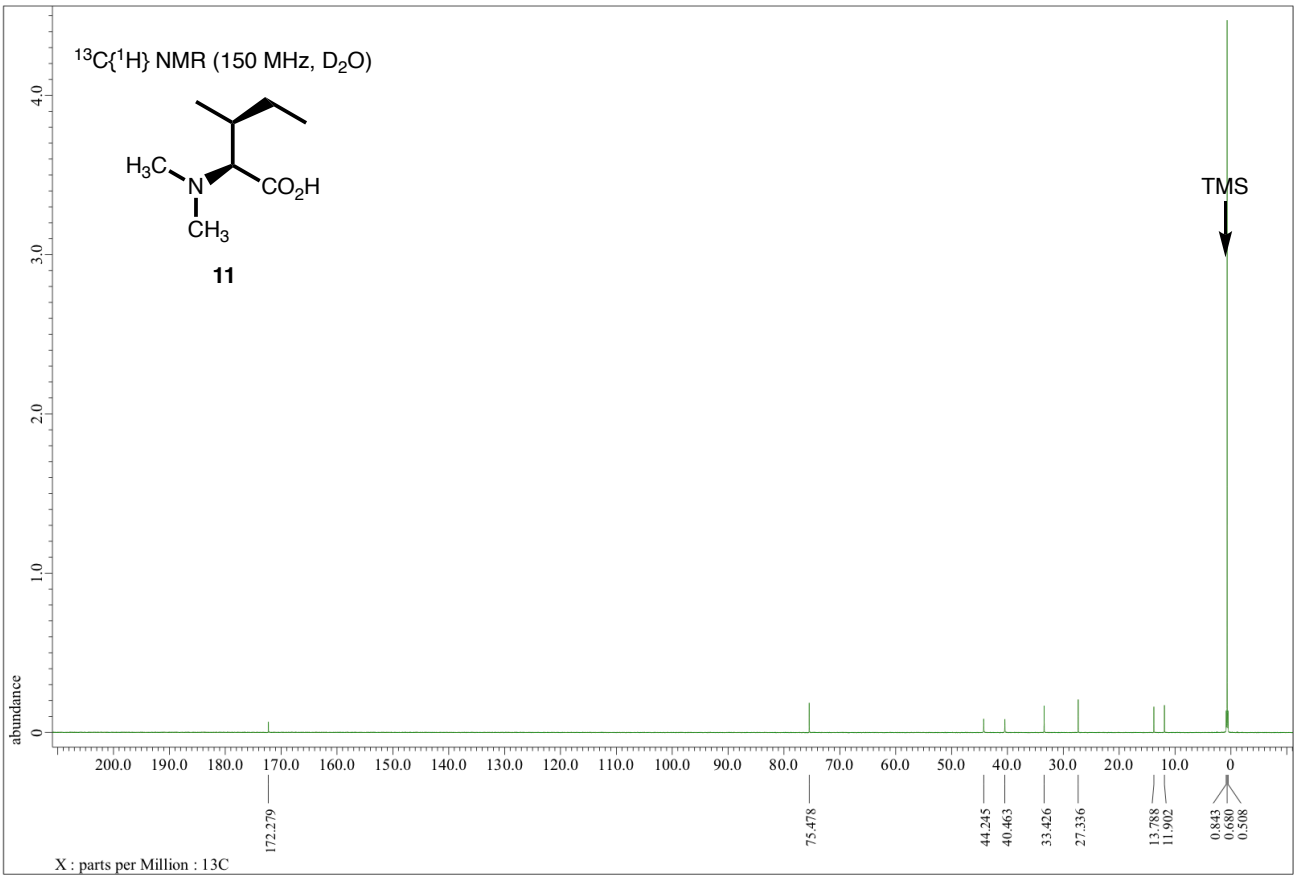
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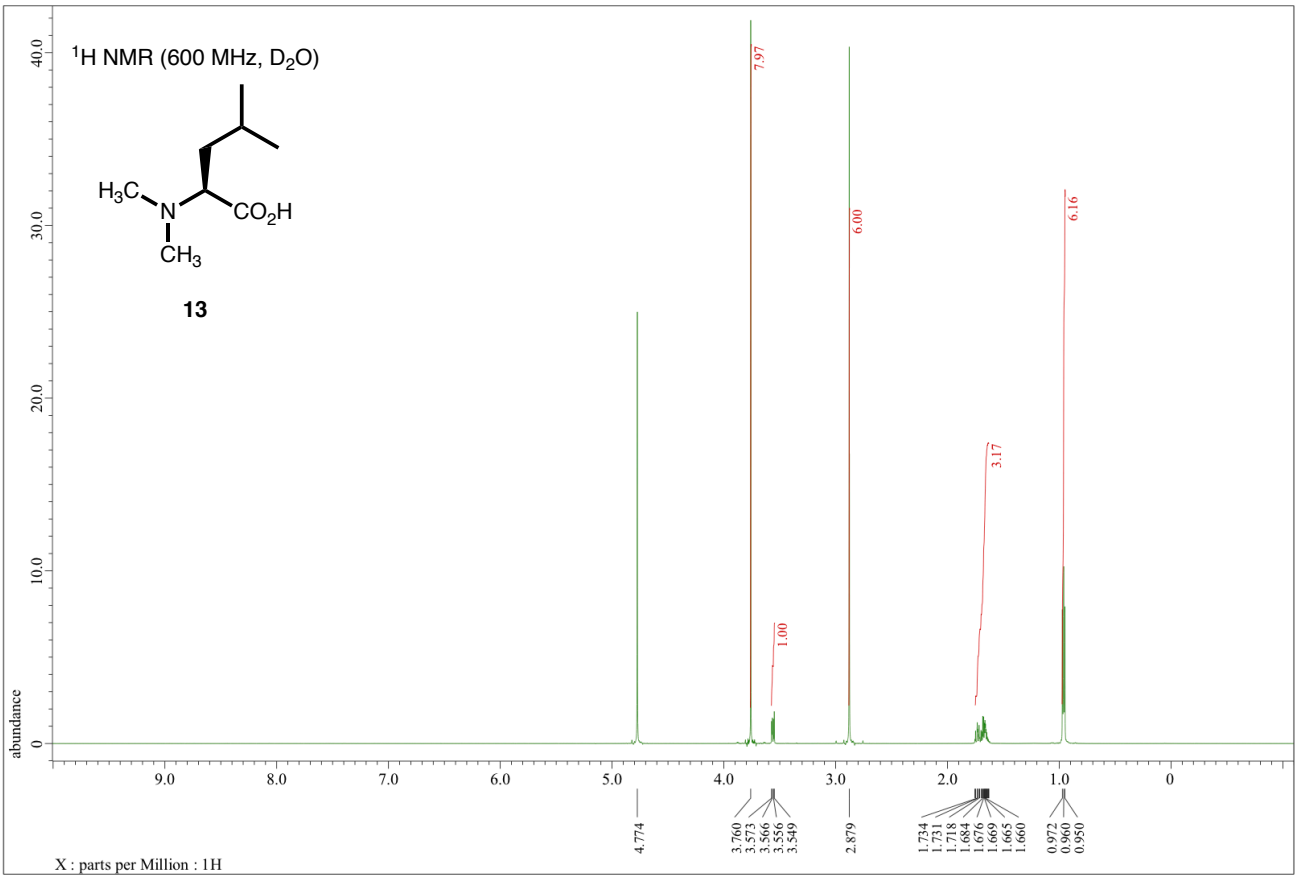
11
TMS
abundance
X : parts per Million : 13C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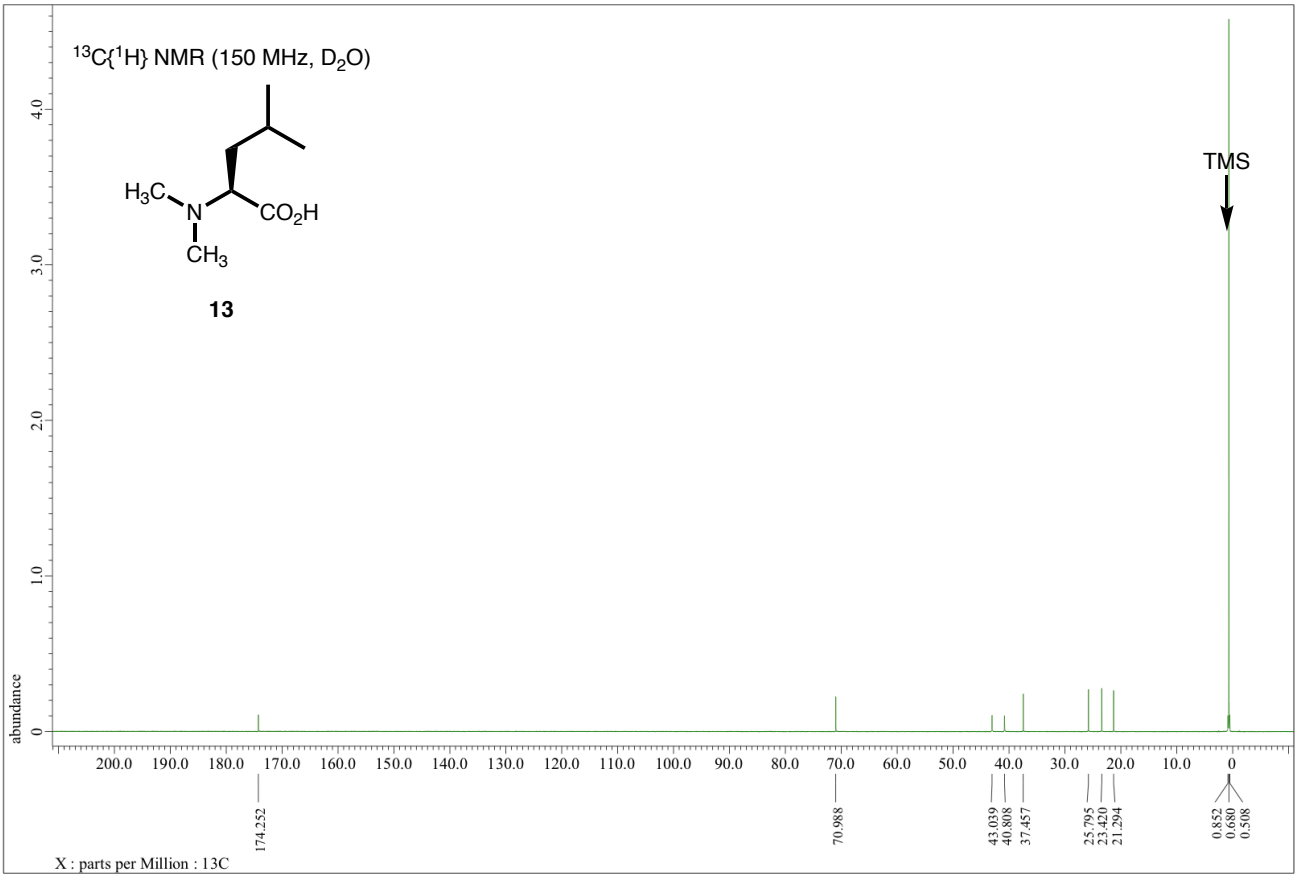
1.00
abundance
X : parts per Million : 1H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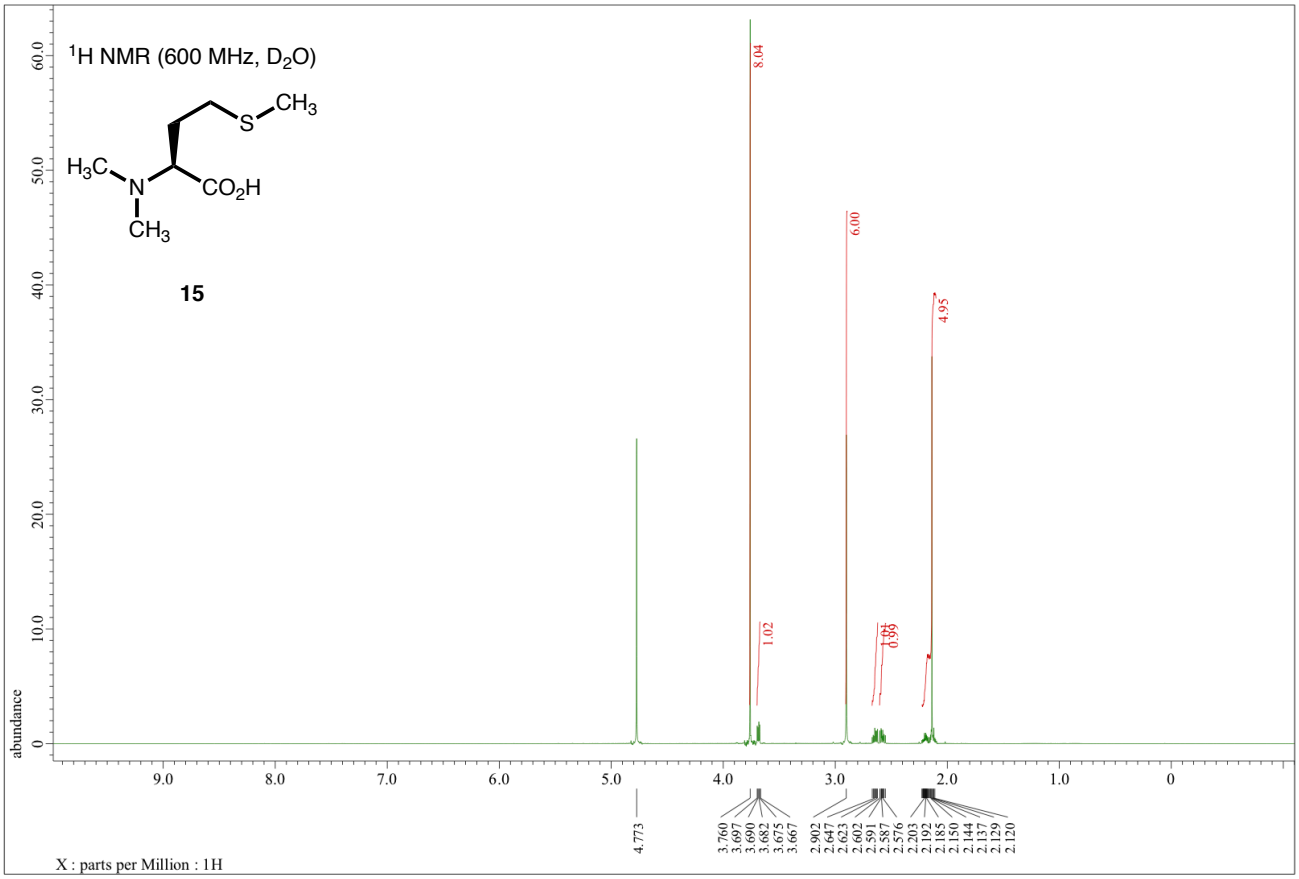
TMS
abundance
X : parts per Million : 13C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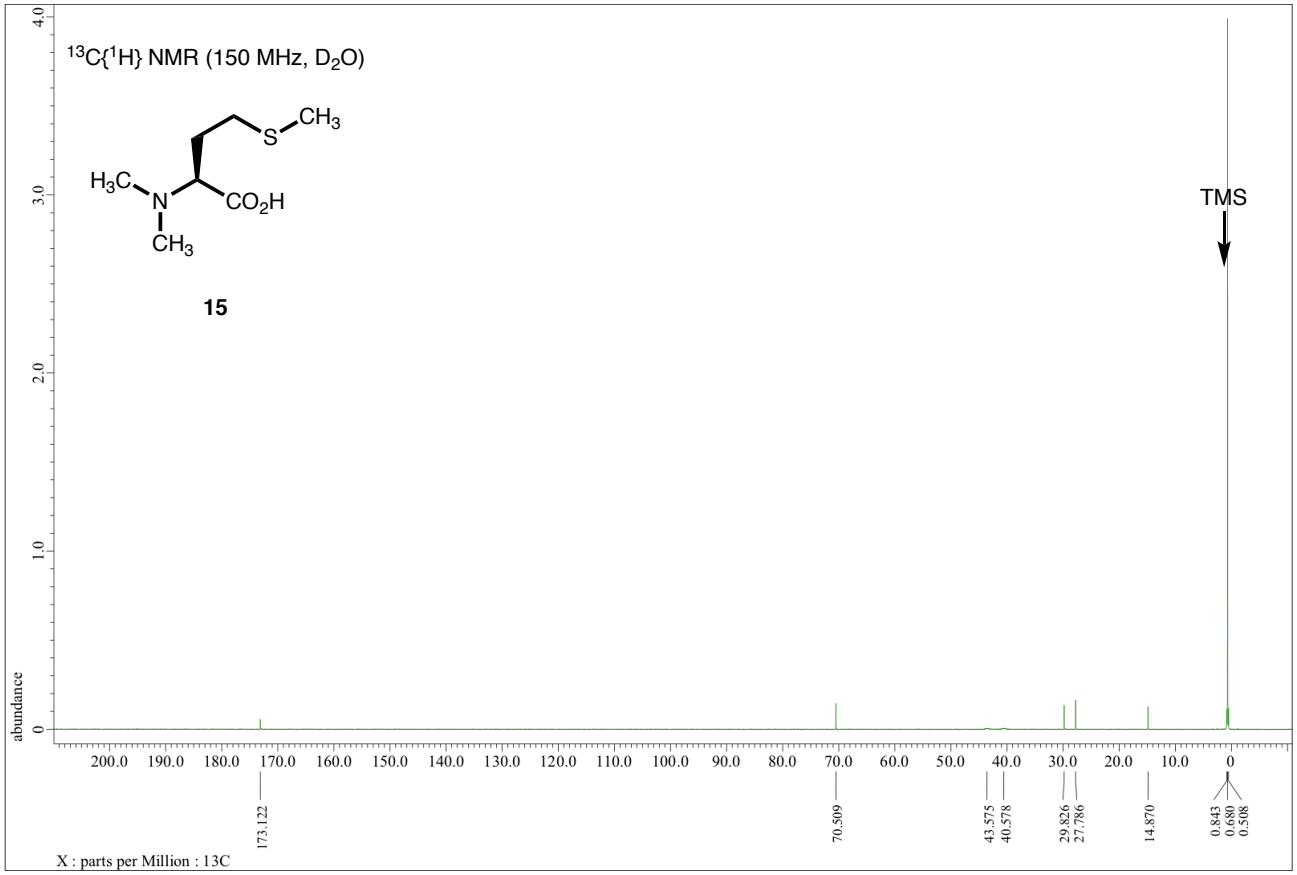
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15
TMS
abundance
X : parts per Million : 13C
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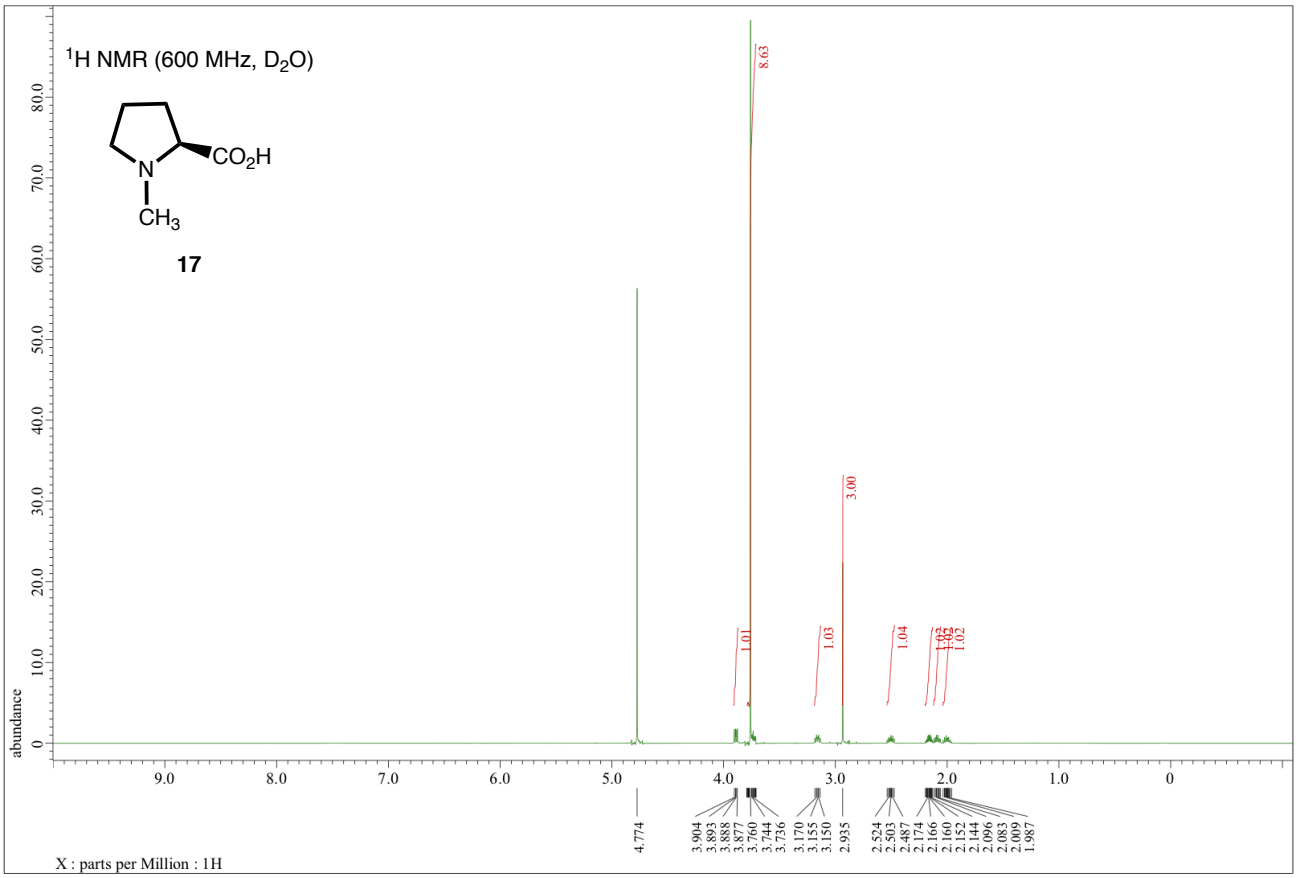
14.870
0.843
0.680
0.508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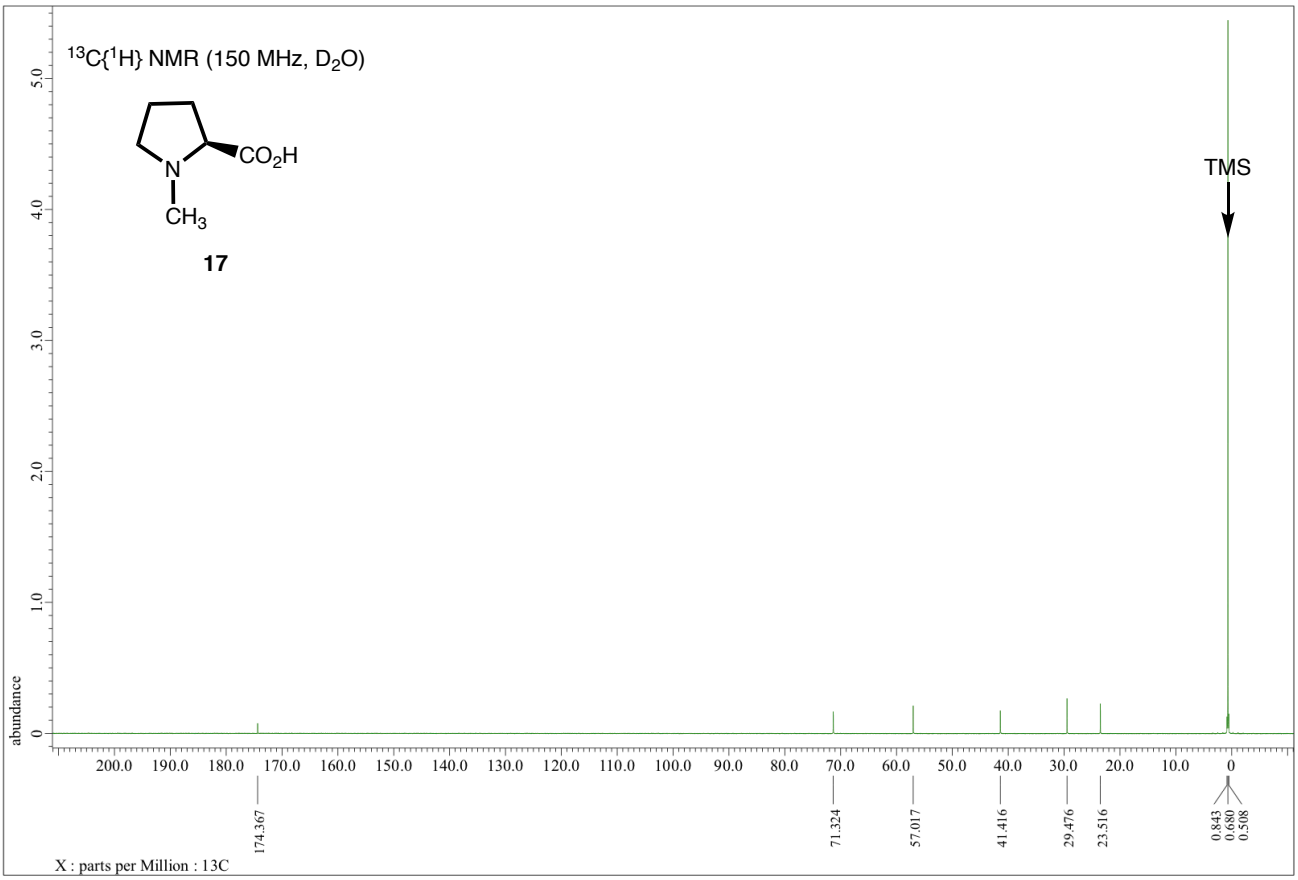
CO_2H
N
CH_3
17
abundance
X : parts per Million : 1H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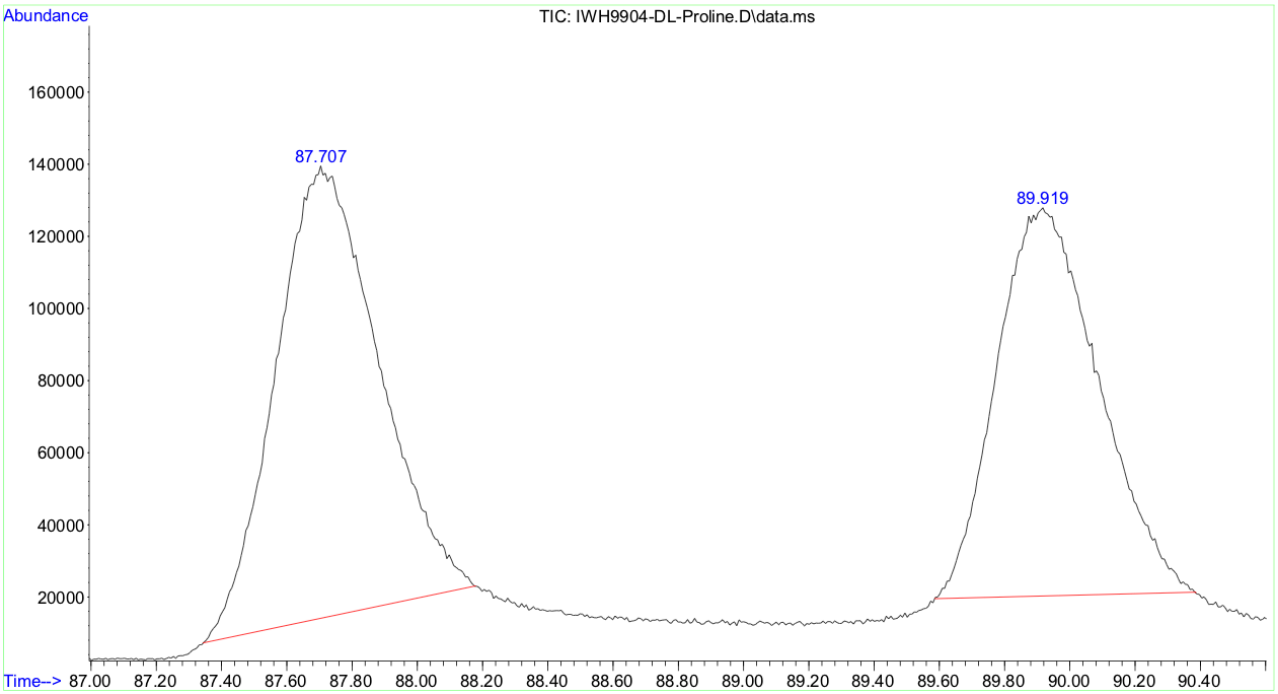
CO_2H
N
CH_3
17
TMS
abundance
X : parts per Million : 13C


Abundance
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60000
40000
20000
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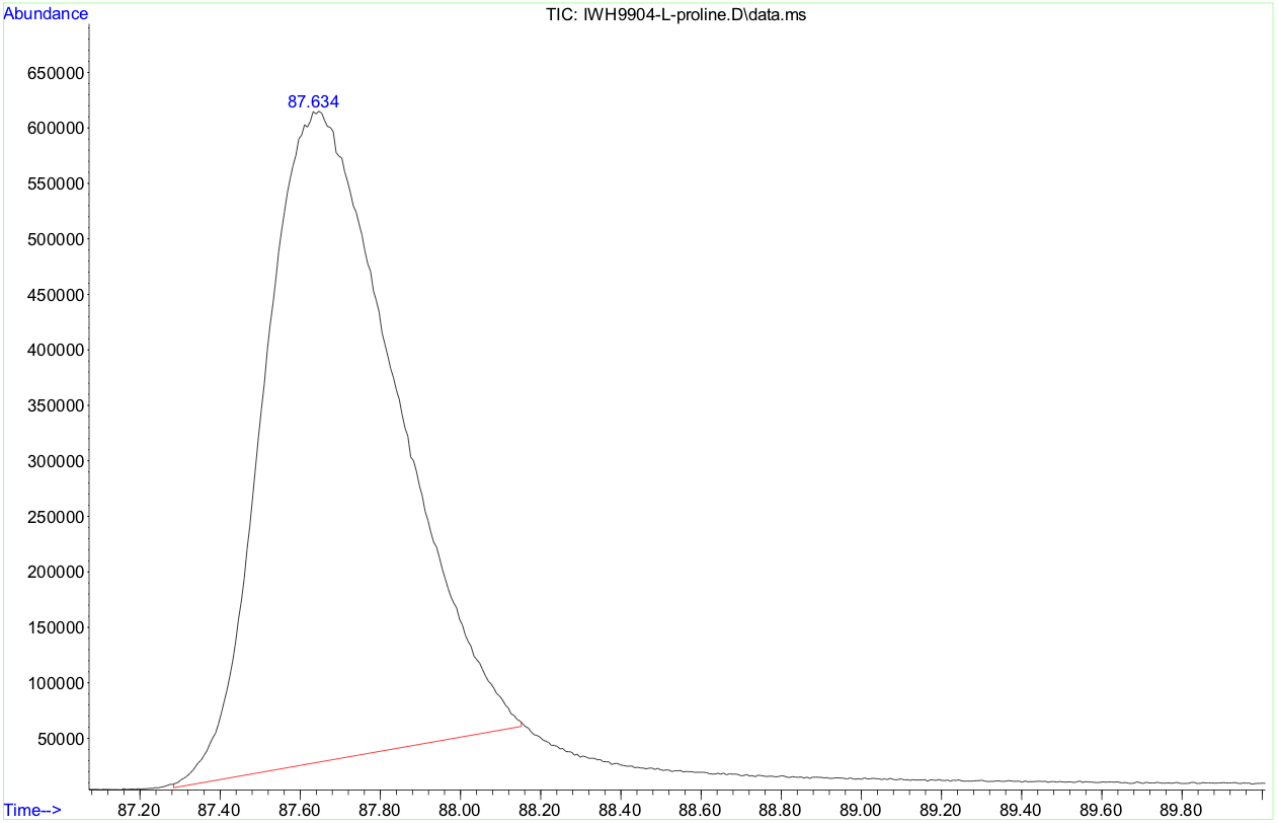
89.919
Time-->
87.00
87.20
87.40
87.60
87.80
88.00
88.20
88.40
88.60
88.80
89.00
89.20
89.40
89.60
89.80
90.00
90.20
90.40


Abundance
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550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
87.634
Time-->
87.20
87.40
87.60
87.80
88.00
88.20
88.40
88.60
88.80
89.00
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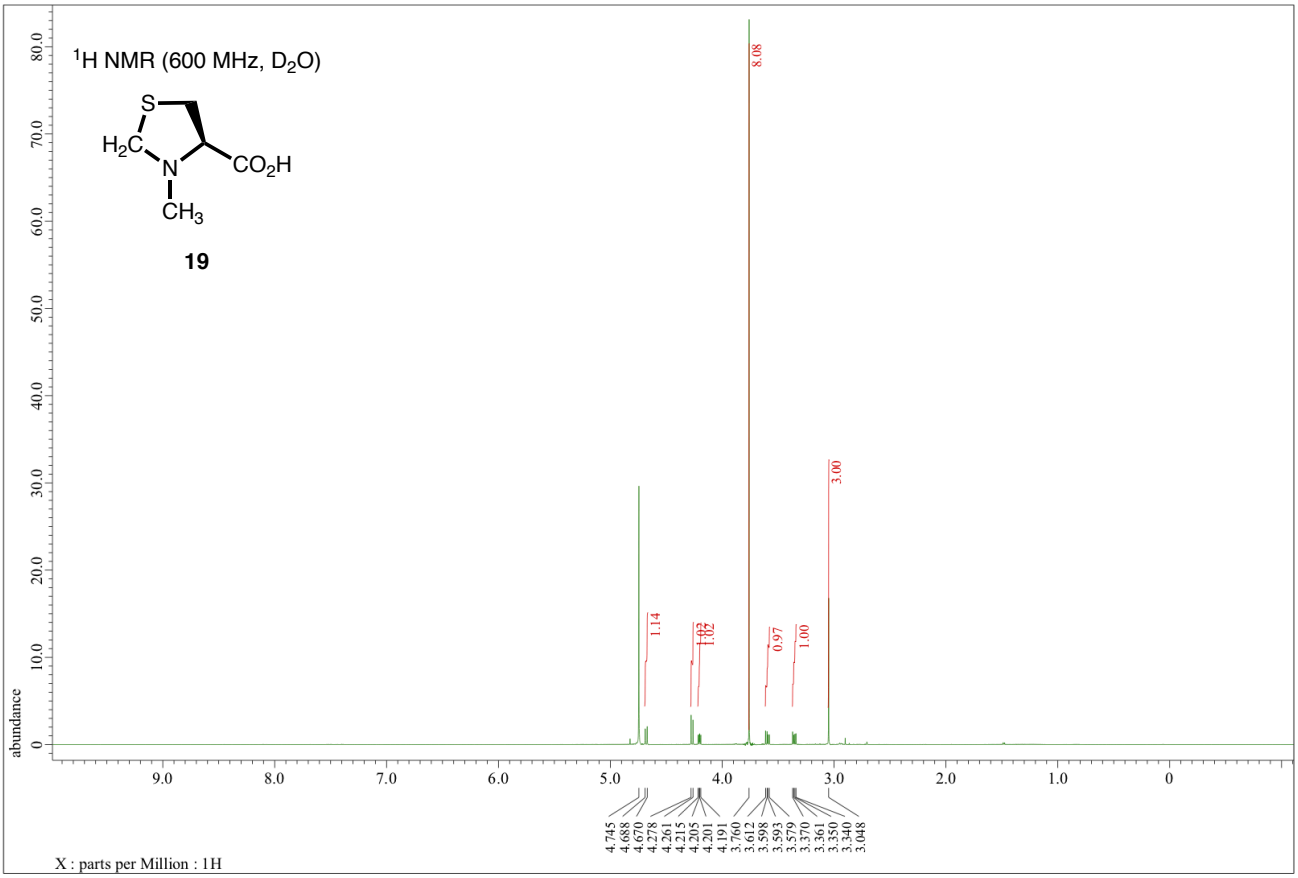
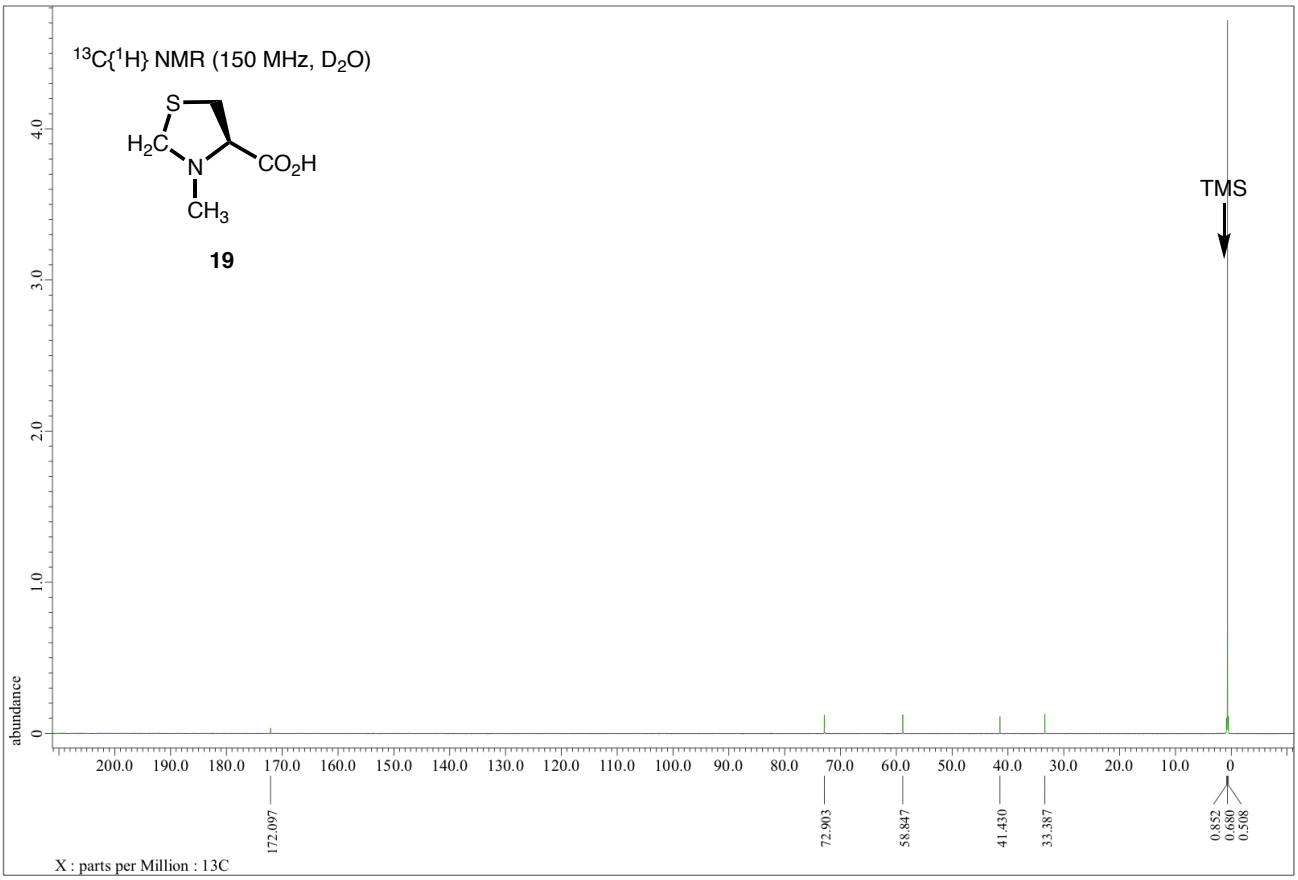
89.40
89.60
89.80


^{1}H NMR (600 MHz, D_2O)
19
abundance
X : parts per Million : 1H


^{13}C{^{1}H} NMR (150 MHz, D_2O)
19
TMS
abundance
X : parts per Million : 13C