10.1071/CH10306_AC

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Accessory Publication

Synthesis of azide-alkyne fragments for ‘click’ chemical applications. Formation of chiral 1,4-disubstituted-(*β*-alkyl)-*γ*-1,2,3-triazole scaffolds from orthogonally protected chiral *β*-alkyl-trialkylsilyl-*γ*-pentynyl azides and chiral *β*-alkyl-*γ*-pentynyl-alcohols

Oliver D. Montagnat, Guillaume Lessene and Andrew B. Hughes[*]

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General Information

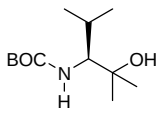
Commercial-grade reagents and solvents were used without further purification unless otherwise stated. CH_2Cl_2 and Et_2O were distilled from CaH_2 in a recycling still. THF was dried with $LiAlH_4$ then distilled from potassium metal in a recycling still. Moisture-sensitive reactions were performed under argon and all glassware was flame-dried. Unless indicated, all reactions were performed at room temperature (rt). Reaction progress was monitored *via* thin-layer chromatography (TLC) using kieselgel 60 F_{254} plates and ethyl acetate/hexane mixtures as the mobile phase. TLC plates were visualised using a 254 nm UV lamp and/or a 10% w/v molybdophosphoric acid/EtOH stain or permanganate stain consisting of $KMnO_4$ (3.0 g), K_2CO_3 (20 g) and 5% w/v aqueous NaOH (5 ml) in H_2O (300 ml). "Flash column chromatography" was performed using silica gel (silica gel 60, 230-400 mesh ASTM) as the stationary phase and ethyl acetate/hexane mixtures as the mobile phase. ^1H, ^{13}C, DEPT and $^1H/^{13}C$-HSQC Nuclear Magnetic Resonance (NMR) spectra were obtained on a 300 MHz spectrometer (^1H at 300.13 MHz and ^{13}C at 75.47 MHz, respectively). $^1H/^1H$-mCOSY [1] and $H/^1H$-NOESY NMR spectra were obtained on a 400 MHz spectrometer (^1H at 400.01 MHz). Proton and carbon chemical shifts reported as δ values in parts per million (ppm) are relative to residual solvent and coupling constants (J) are in Hz. Infrared (IR) spectra were recorded on a fourier-transform IR spectrometer. Oils were analysed using sodium chloride plates. Solids were analysed using KBr discs or a diffuse reflectance accessory. Mass spectra were obtained using an ISQ mass spectrometer at an ionisation energy of 70 eV; *m/z* values reported include the parent ion peak. Optical rotation ($[\alpha]_D$) values were determined using a polarimeter with a 1 dm path length quartz cell.

NMR Assignment Conventions

The pentynyl monomers and derivatives thereof have all been assigned starting at the trialkylsilyl end of the triple bond and following along the hydrocarbon chain (i.e H1, H2… C1, C2… etc). Cycloadducts and higher order oligomers have all been assigned along the backbone using Greek symbols followed by a superscript (i.e. α^1, β^1, γ^1… α^2, β^2, γ^2… etc). Specific side chains within a molecule have been assigned by representing a bold atom amongst the side chain shown (i.e. *iso*-propyl CH hydrogen), C**H**$(CH_3)_2$). Note that these assignment conventions are independent of the conventions used for nomenclature.

Preparation of chiral SQ compounds 11a-11b and related precursors 14-15

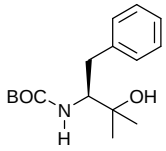
2-Hydroxy-1-(*S*)-*iso*-propyl-2-methyl-propyl)-carbamic acid *tert*-butyl ester 14:



14

Compound **14** was prepared as described in the literature. Data for compound **14** compared well to literature values.[14]

(1-(*S*)-Benzyl-2-hydroxy-2-methyl-propyl)-carbamic acid *tert*-butyl ester 15:



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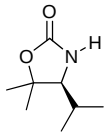
Compound **15** was prepared as described in the literature. Data for compound **15** compared well to literature values.[13]

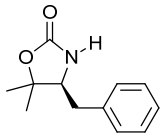
4-(*S*)-*Iso*-propyl-5,5-dimethyl-oxazolidin-2-one 11a:



11a

Compound **11a** was prepared as described in the literature. Data for compound **11a** compared well to literature values.[14]

4-(*S*)-Benzyl-5,5-dimethyl-oxazolidin-2-one 11b:

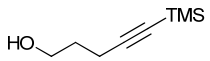


11b

Compound **11b** was prepared as described in the literature. Data for compound **11b** compared well to literature values.[13]

Preparation of 5-trimethylsilyl-pent-5-yn-1-oic acid 10 and related precursor 17

5-Trimethylsilanyl-pent-4-yn-1-ol 17:



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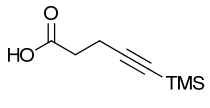
Compound **17** was prepared as described in the literature. Data for compound **17** compared well to literature values.[25]

5-Trimethylsilanyl-pent-4-ynoic acid 10:



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Compound **10** was prepared as described in the literature. Data for compound **10** compared well to literature values.[19]

References

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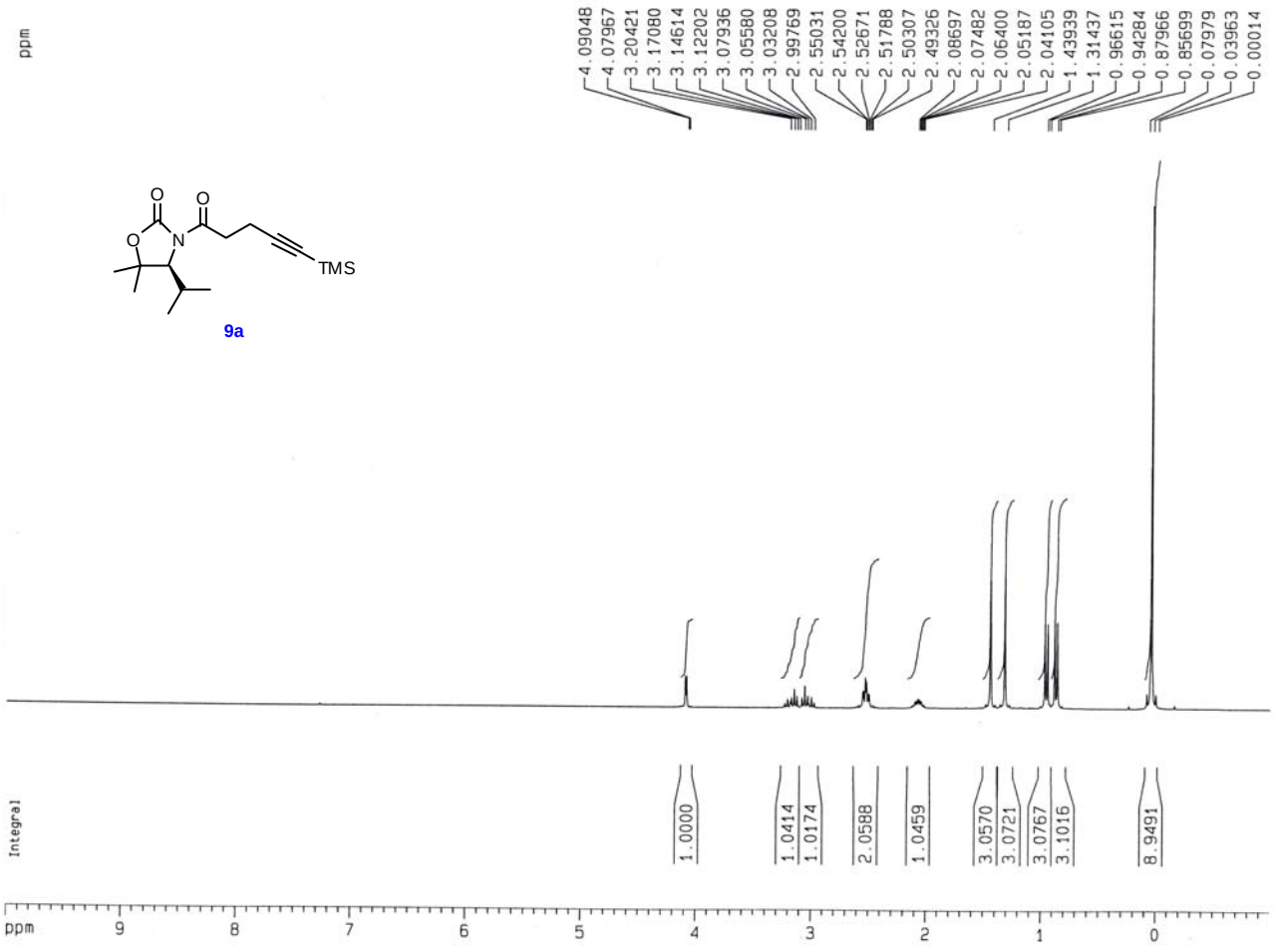
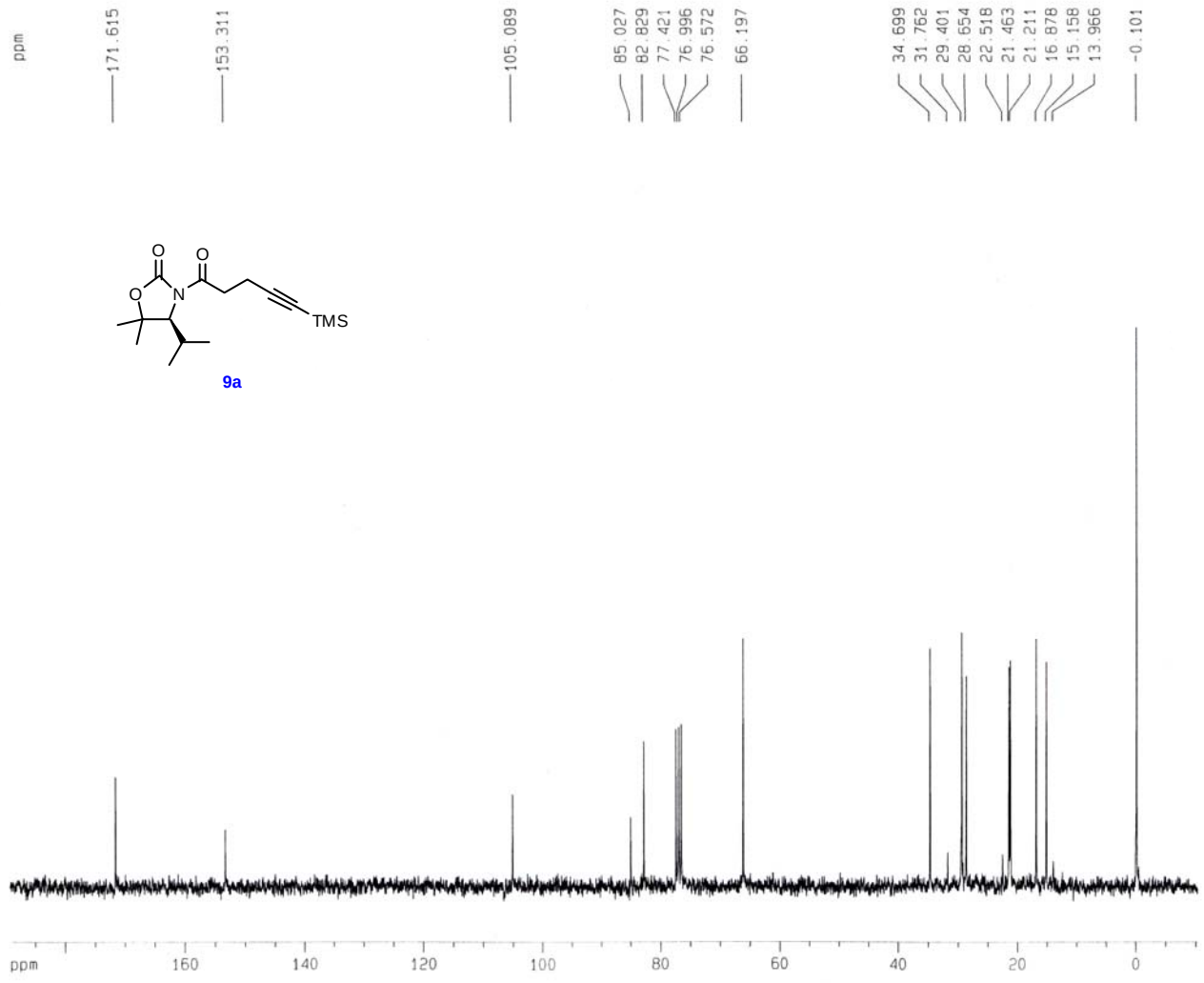
^{1}H and ^{13}C NMR spectra of selected compounds

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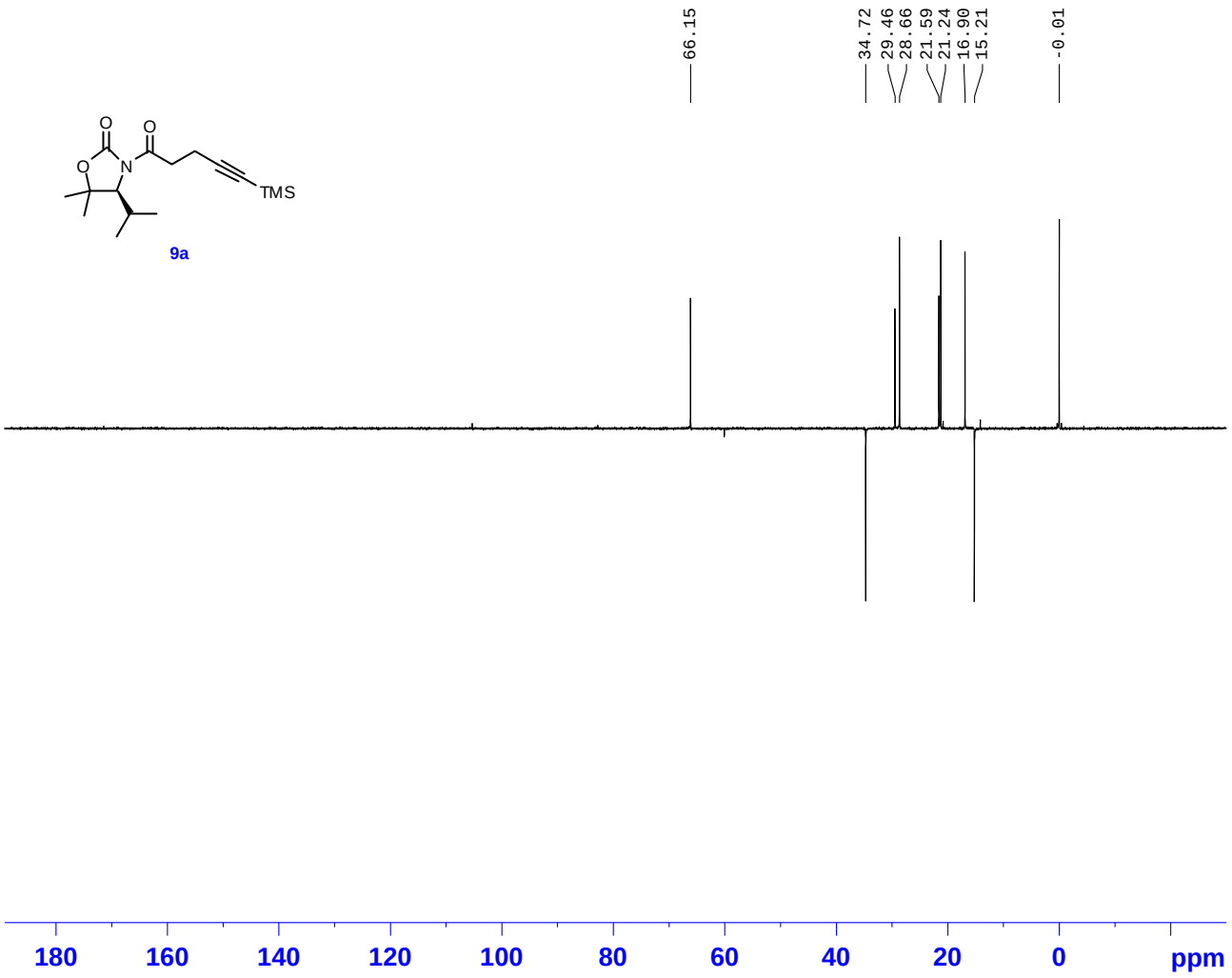
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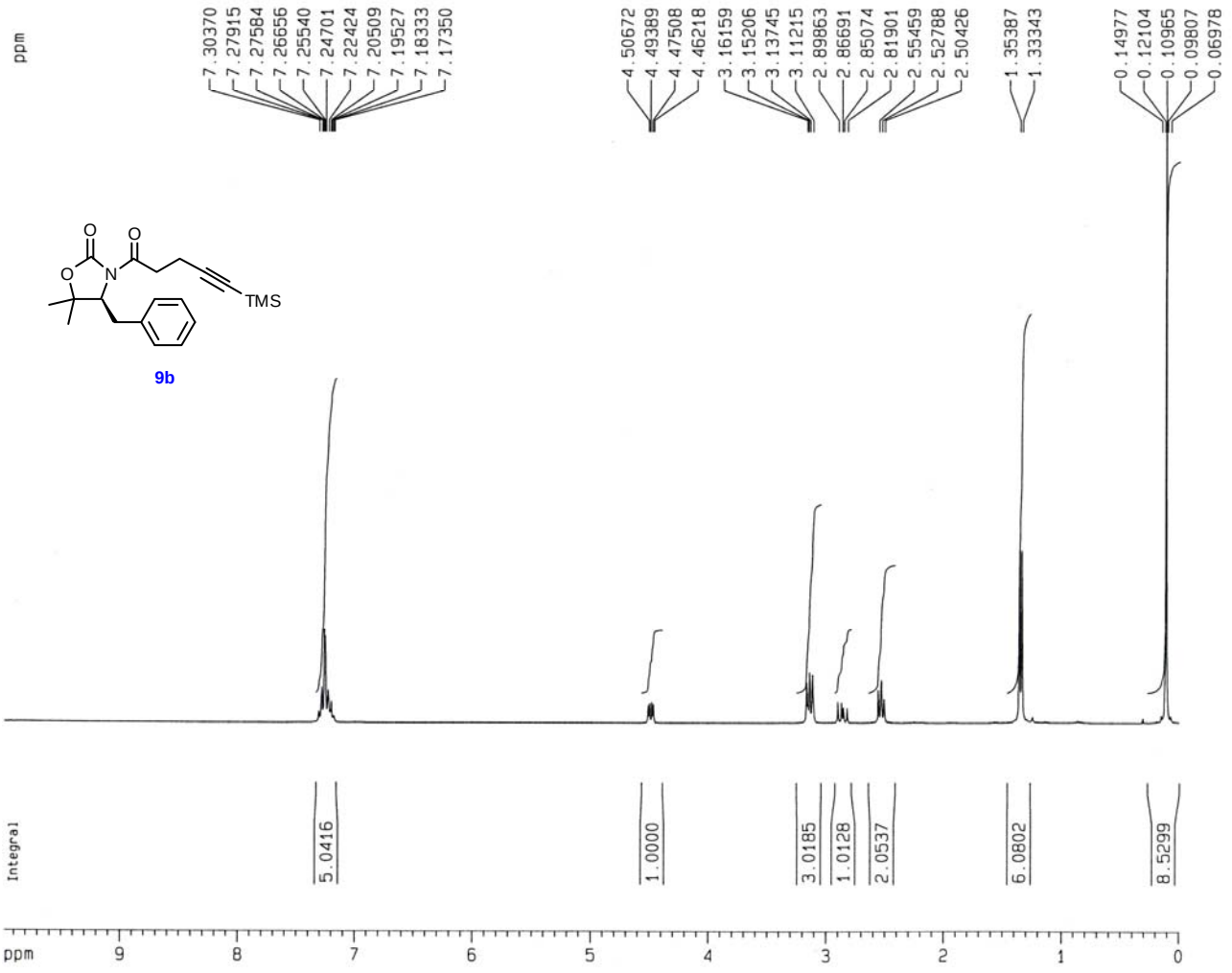
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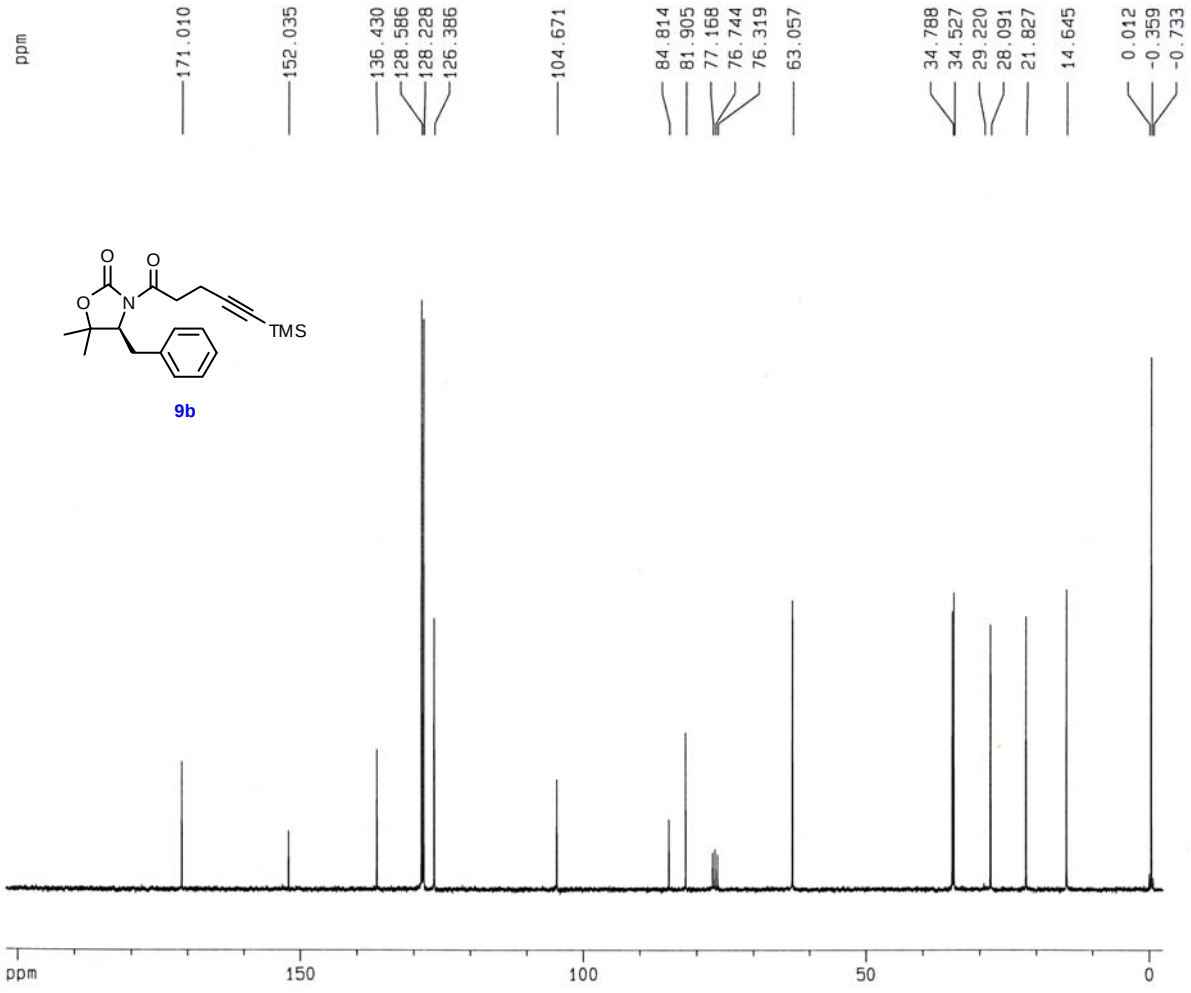
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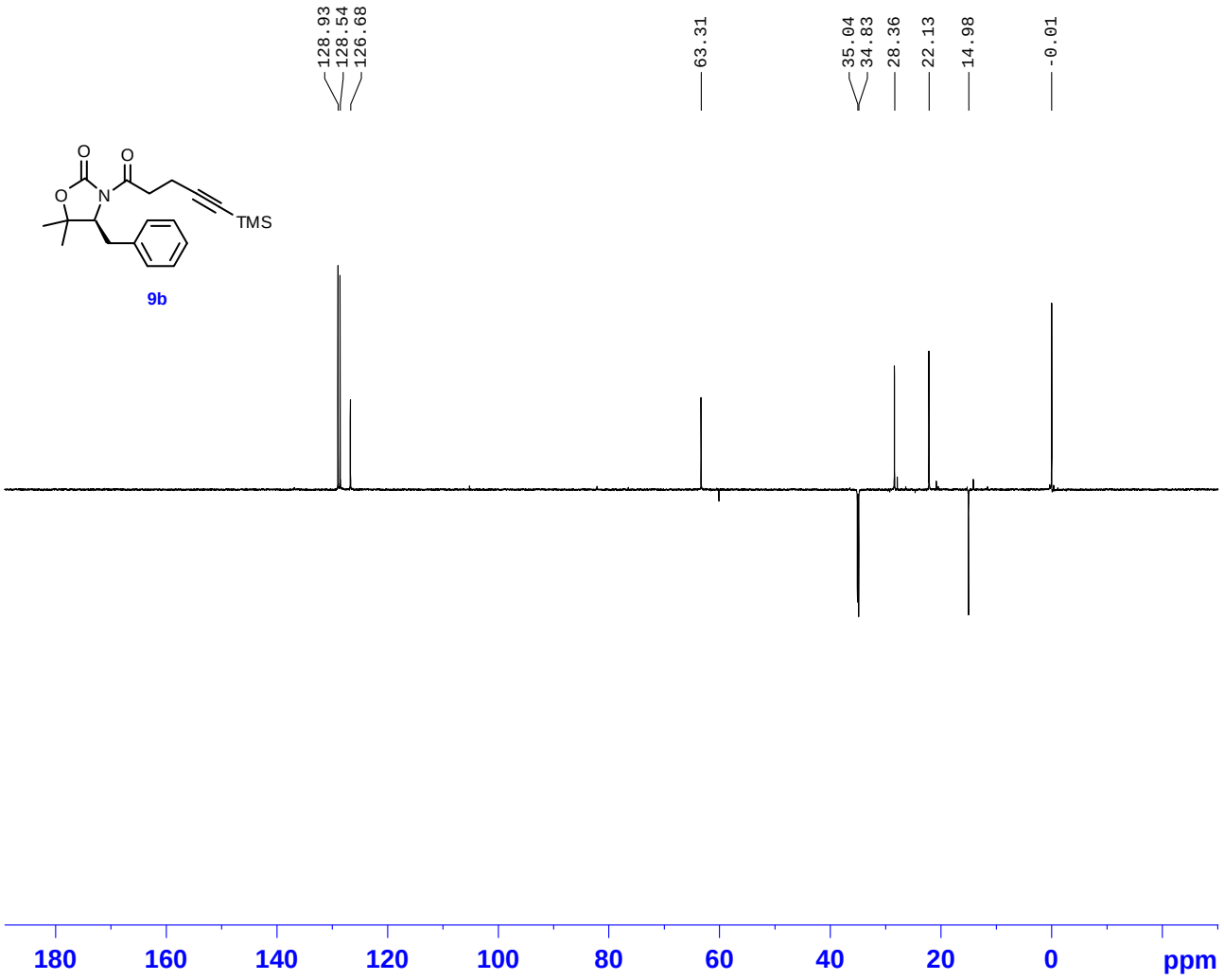
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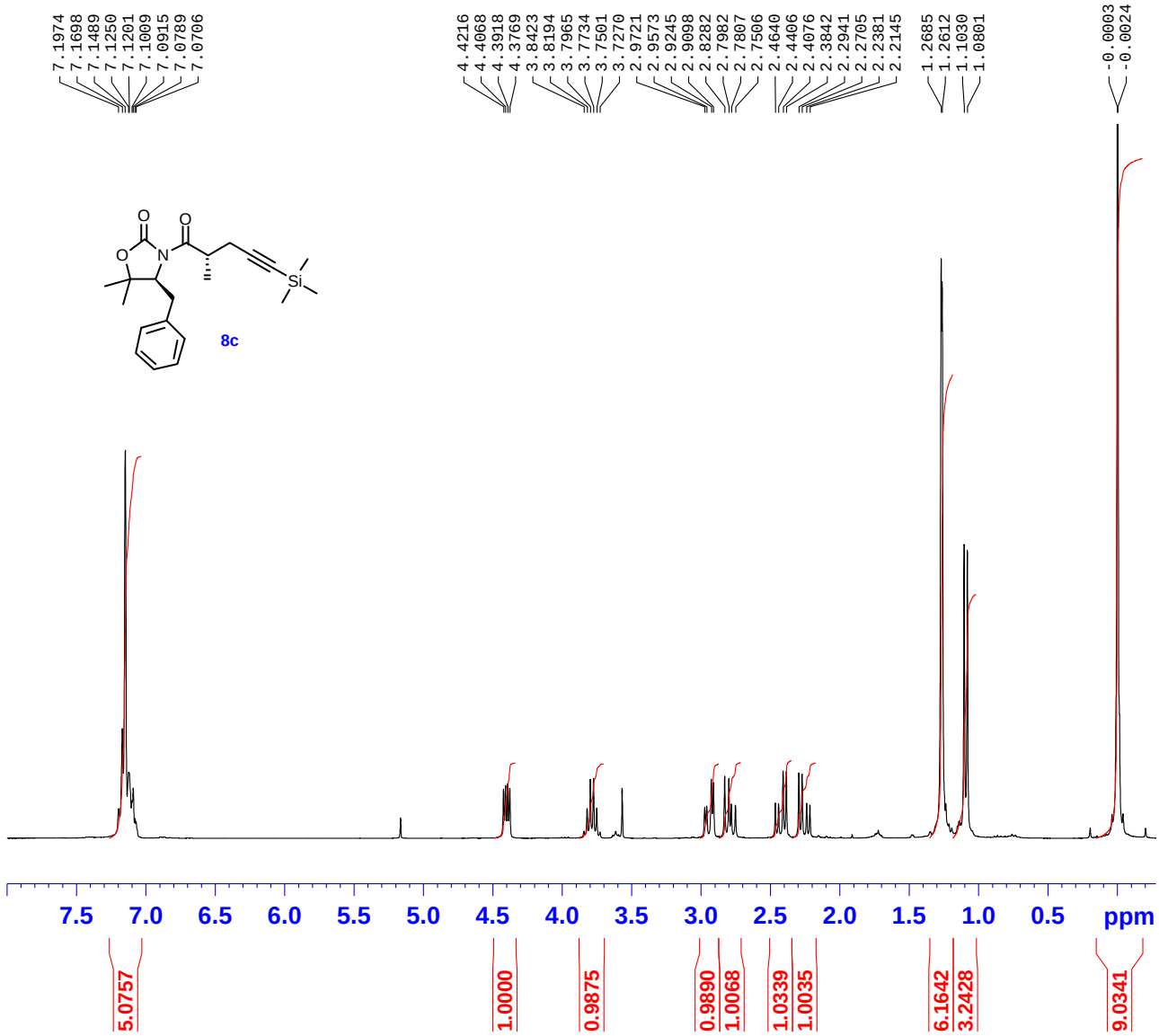
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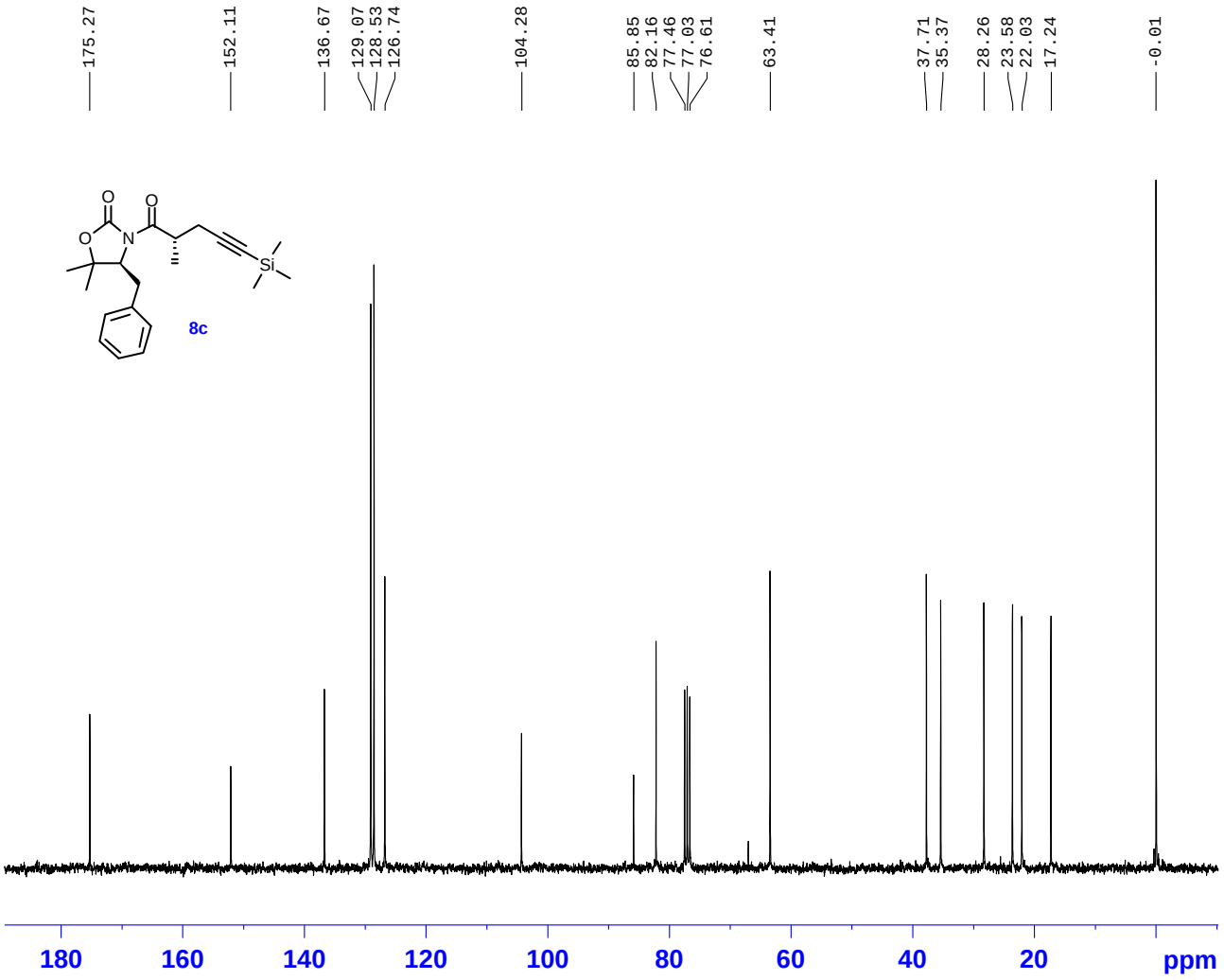
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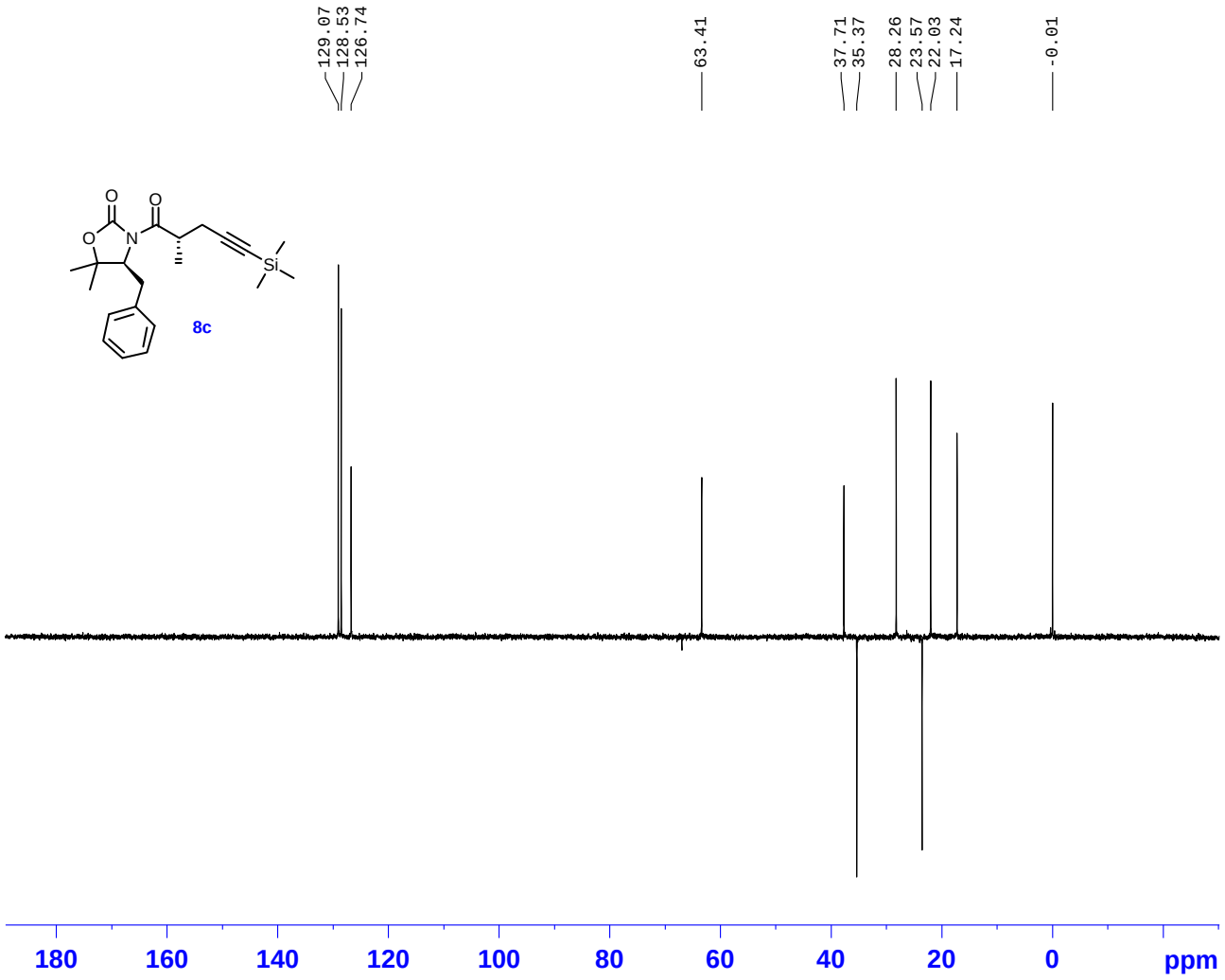
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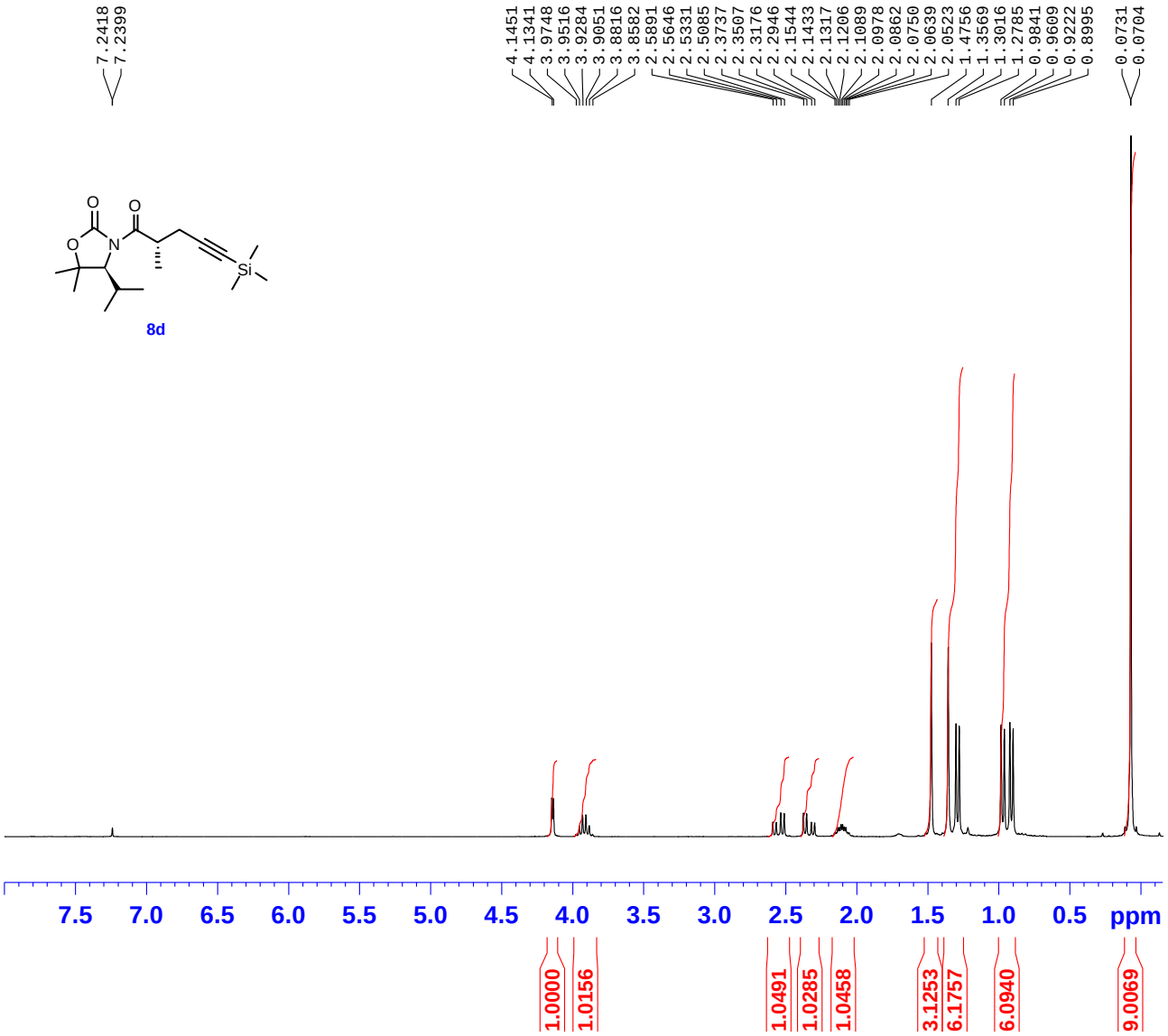
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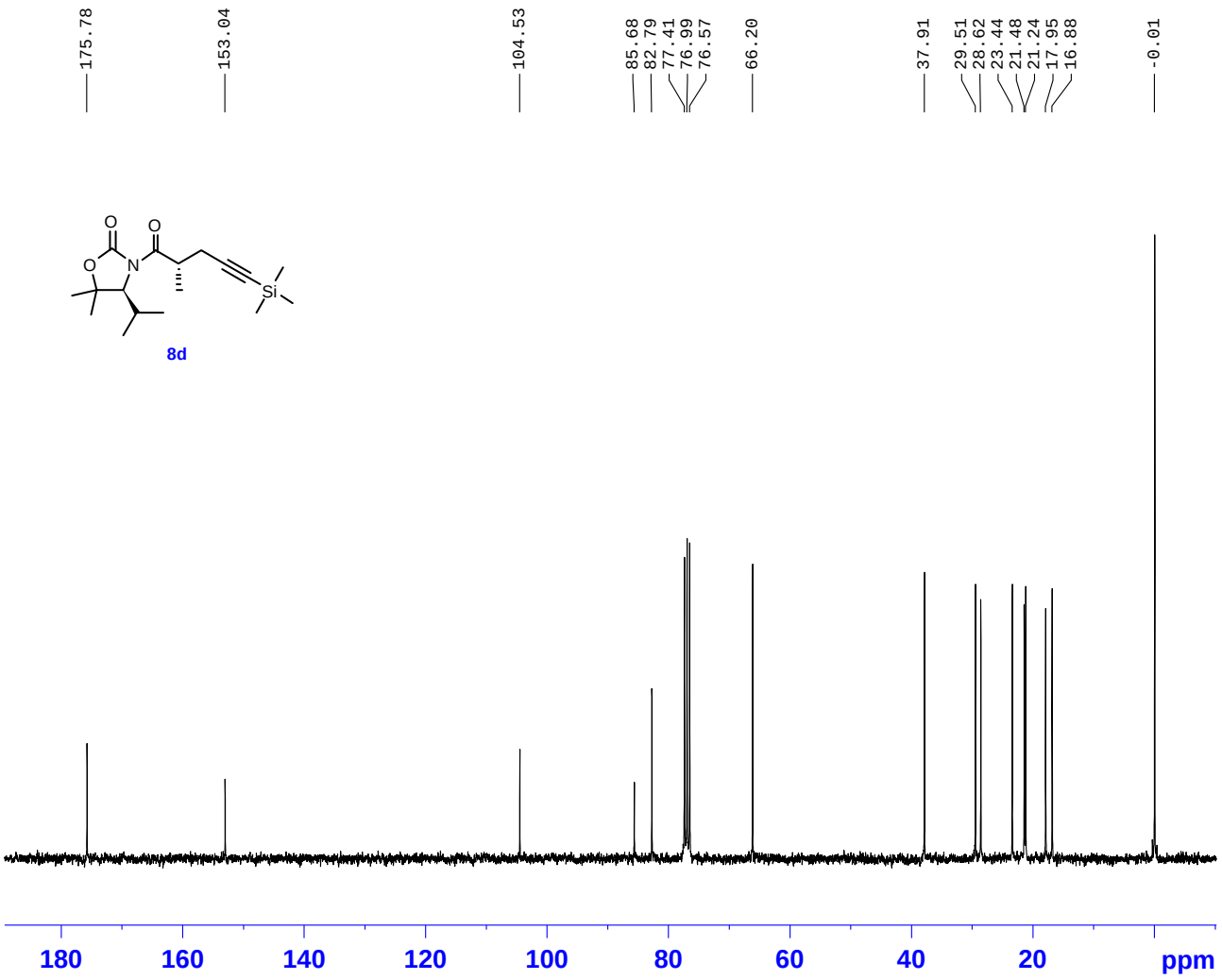
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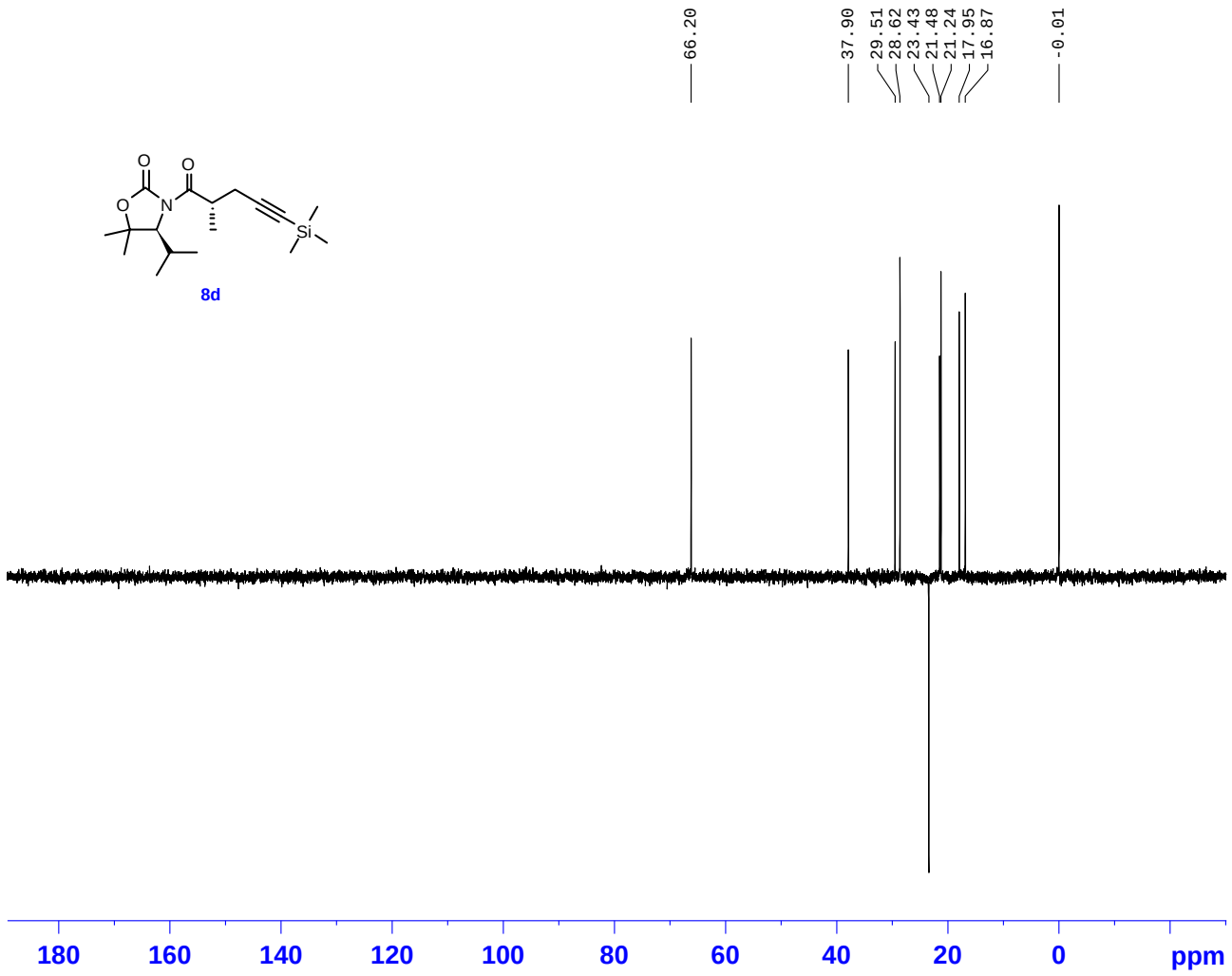
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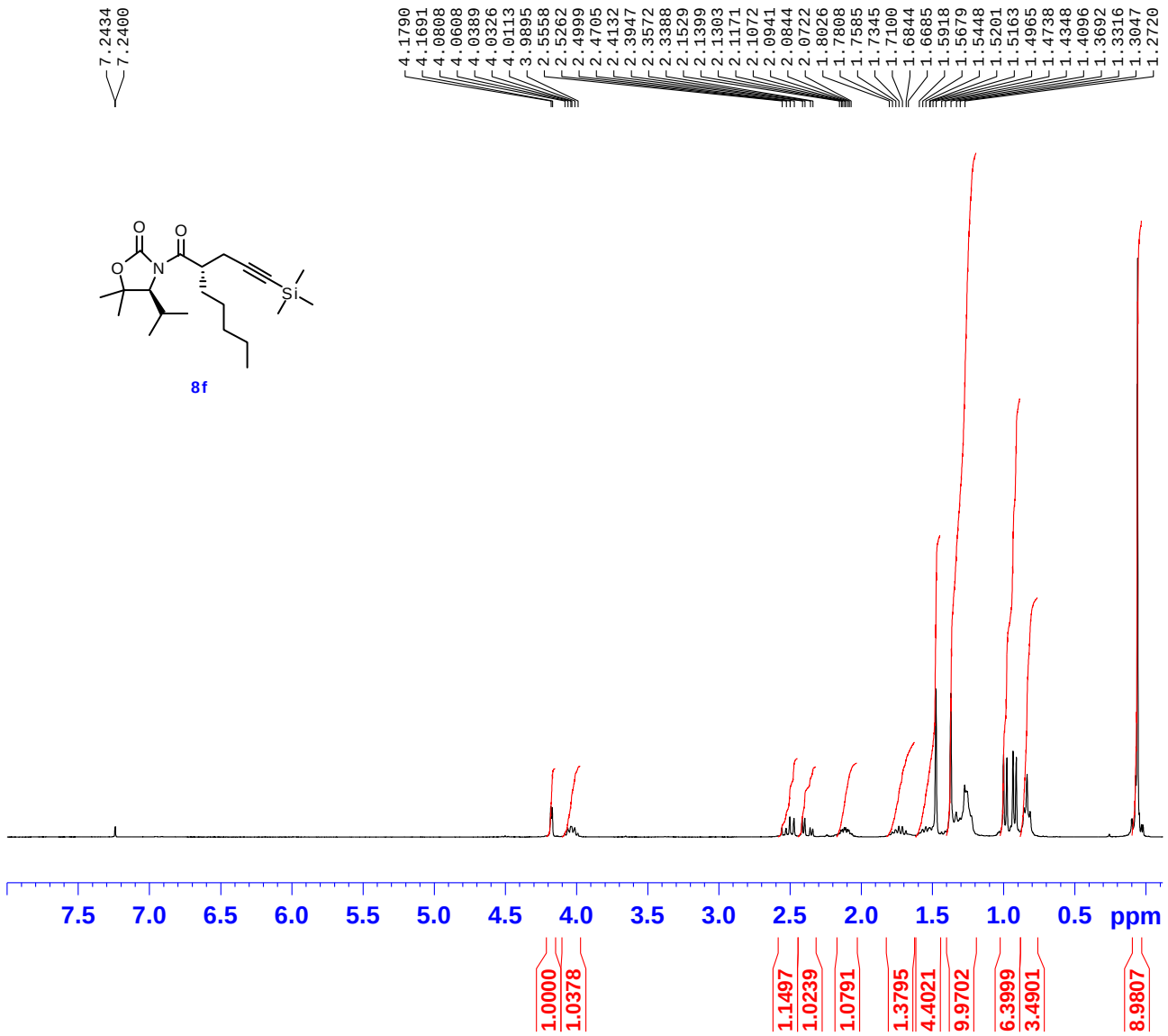
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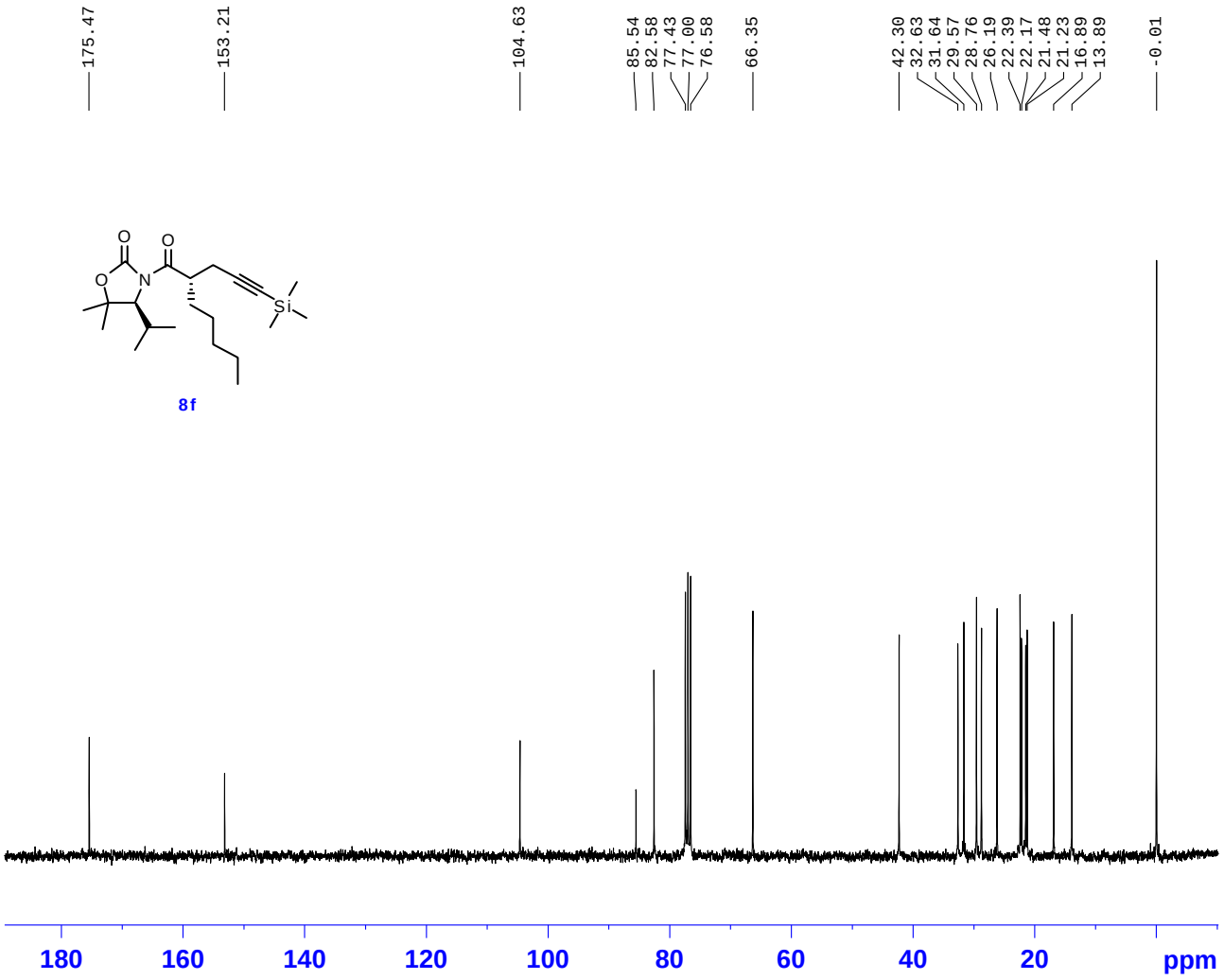
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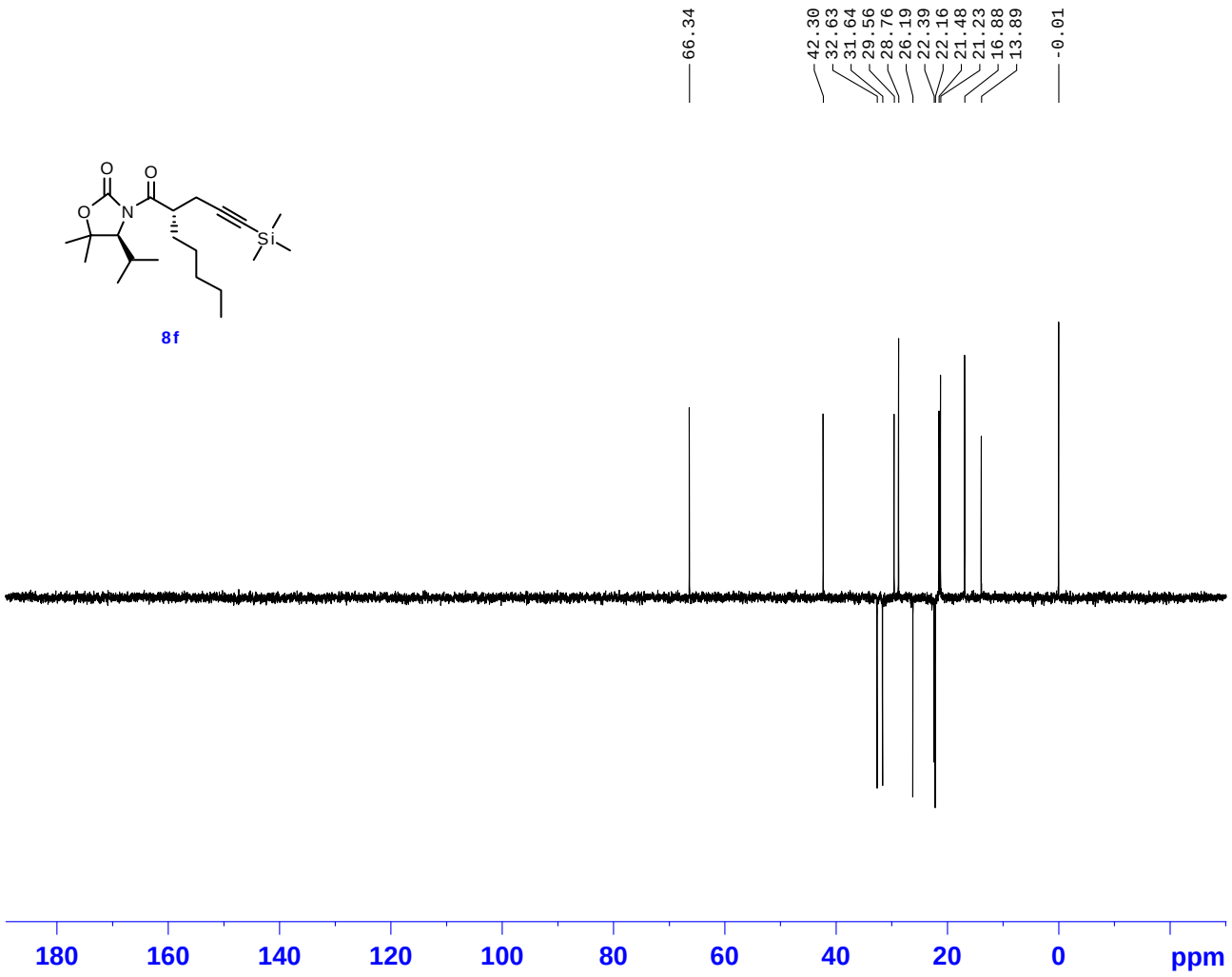
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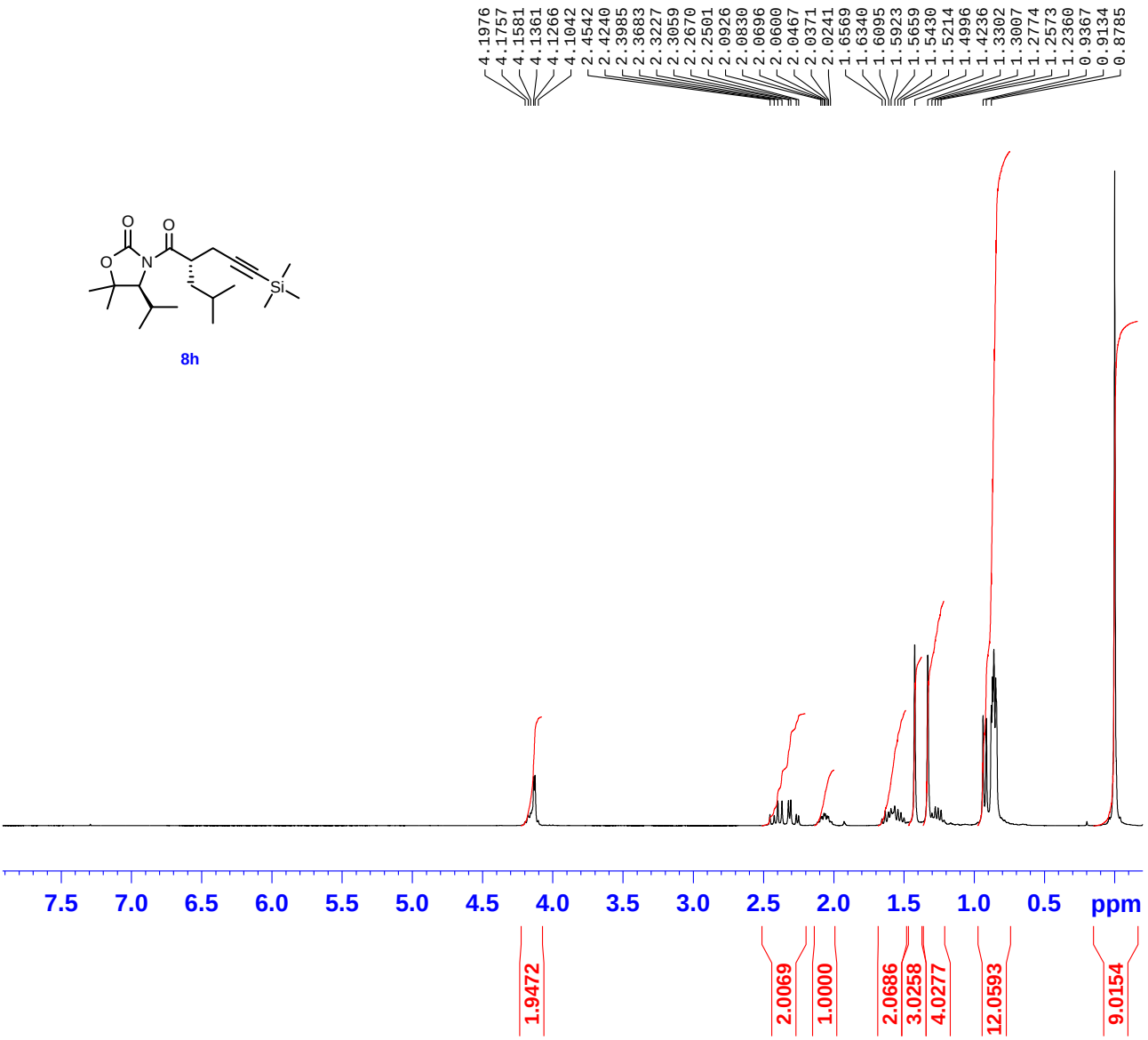
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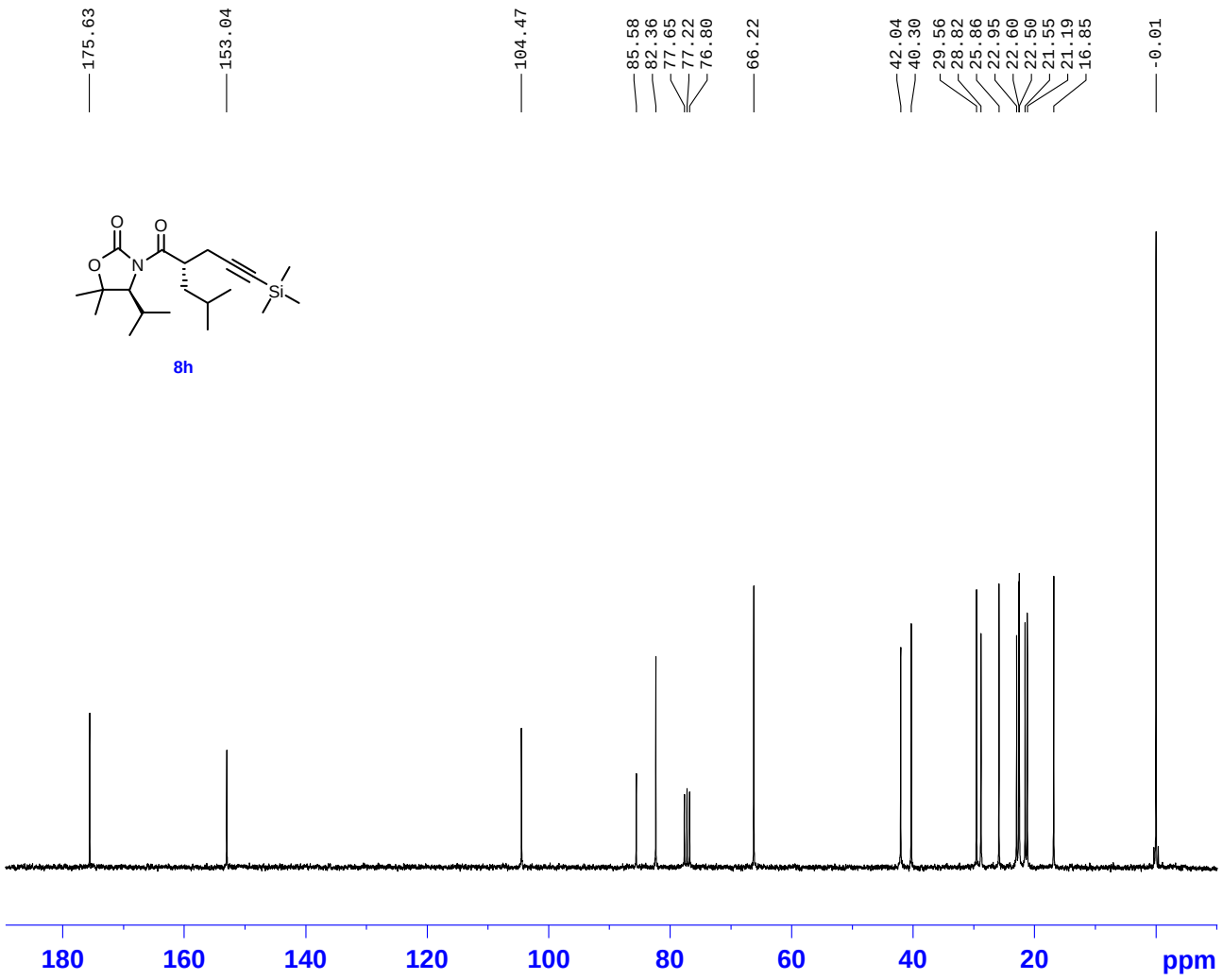
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22.50
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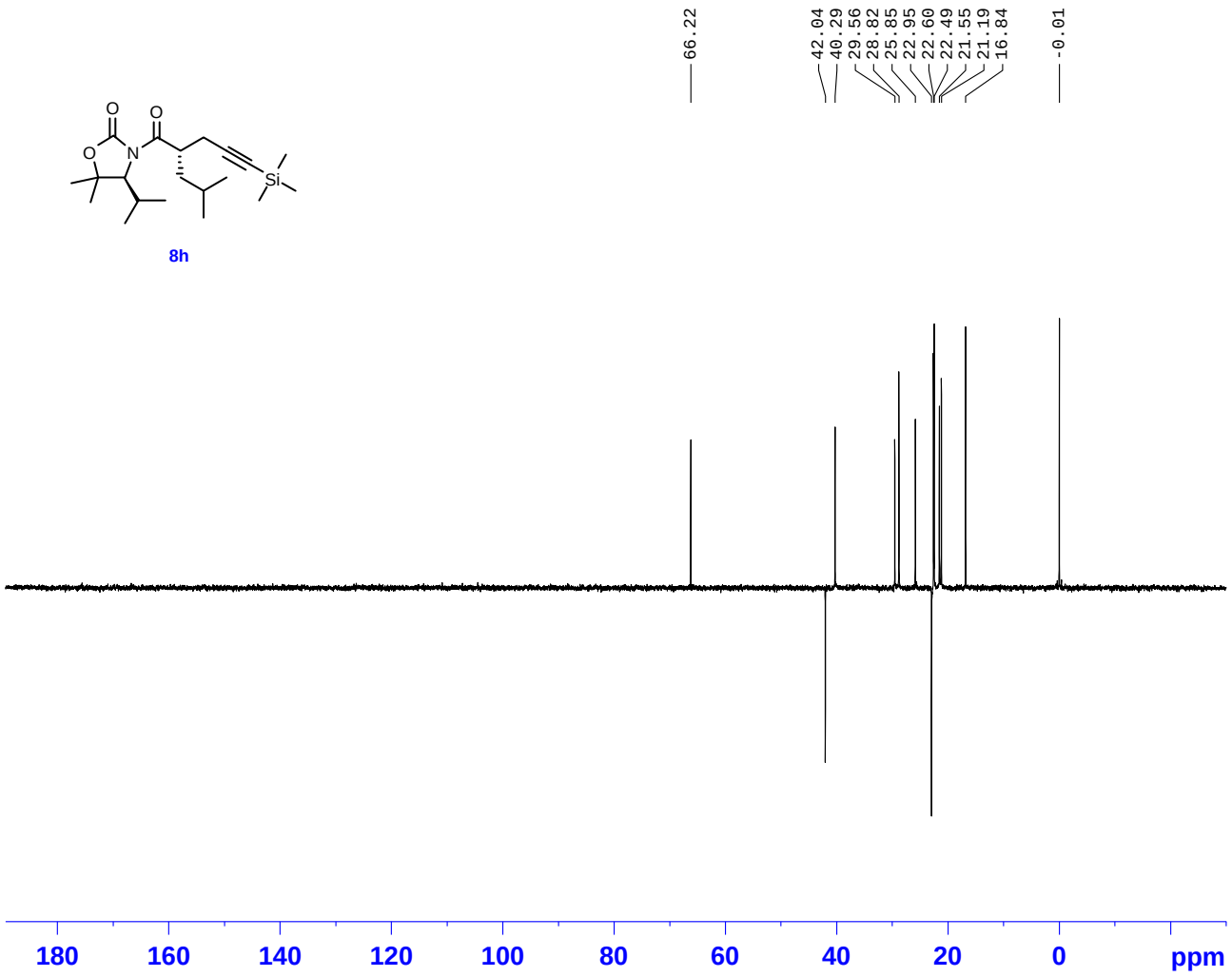
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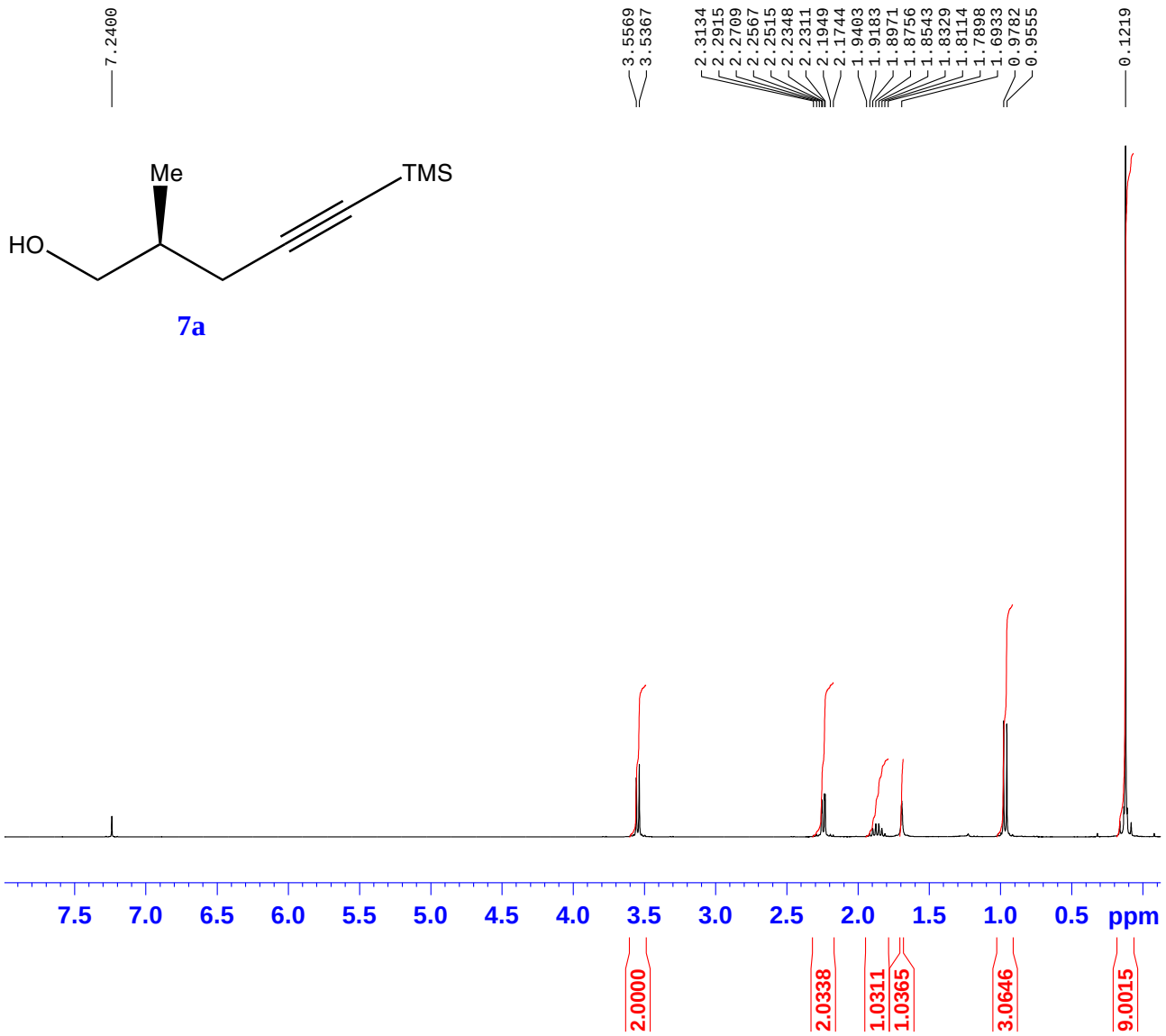
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Me
TMS
HO
7a
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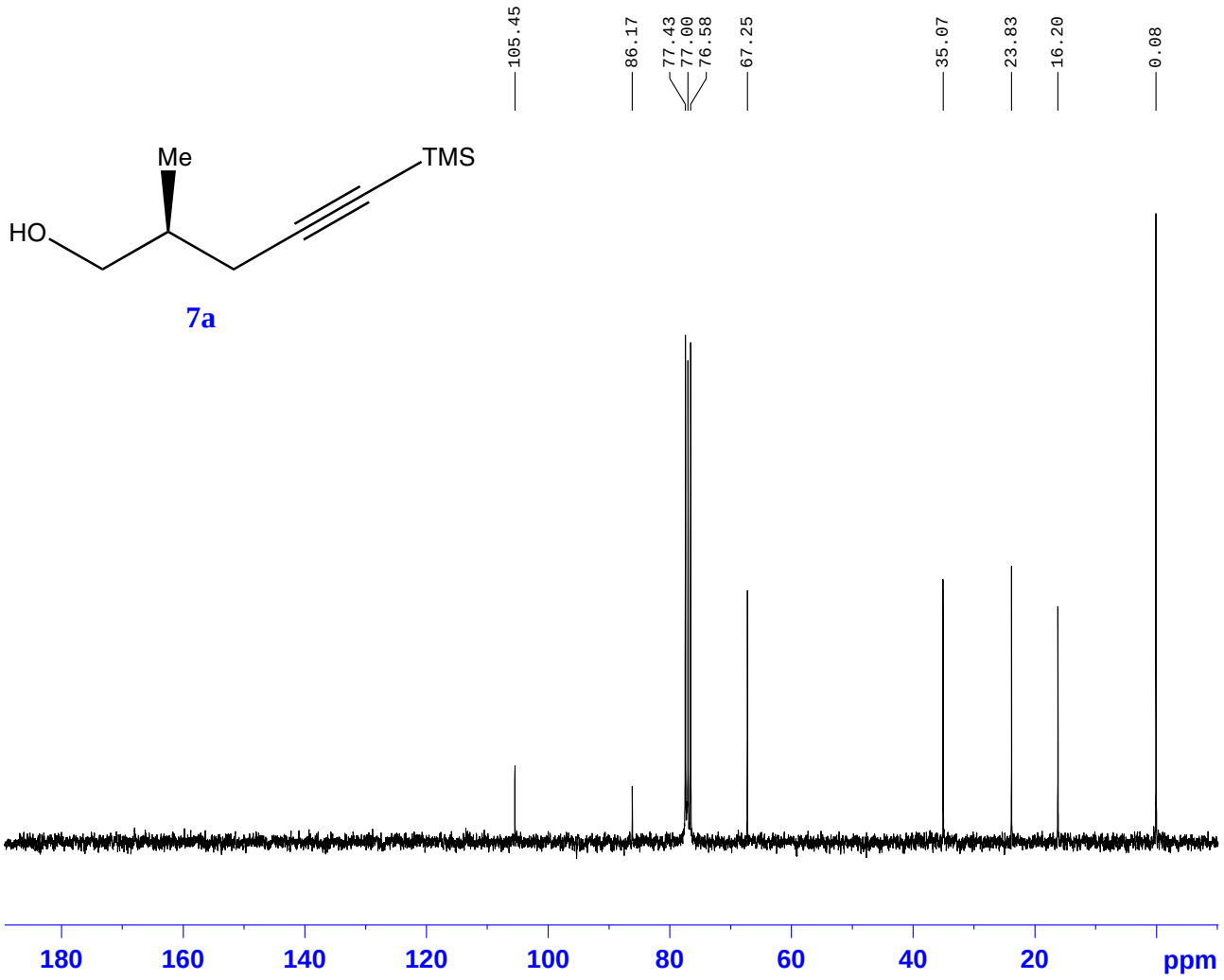
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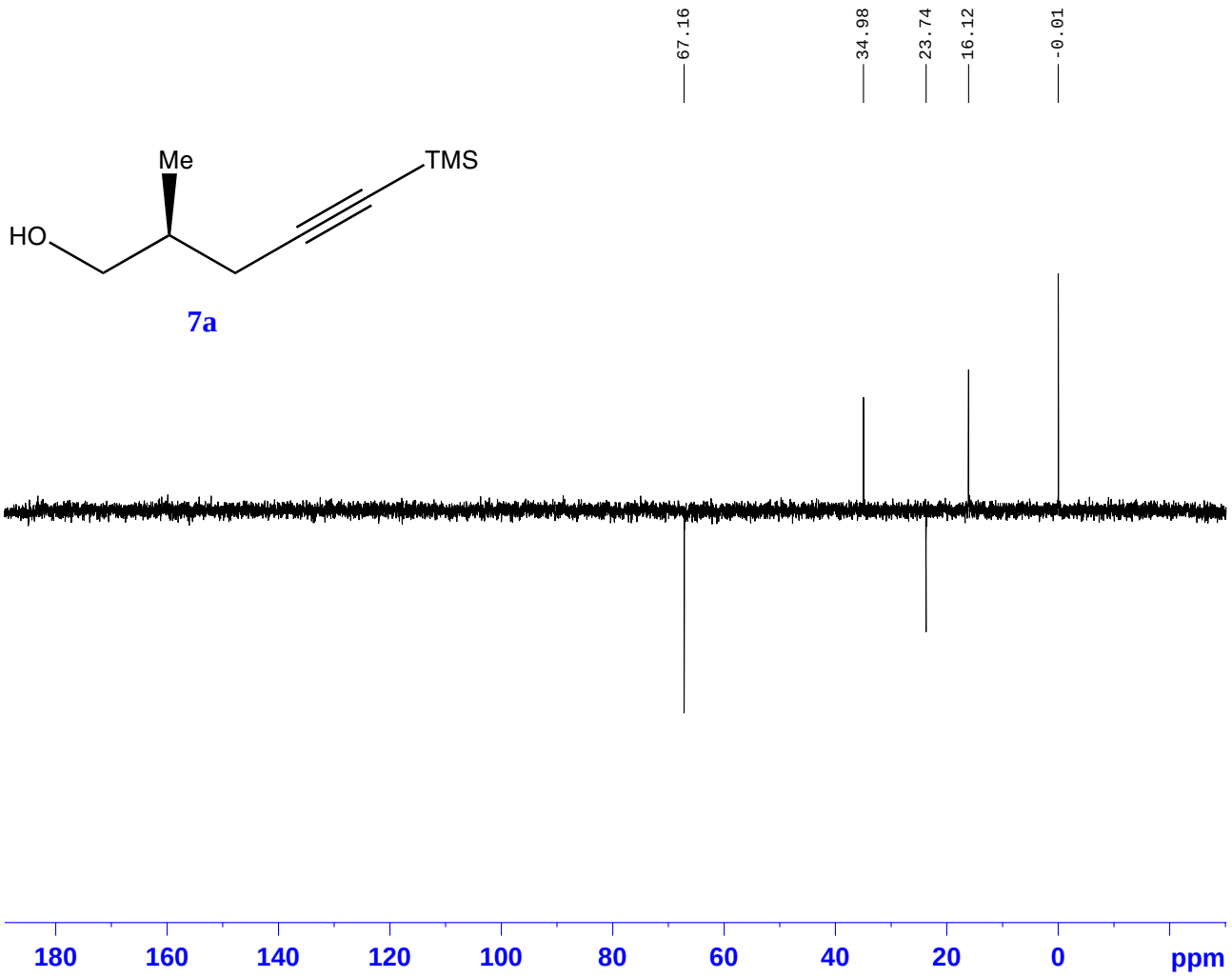
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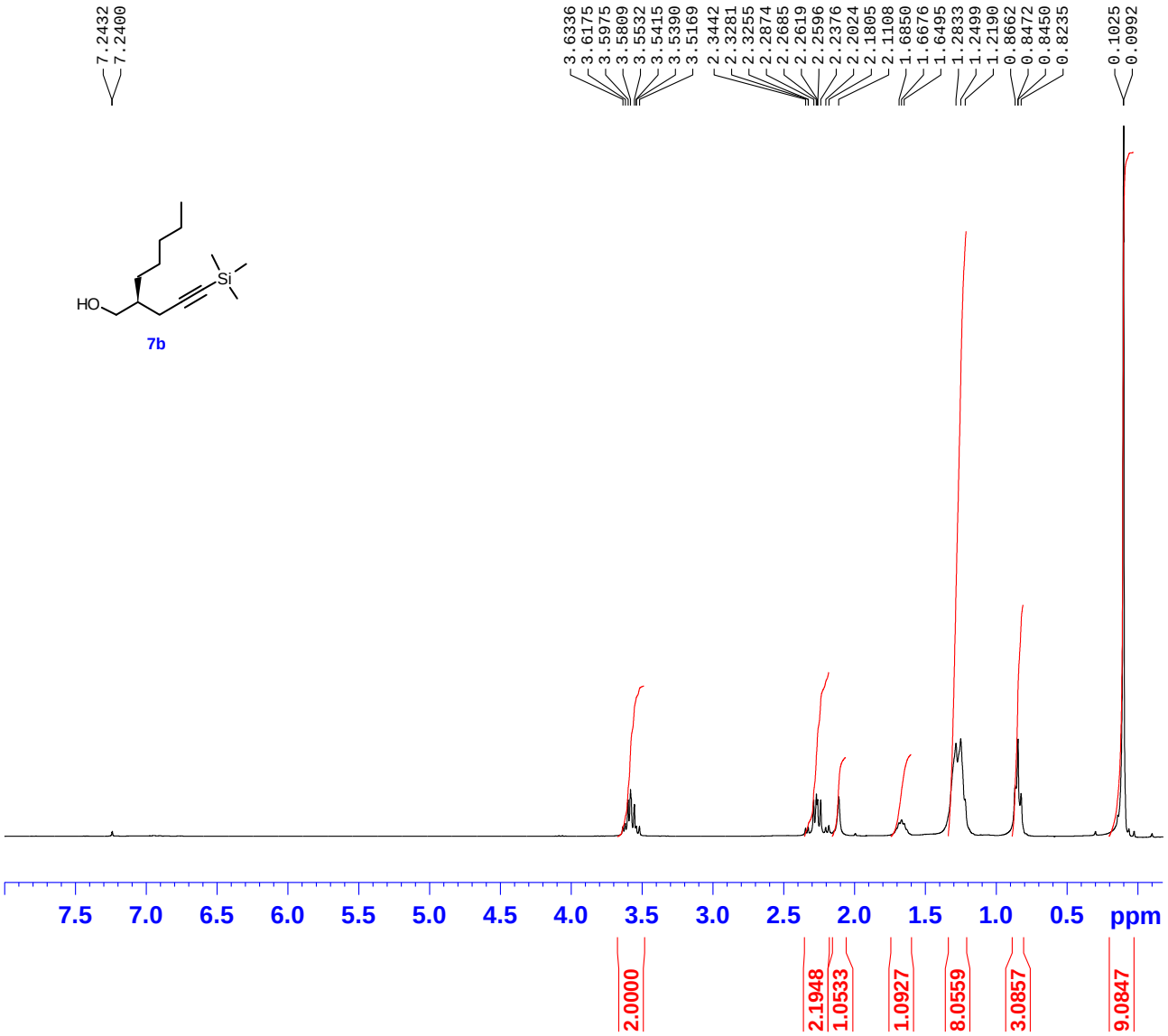
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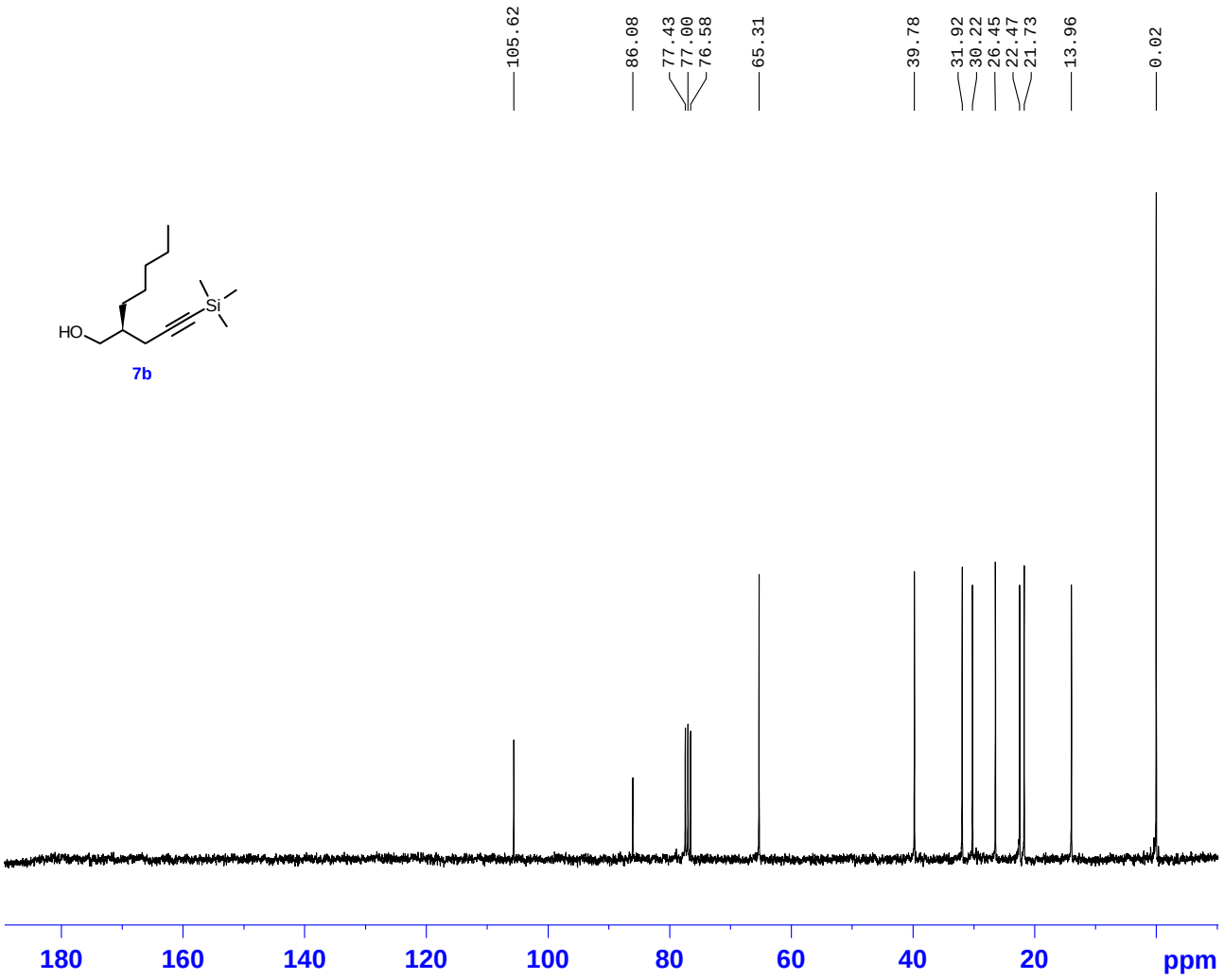
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20
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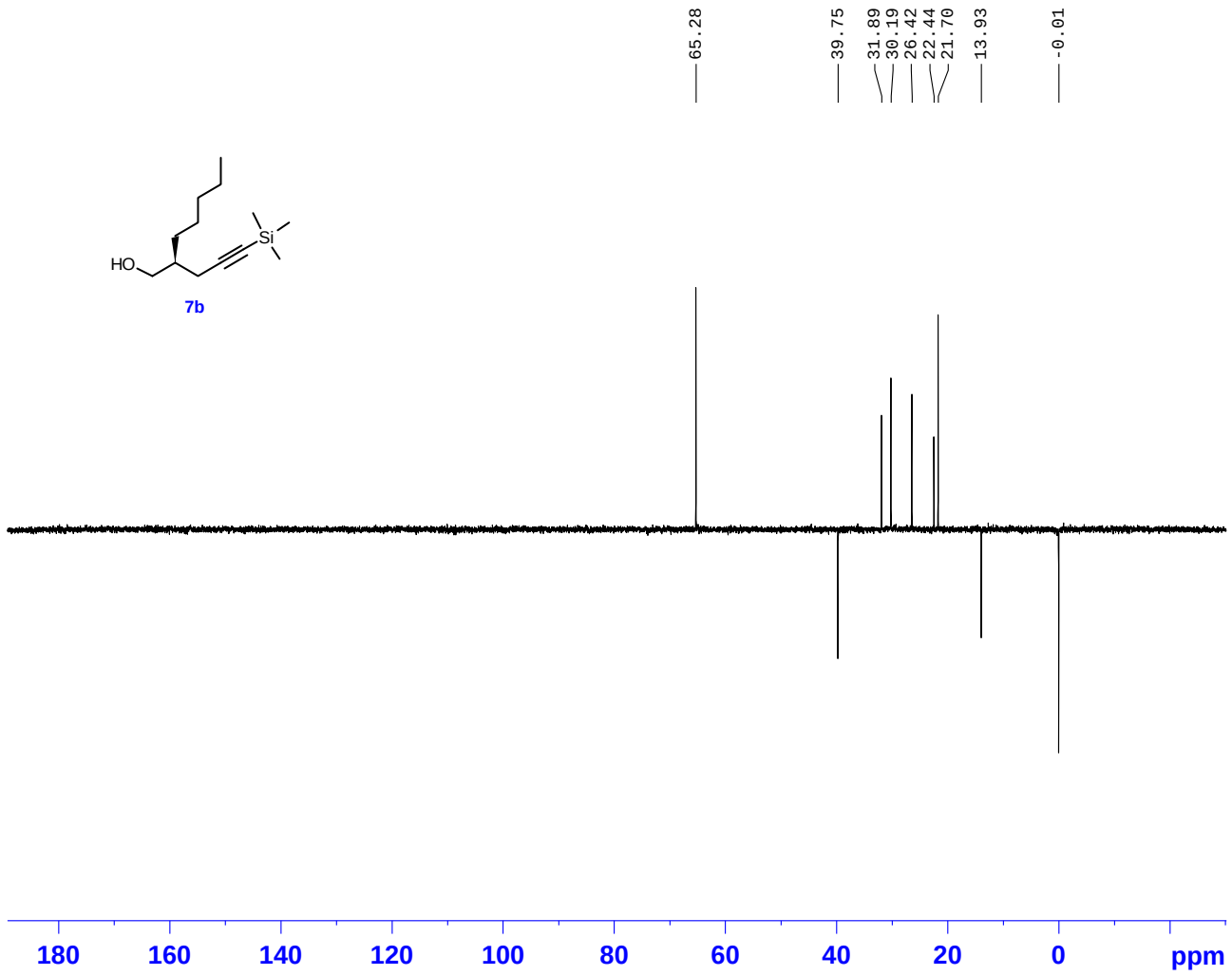
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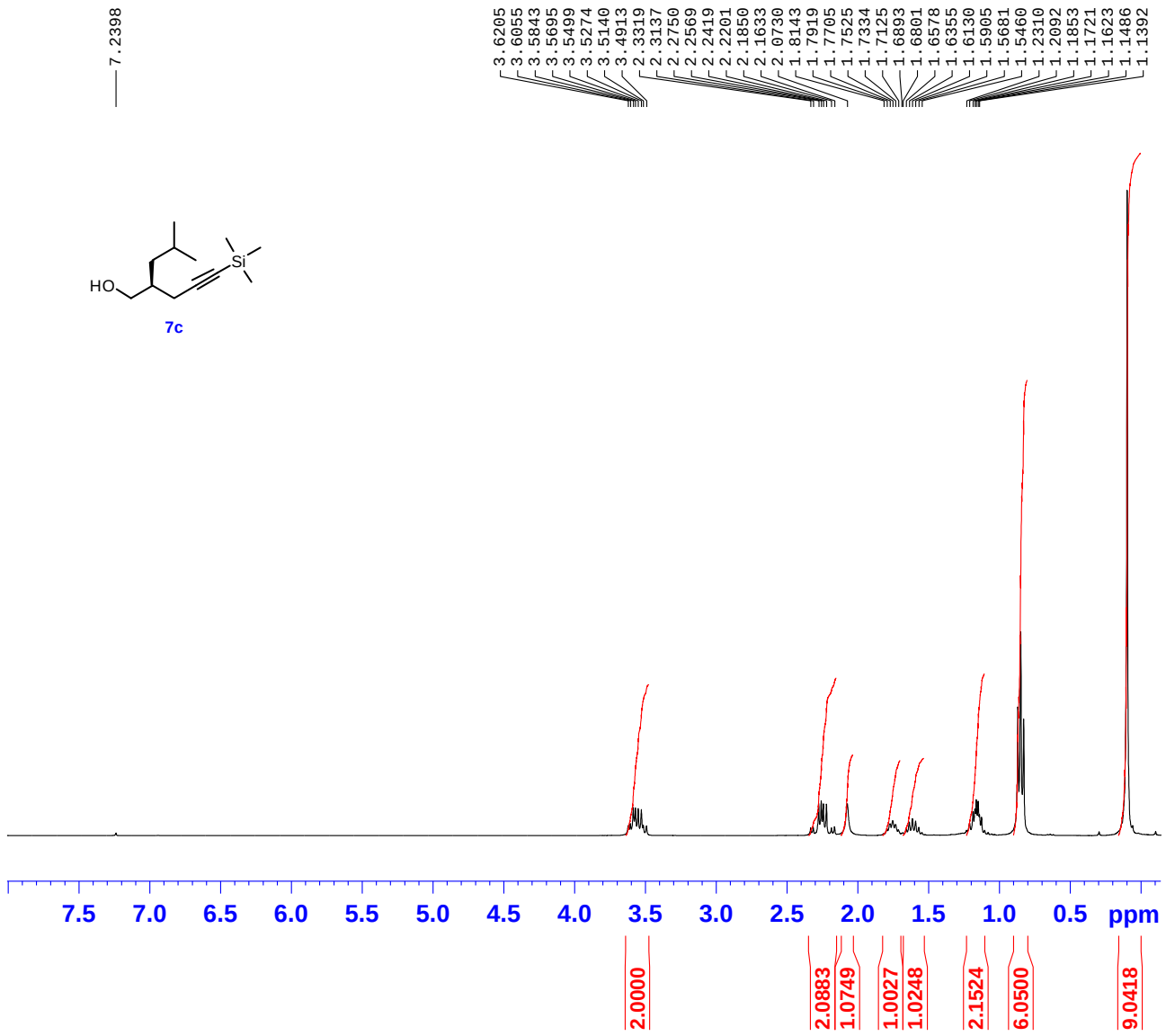
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1.1623
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1.1392
HO
Si
7c
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6.5
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4.0
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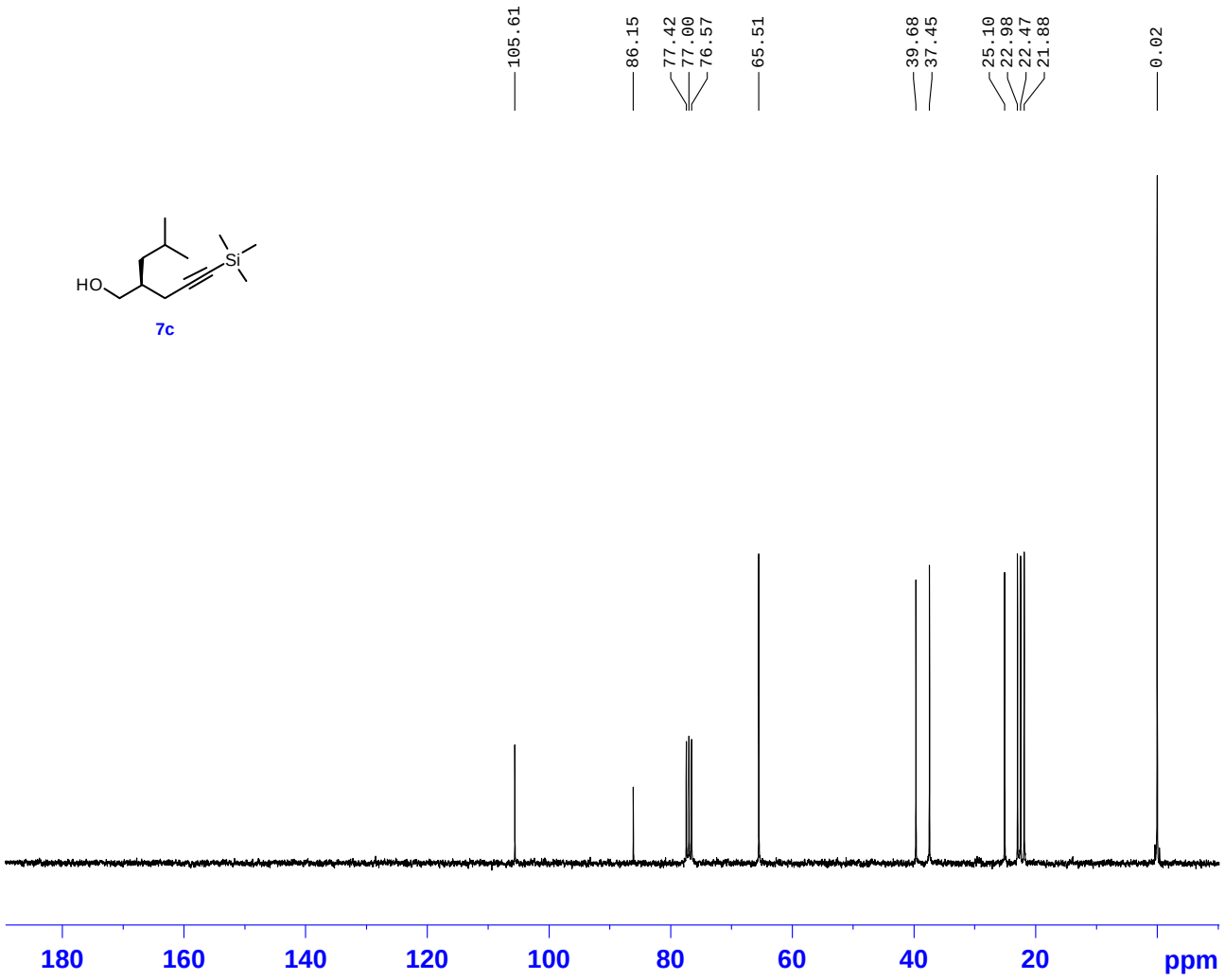
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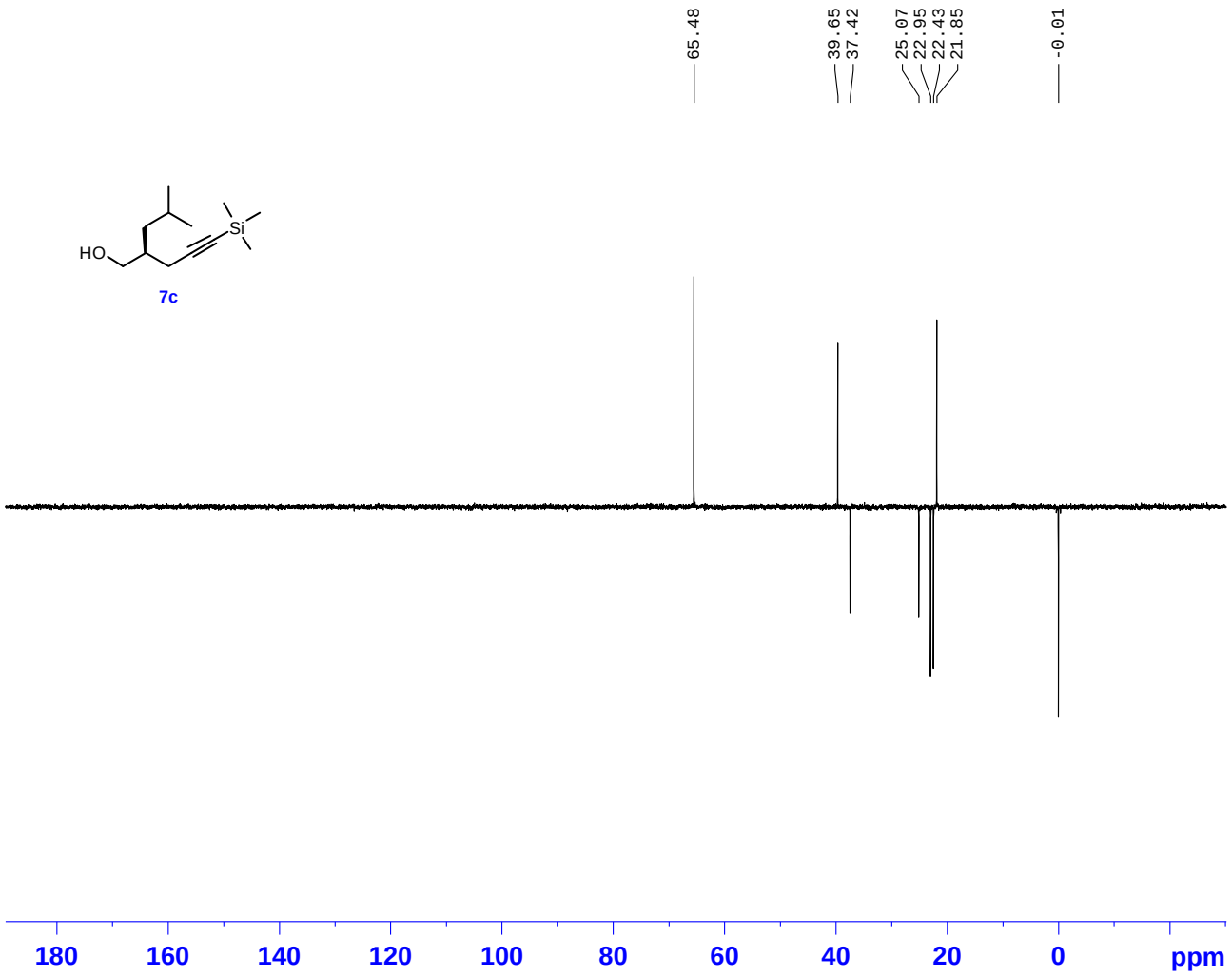
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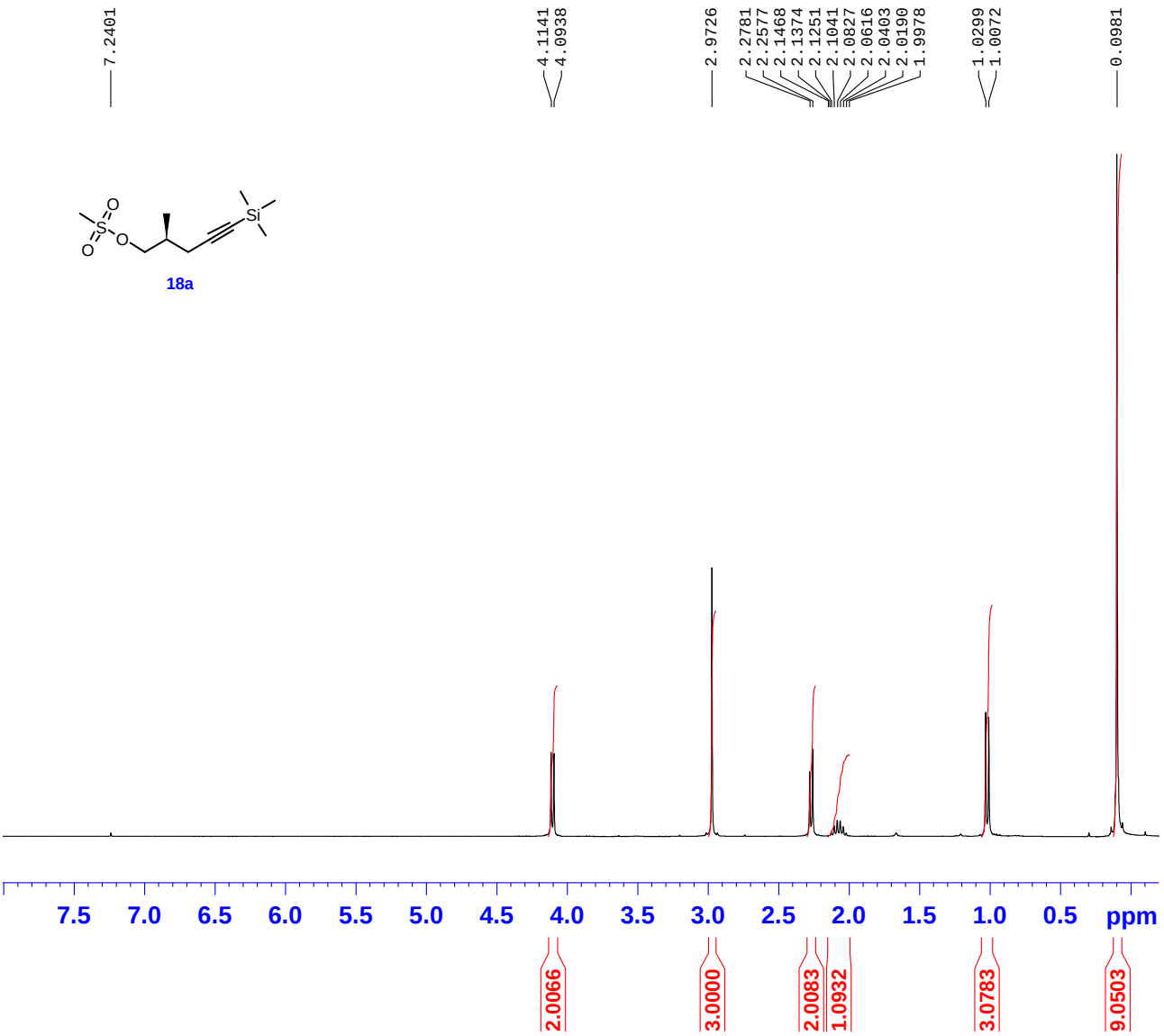
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1.0072
0.0981
18a
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6.0
5.5
5.0
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4.0
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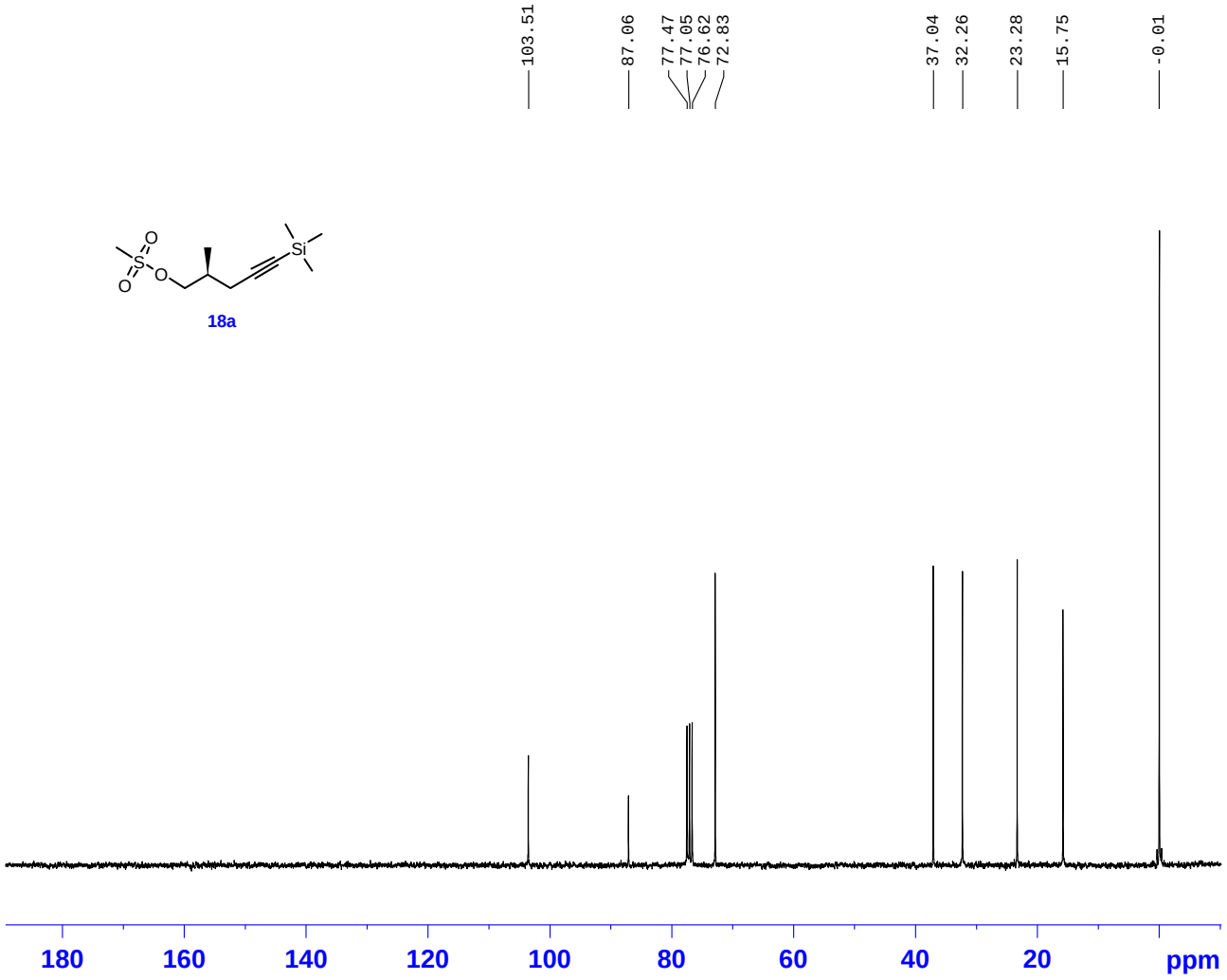
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S
O
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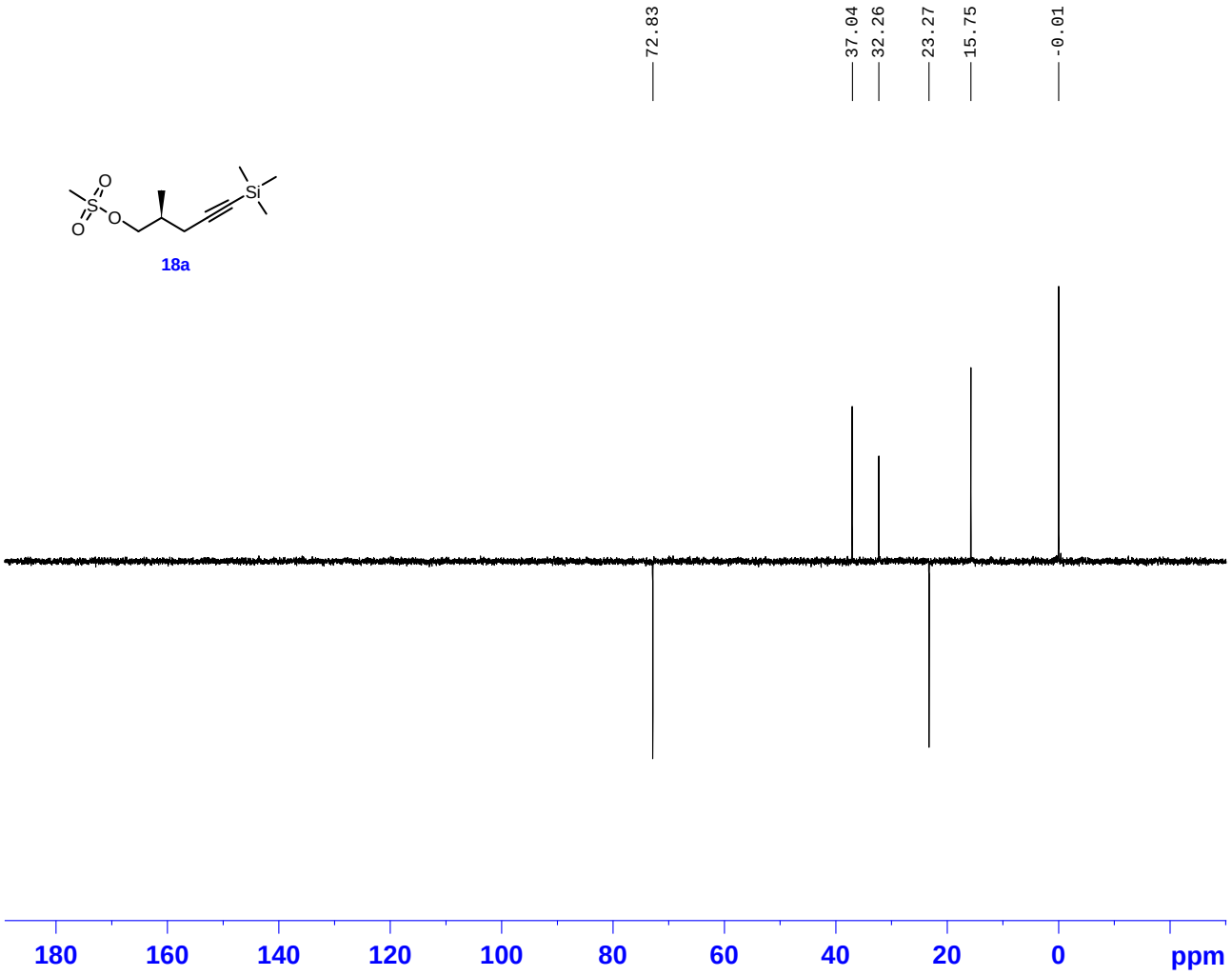
ppm

18a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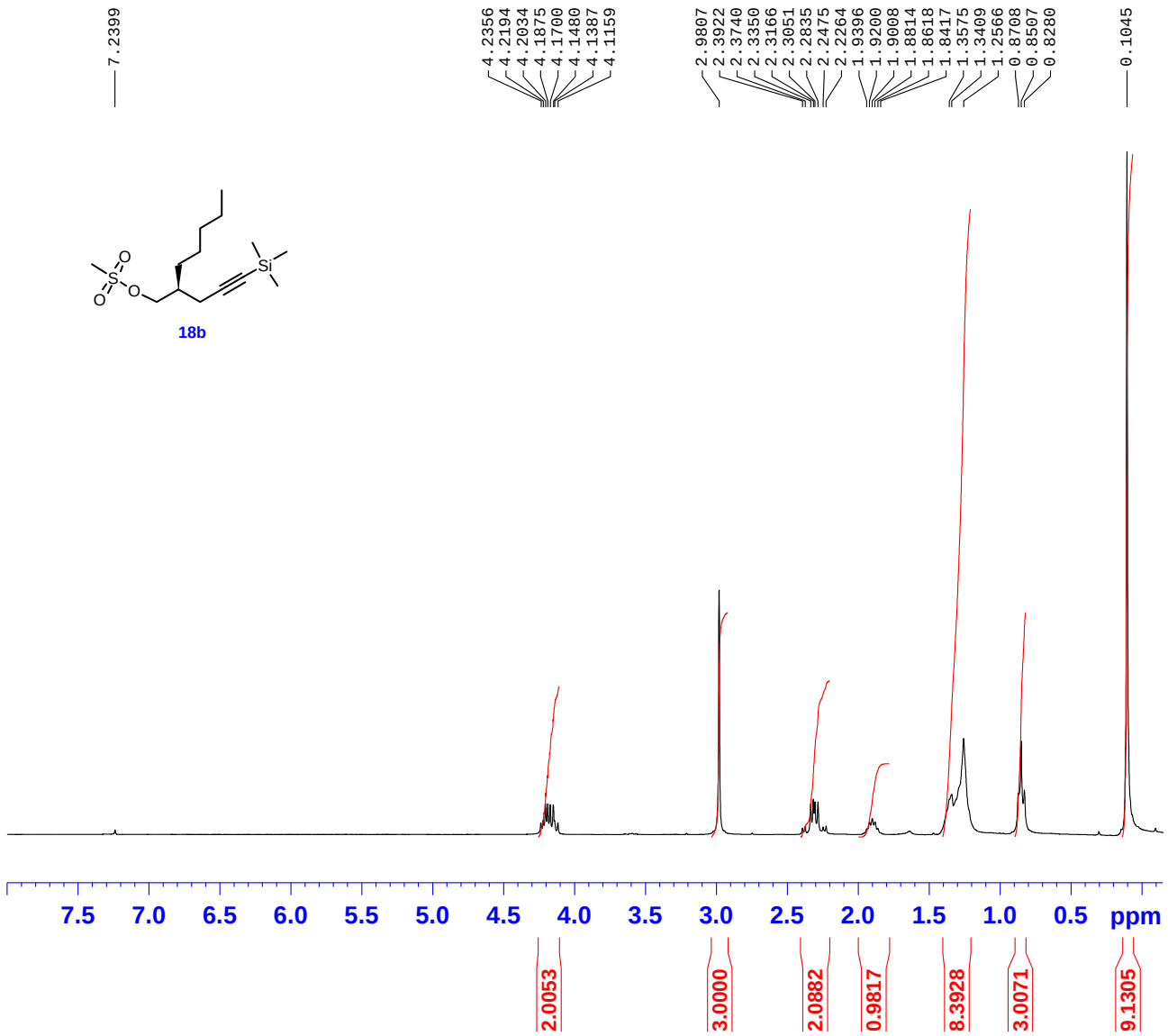
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2.3740
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2.2835
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O
Si
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4.0
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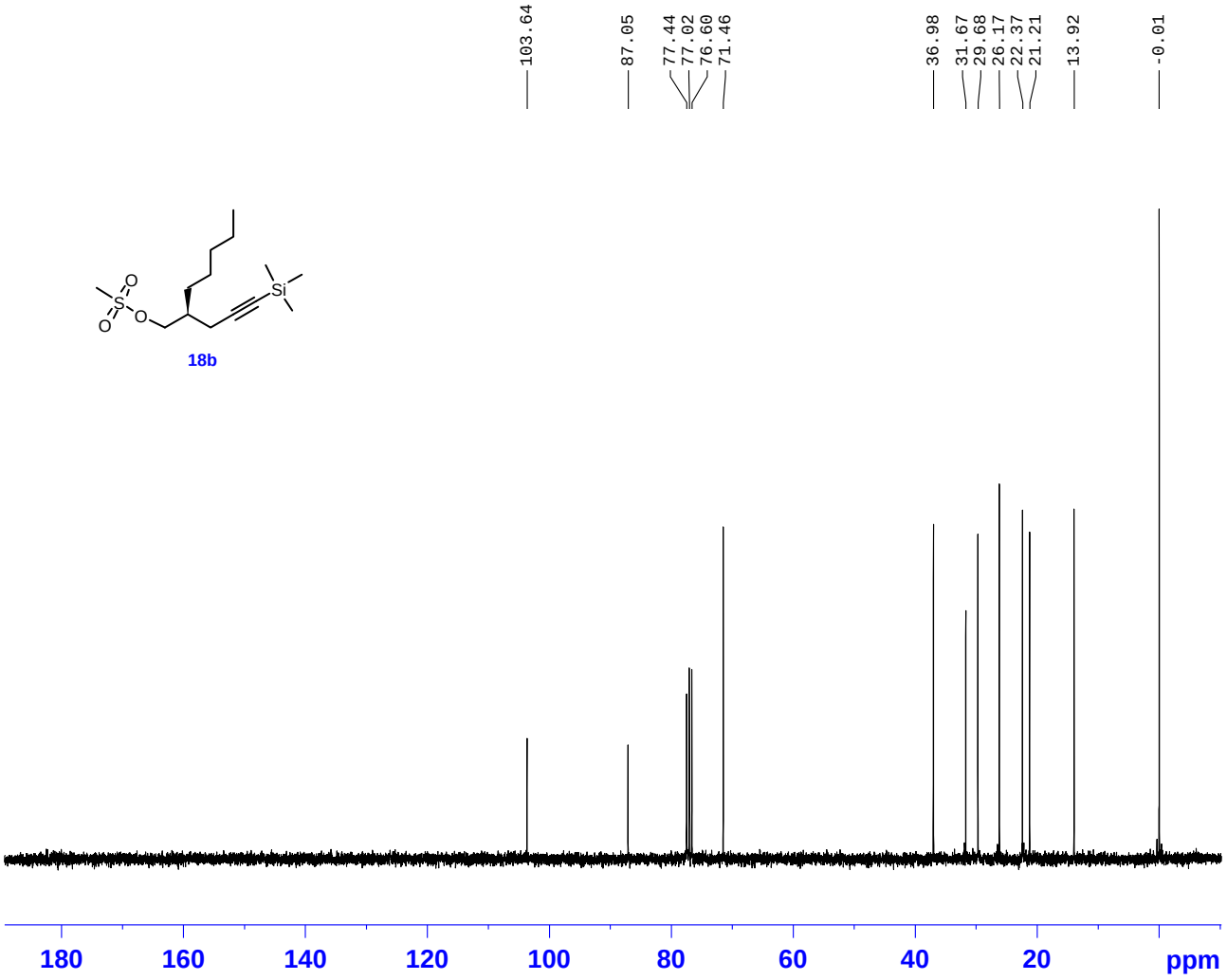
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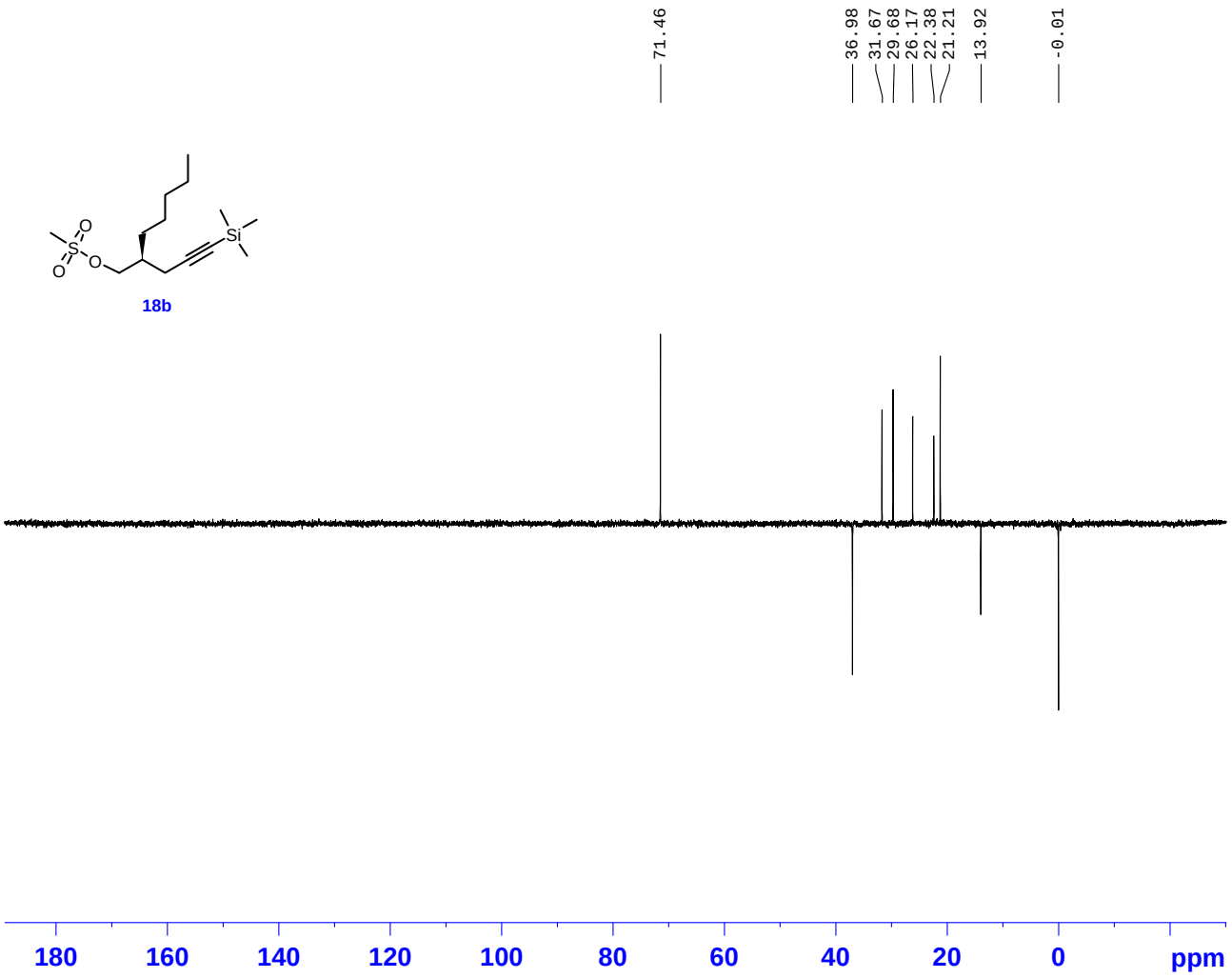
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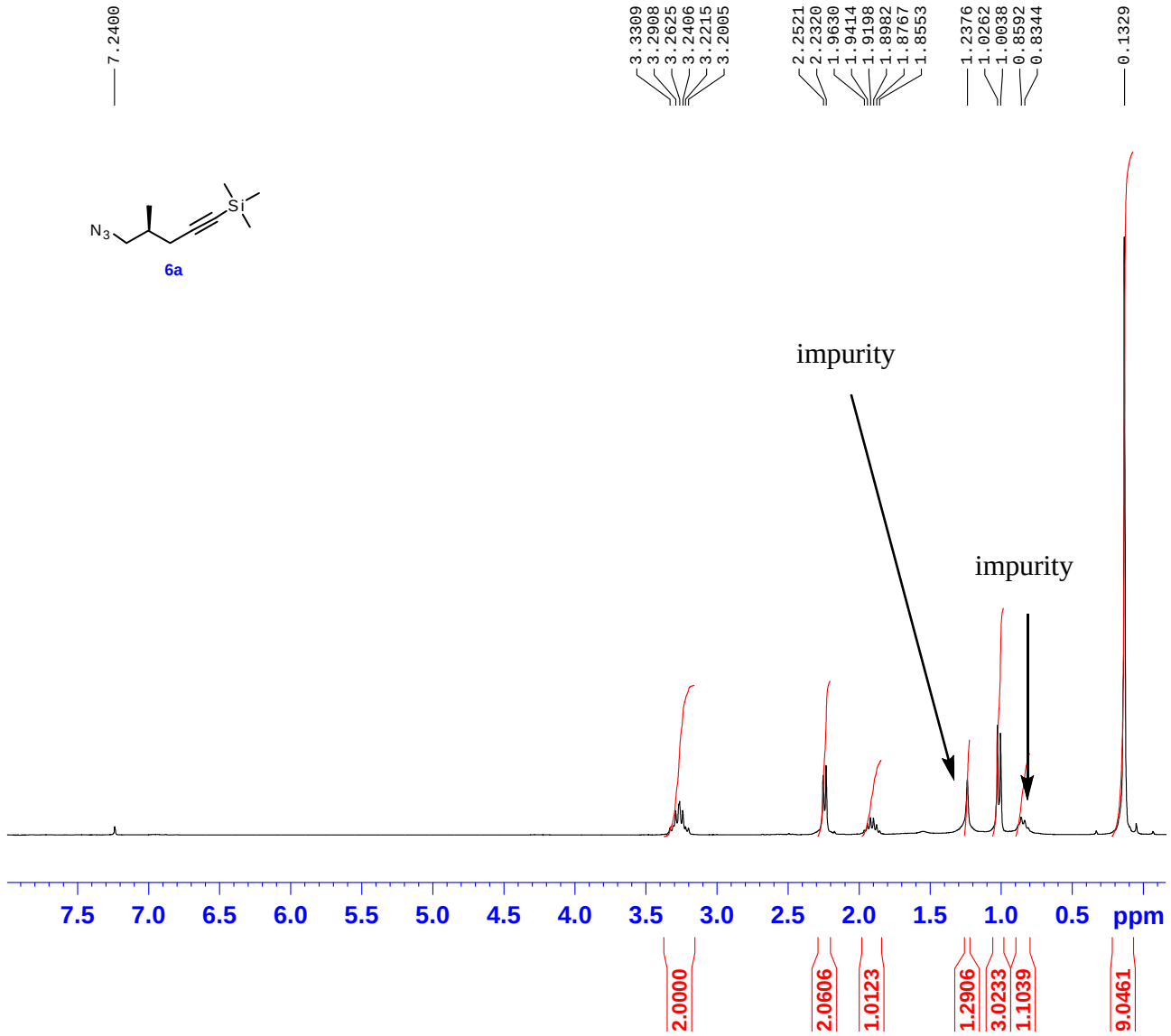
ppm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Si
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impurity
impurity
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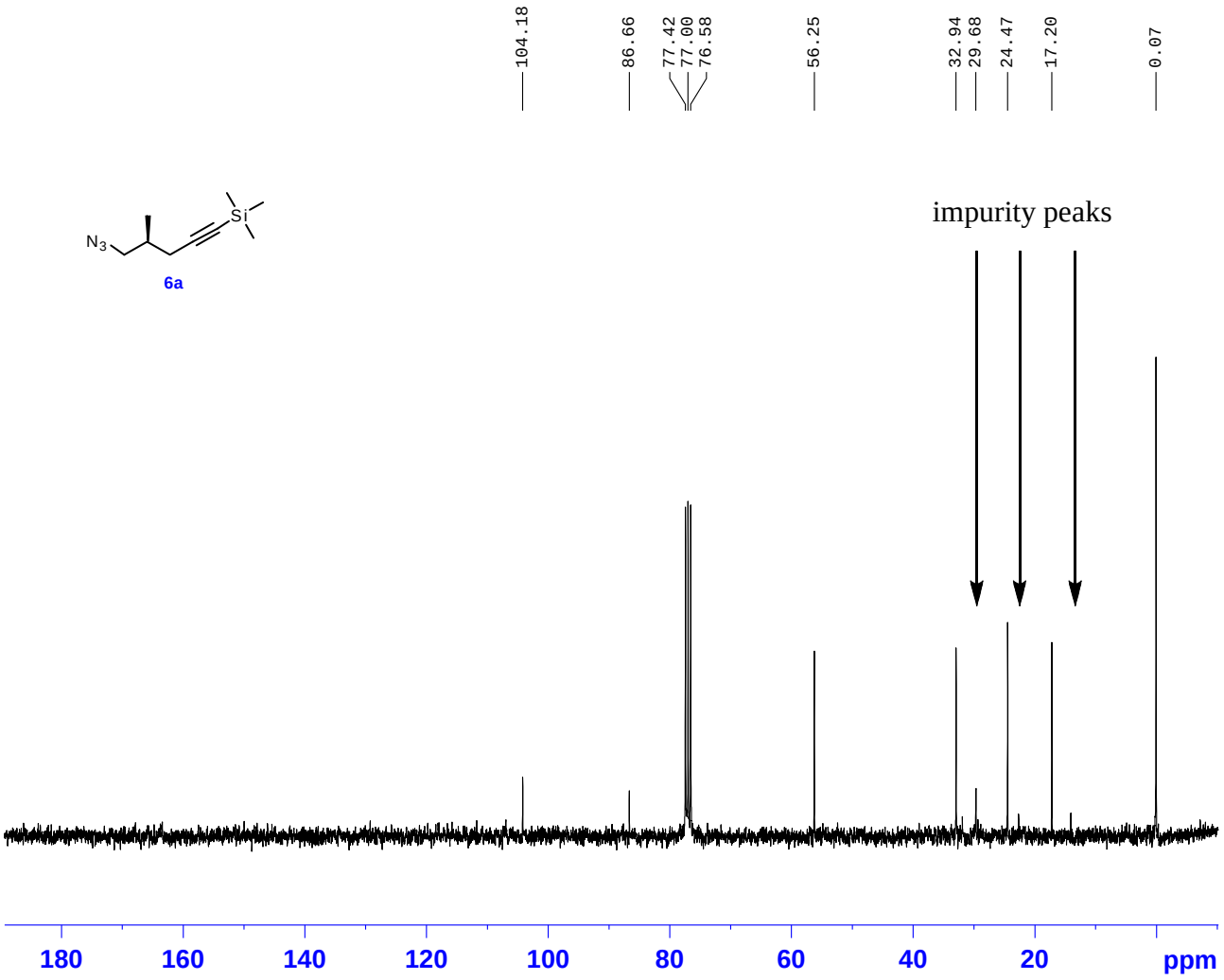
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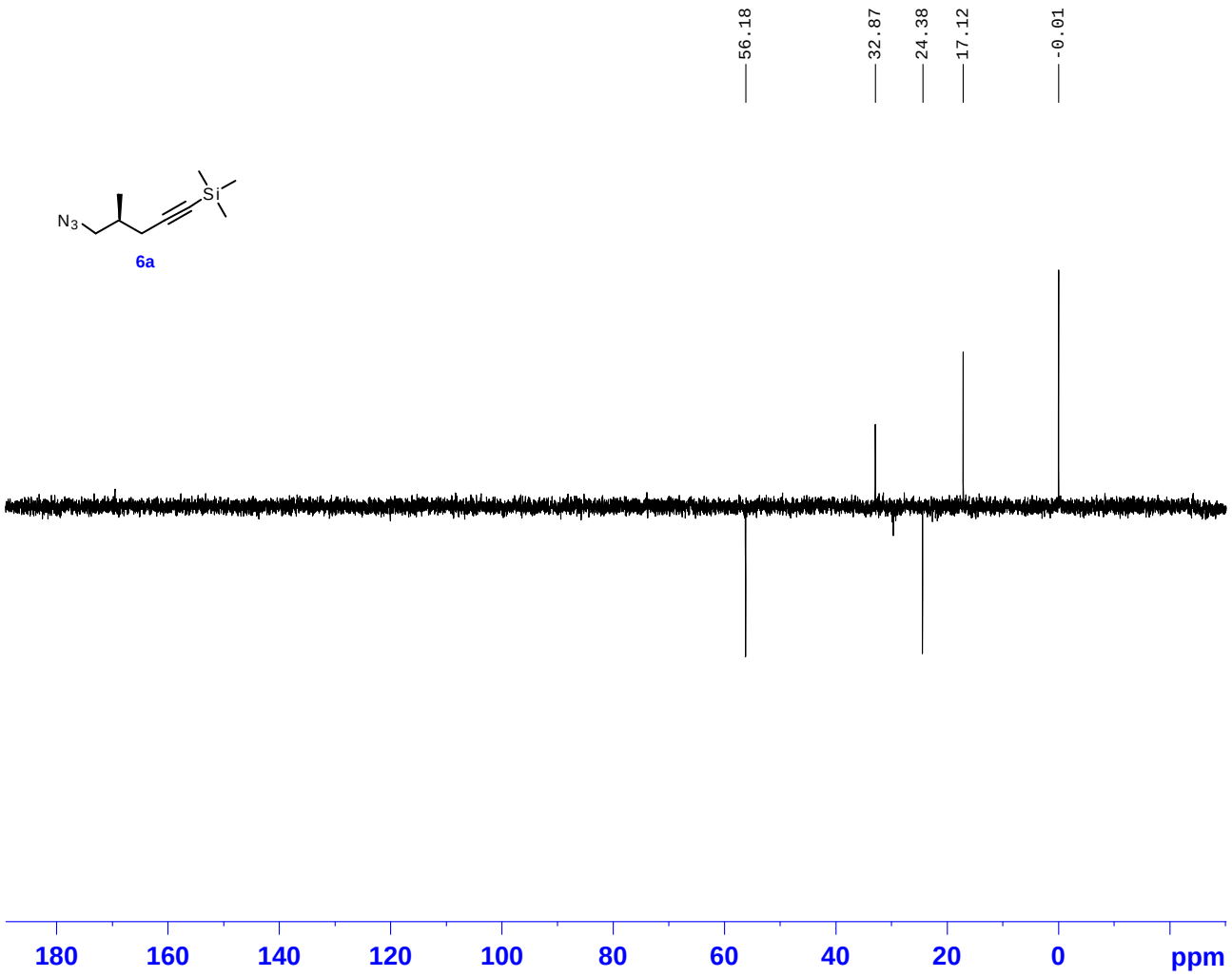
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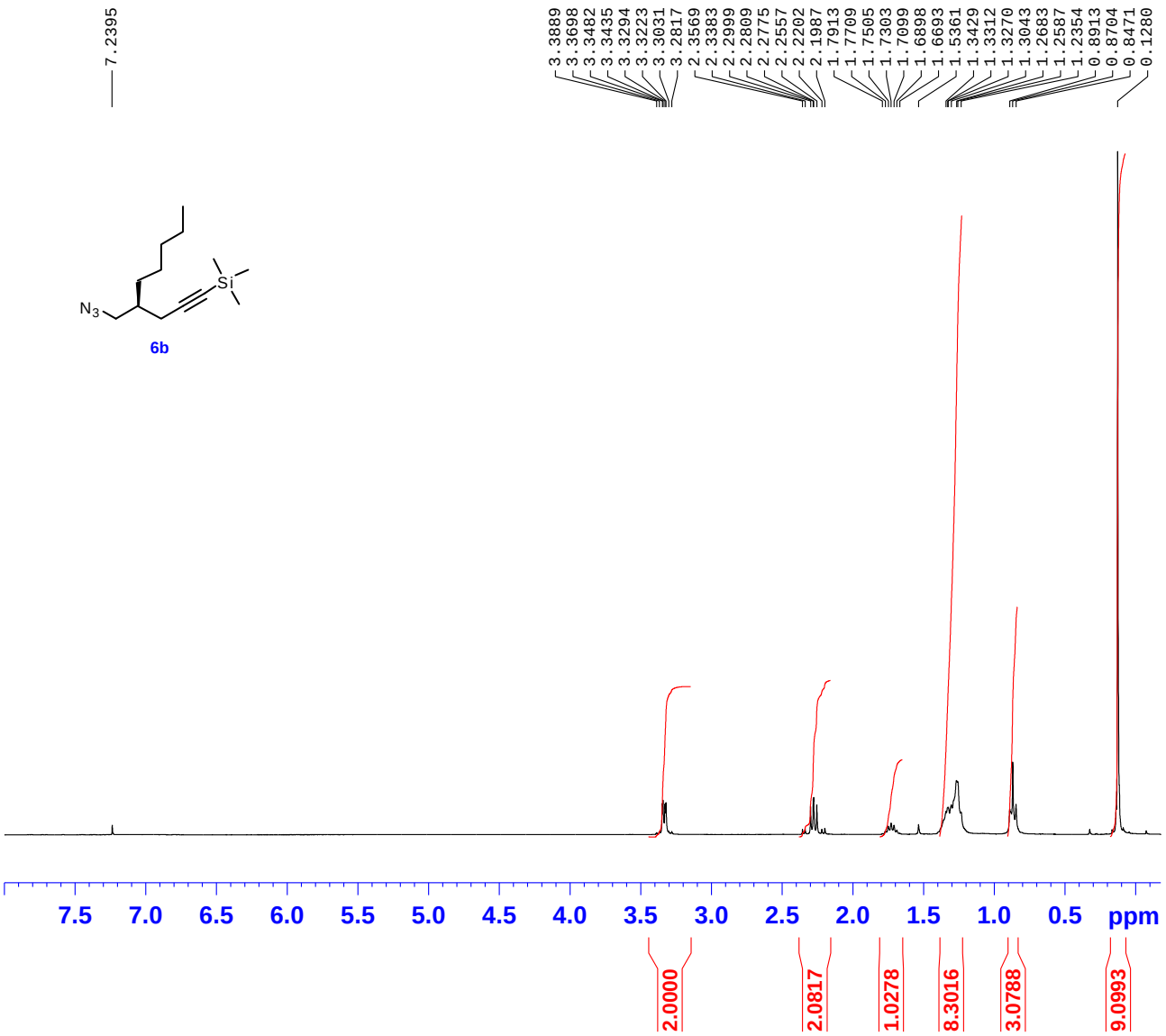
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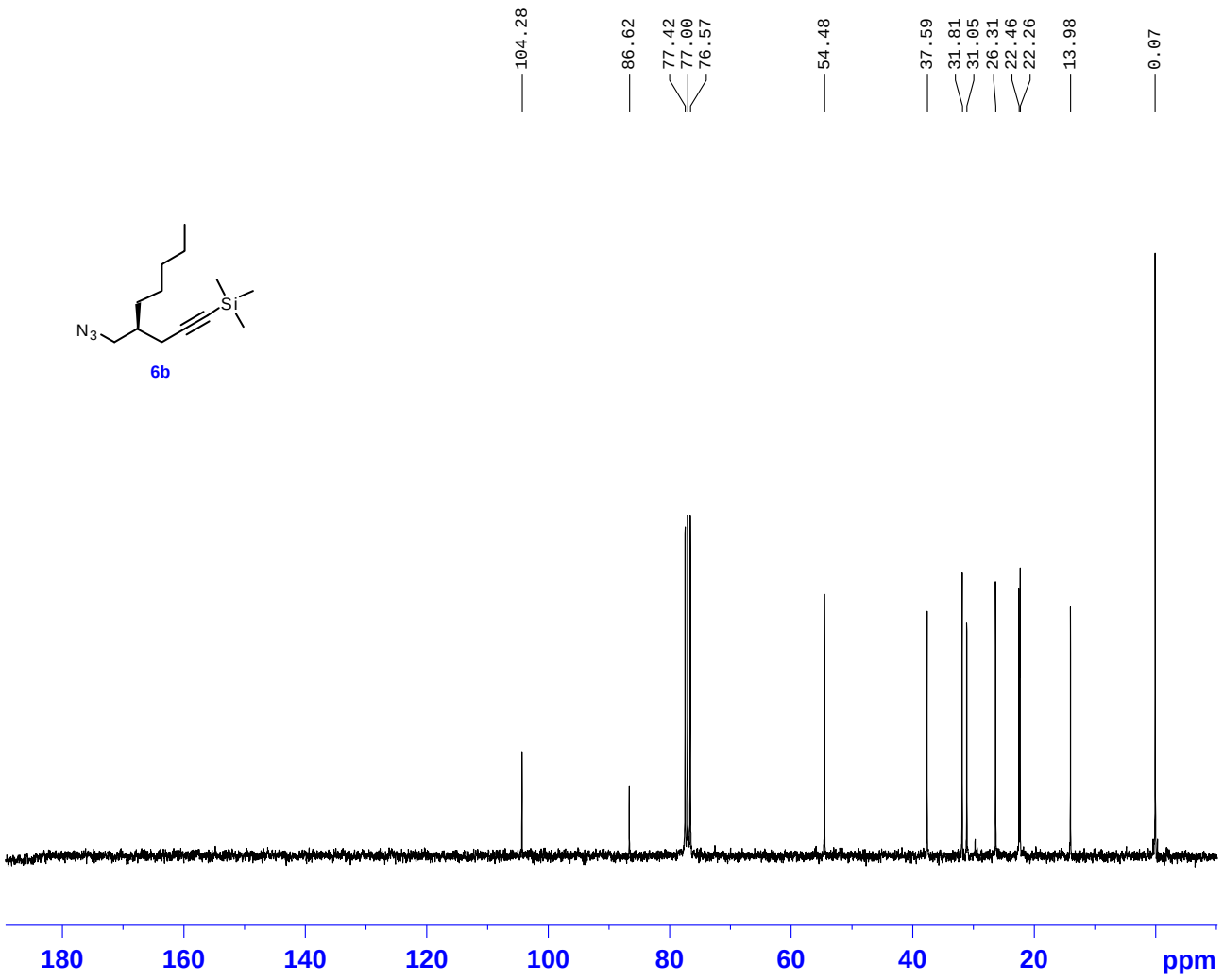
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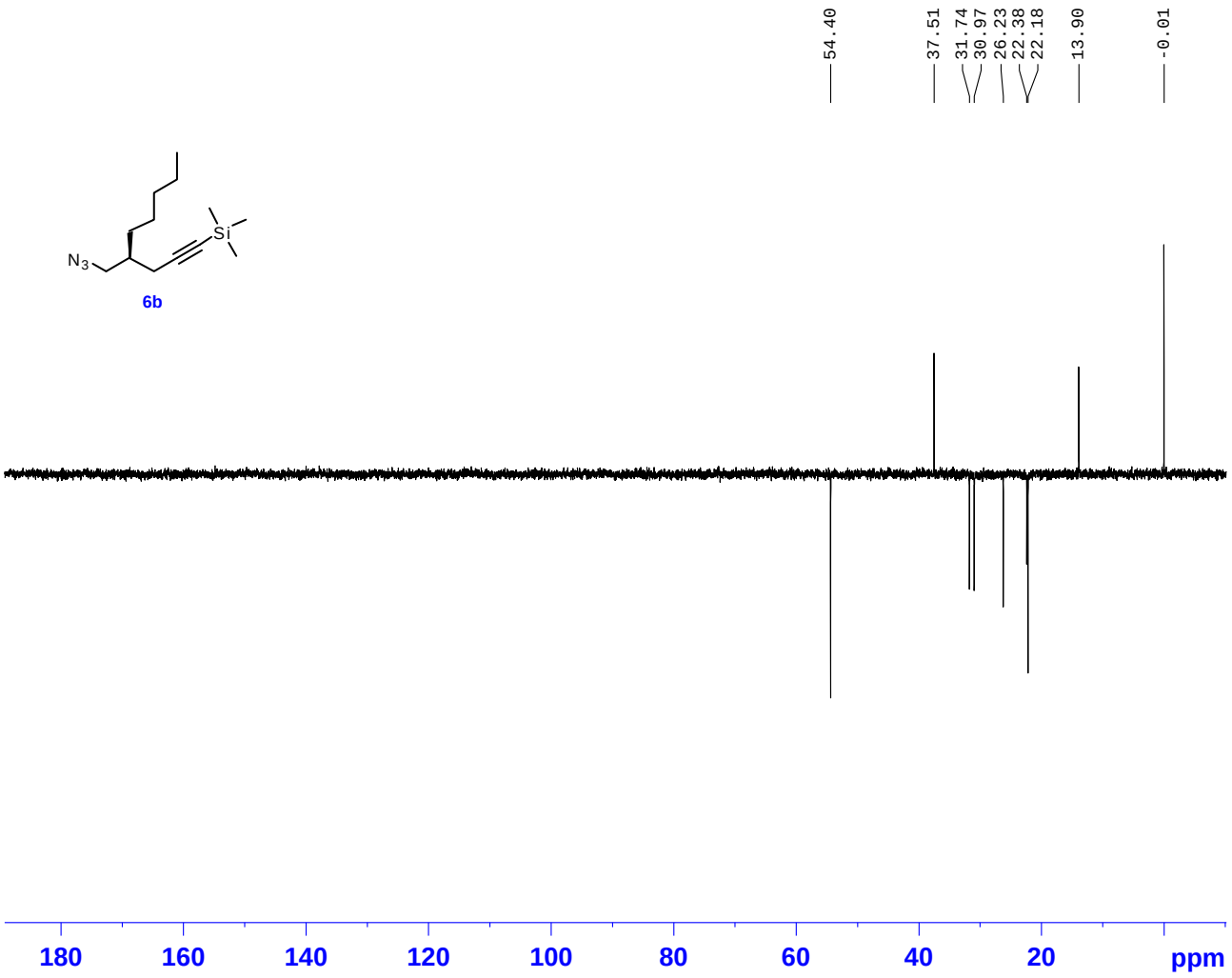
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20
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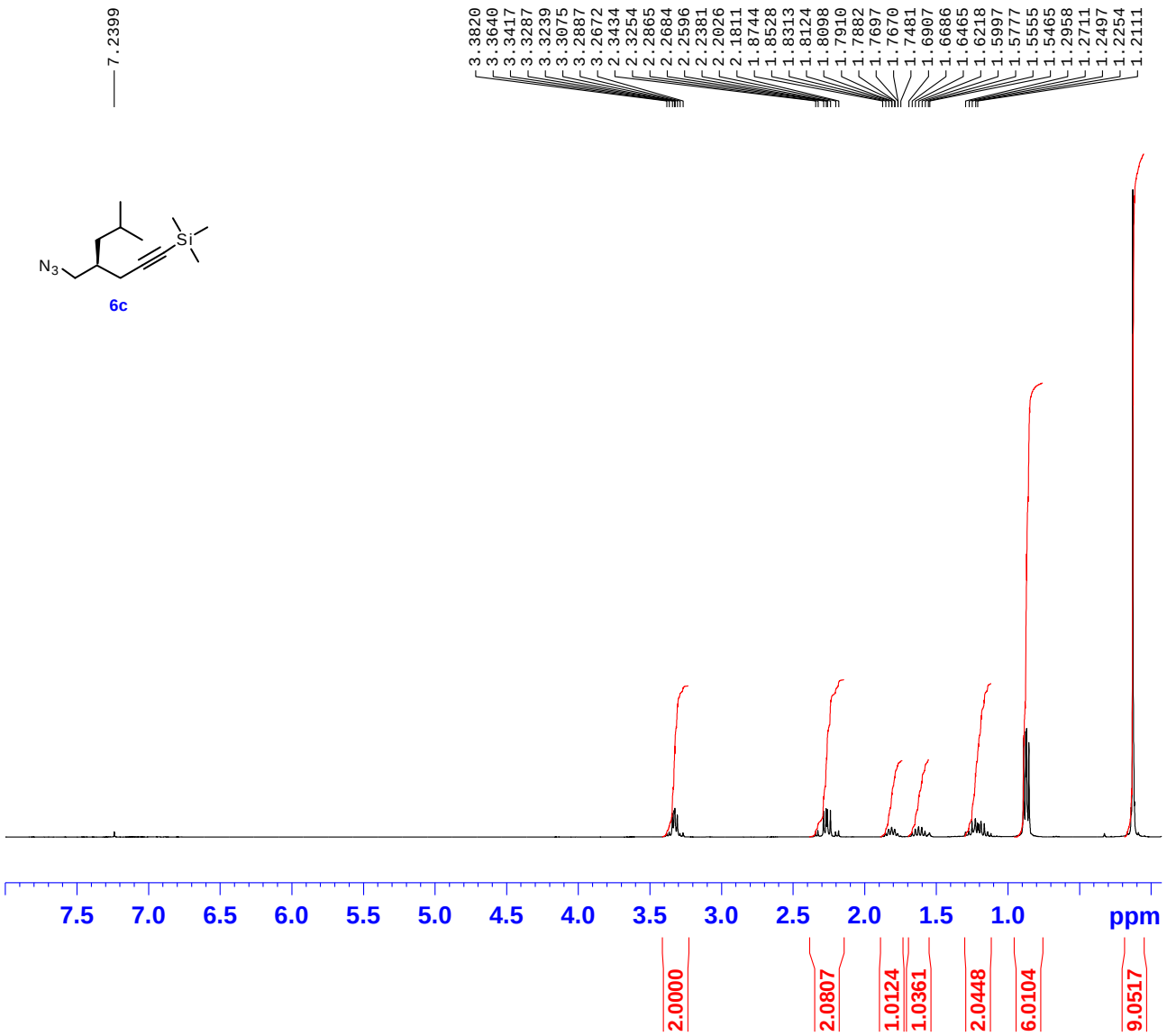
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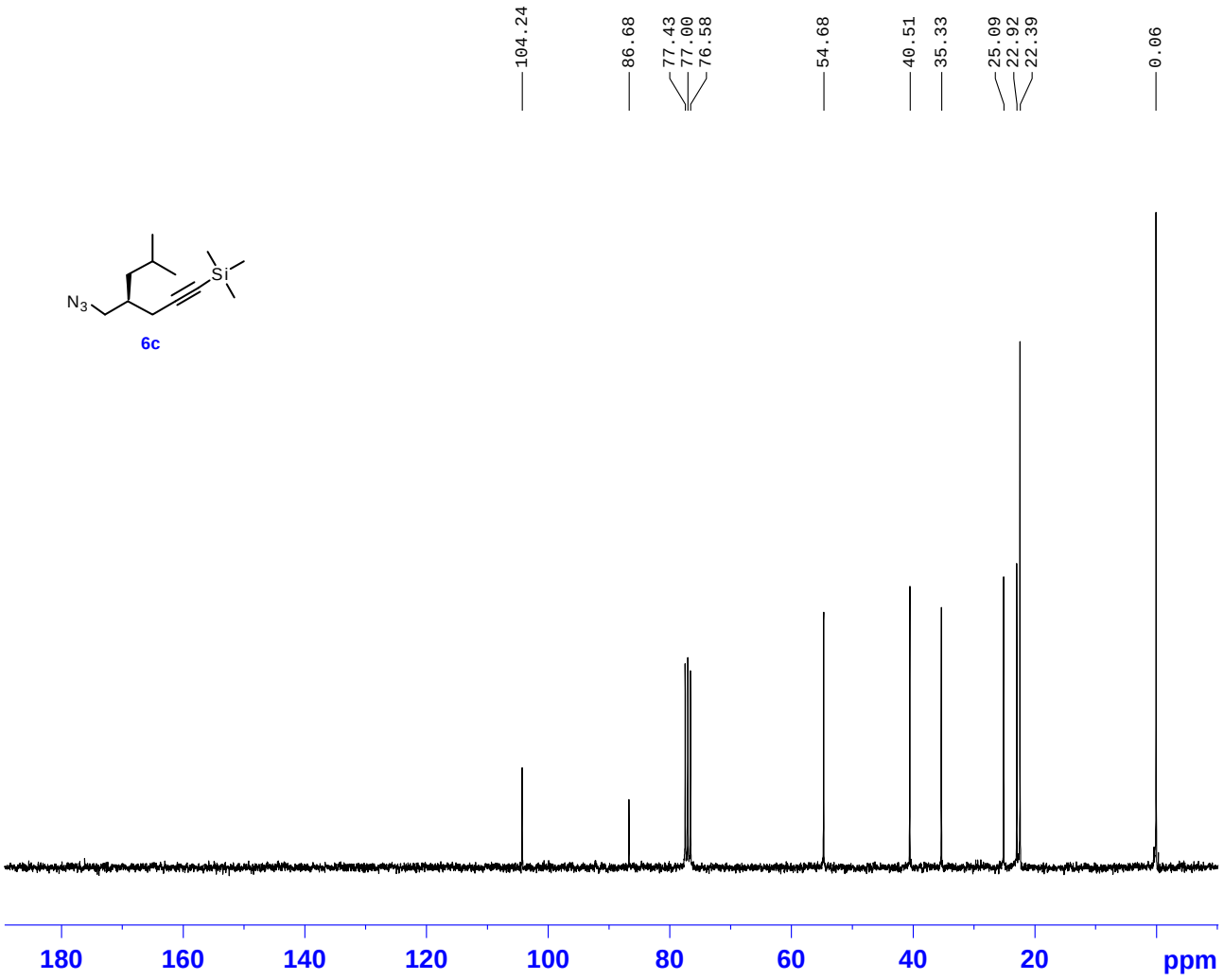
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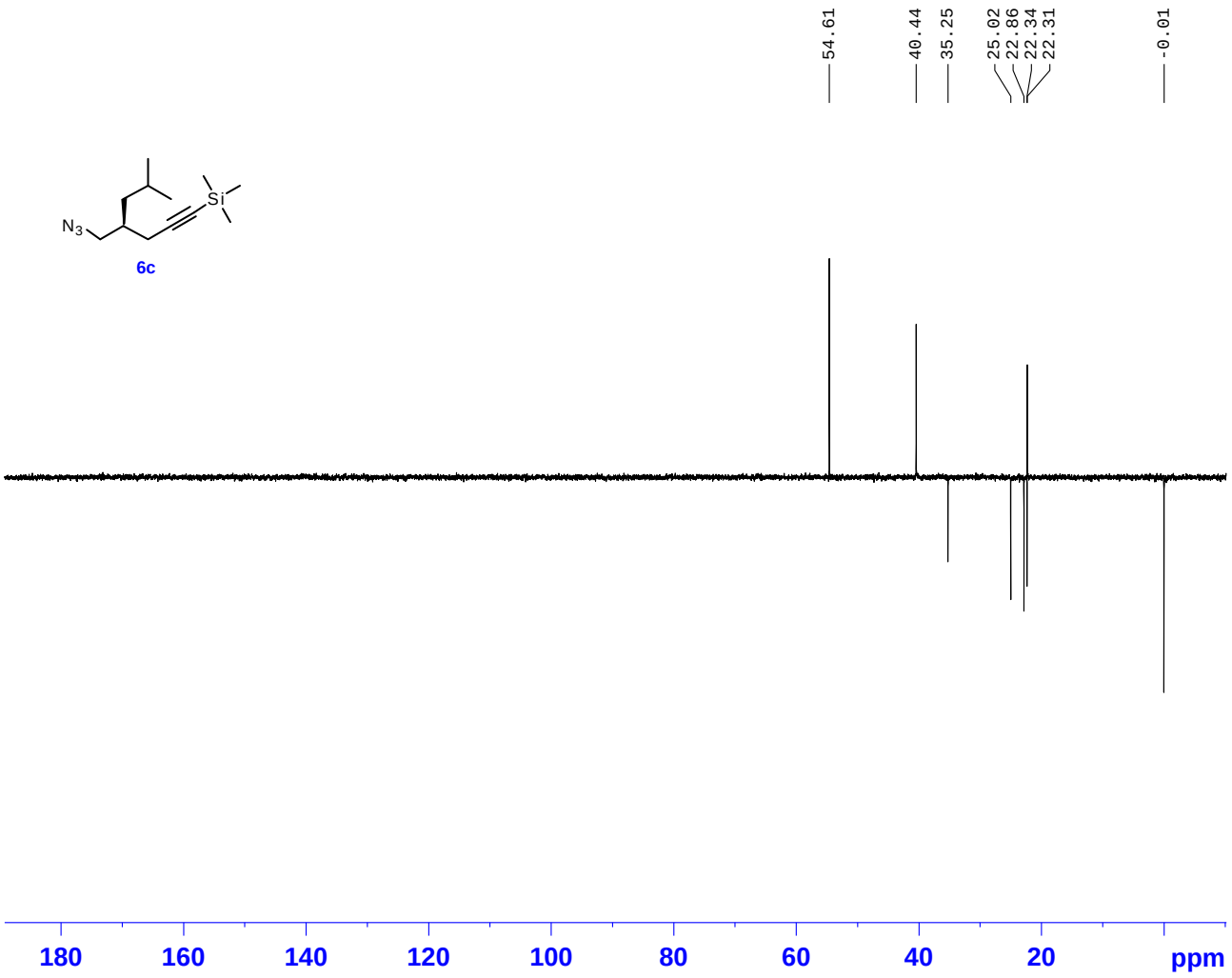
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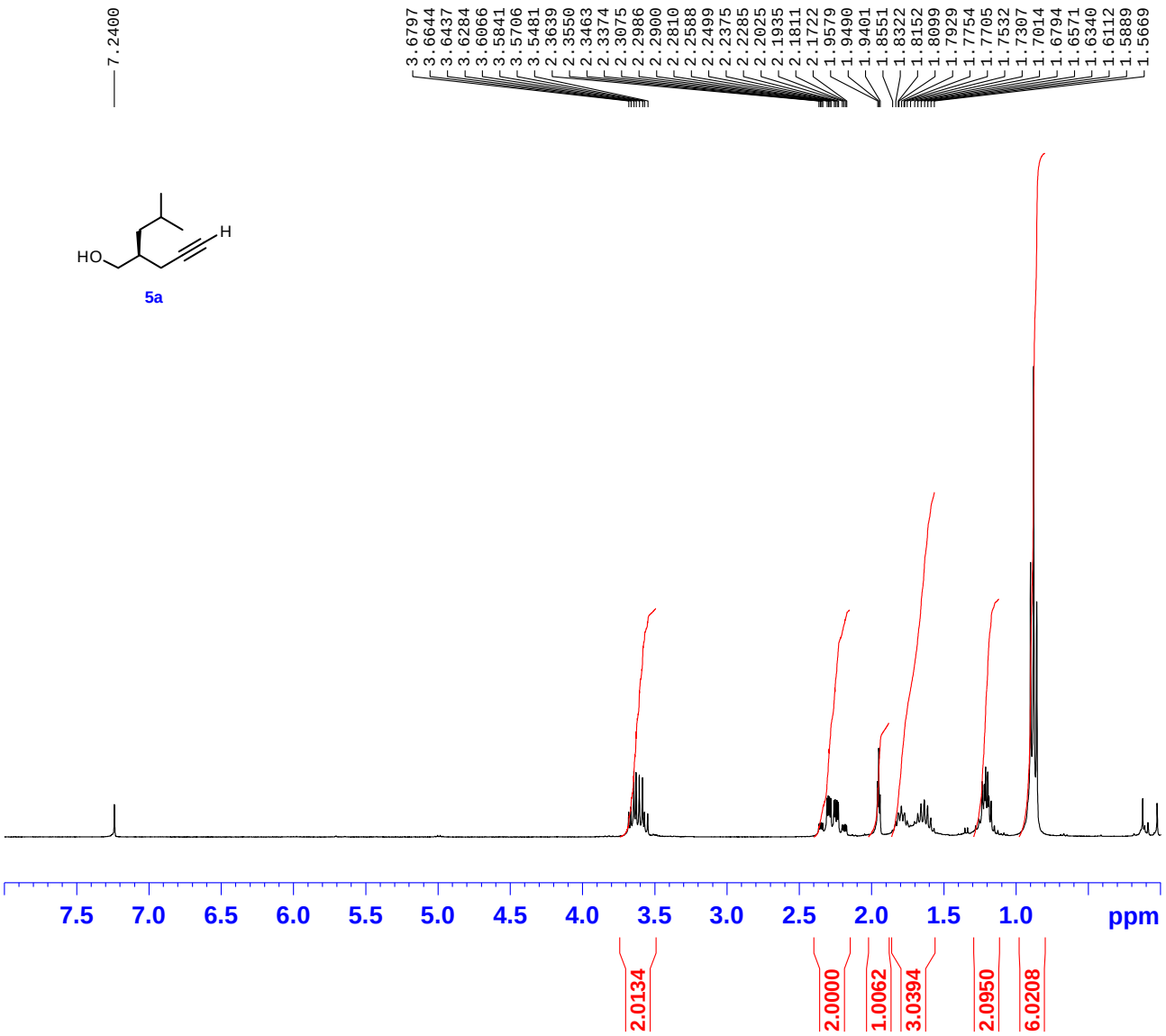
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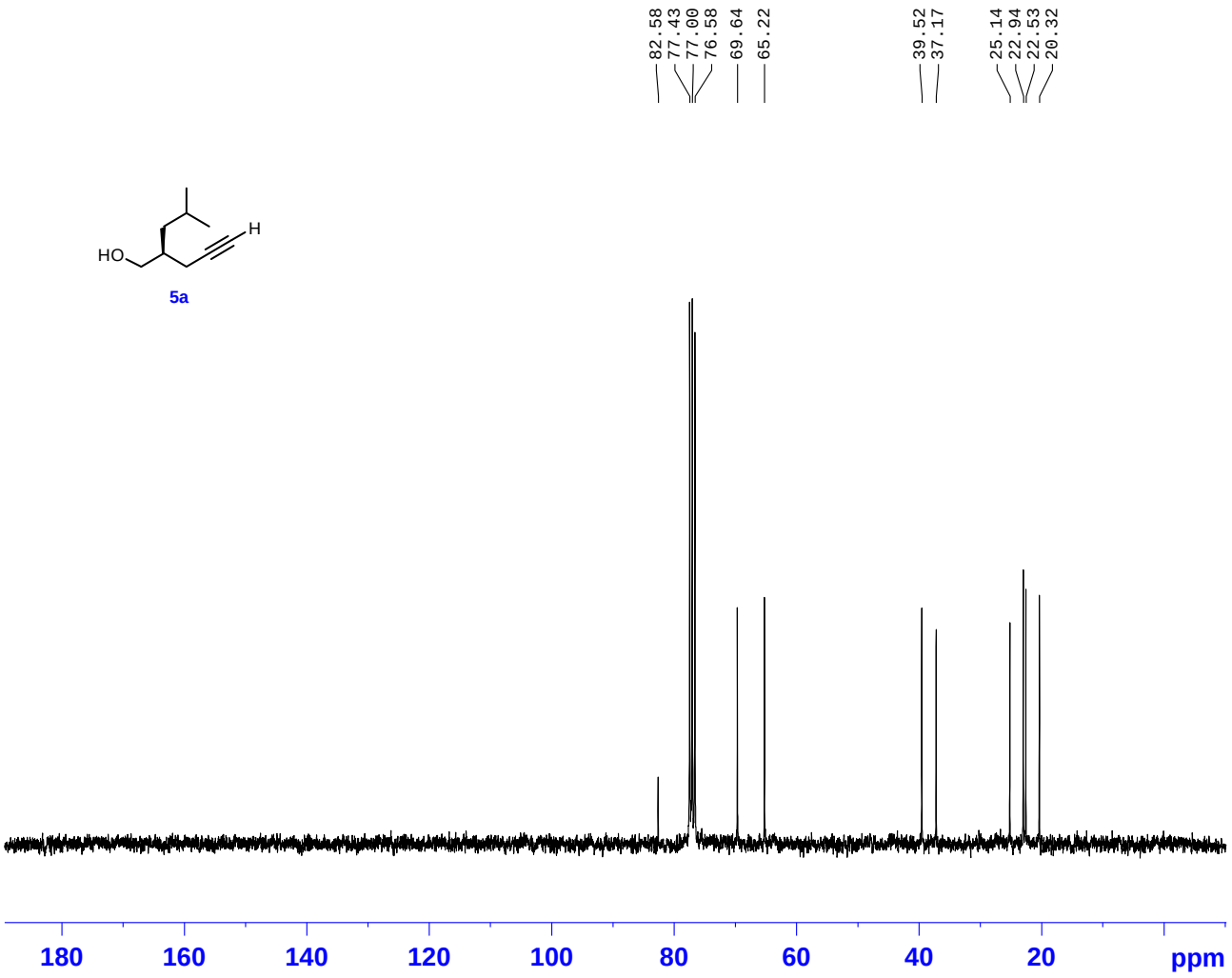
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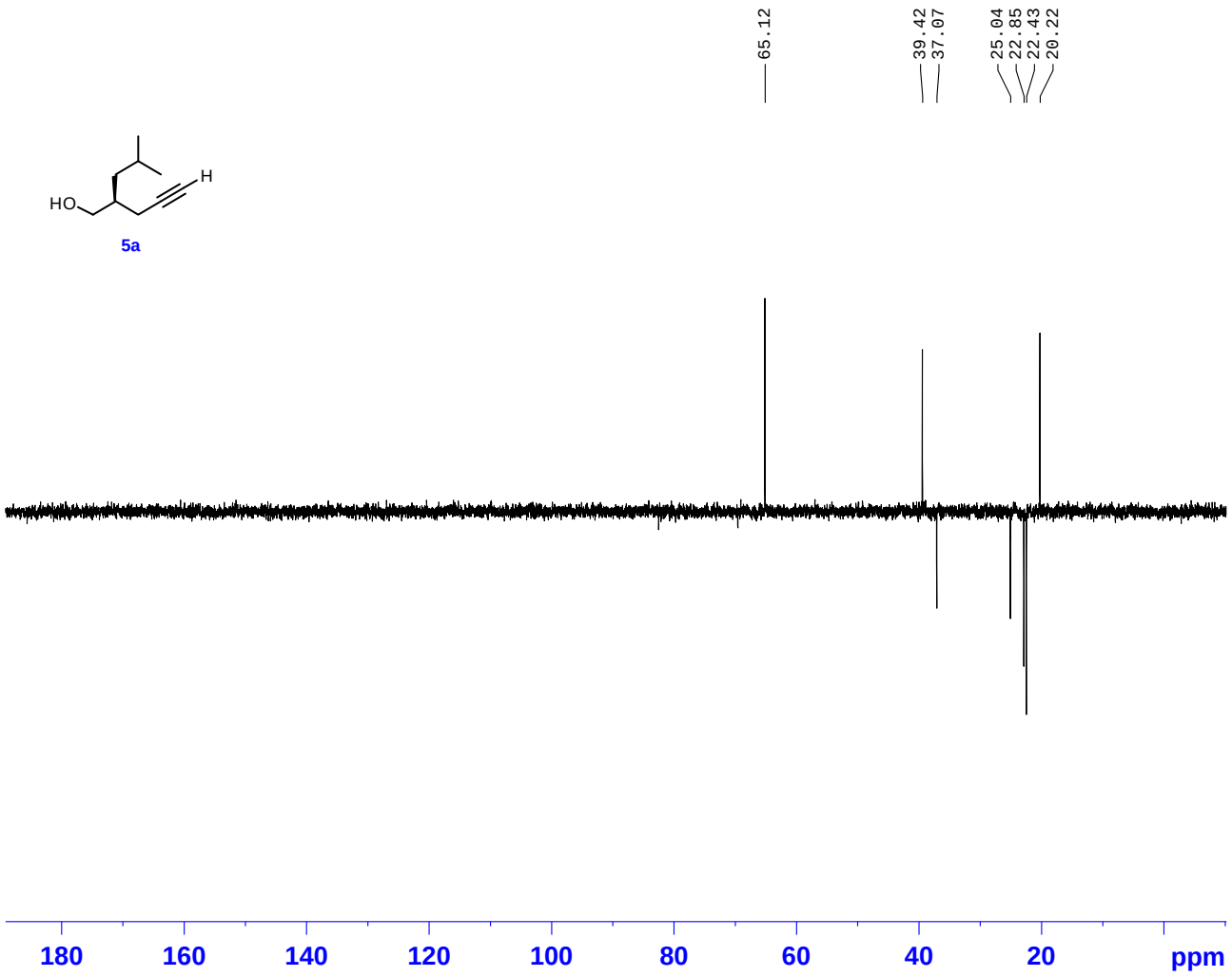
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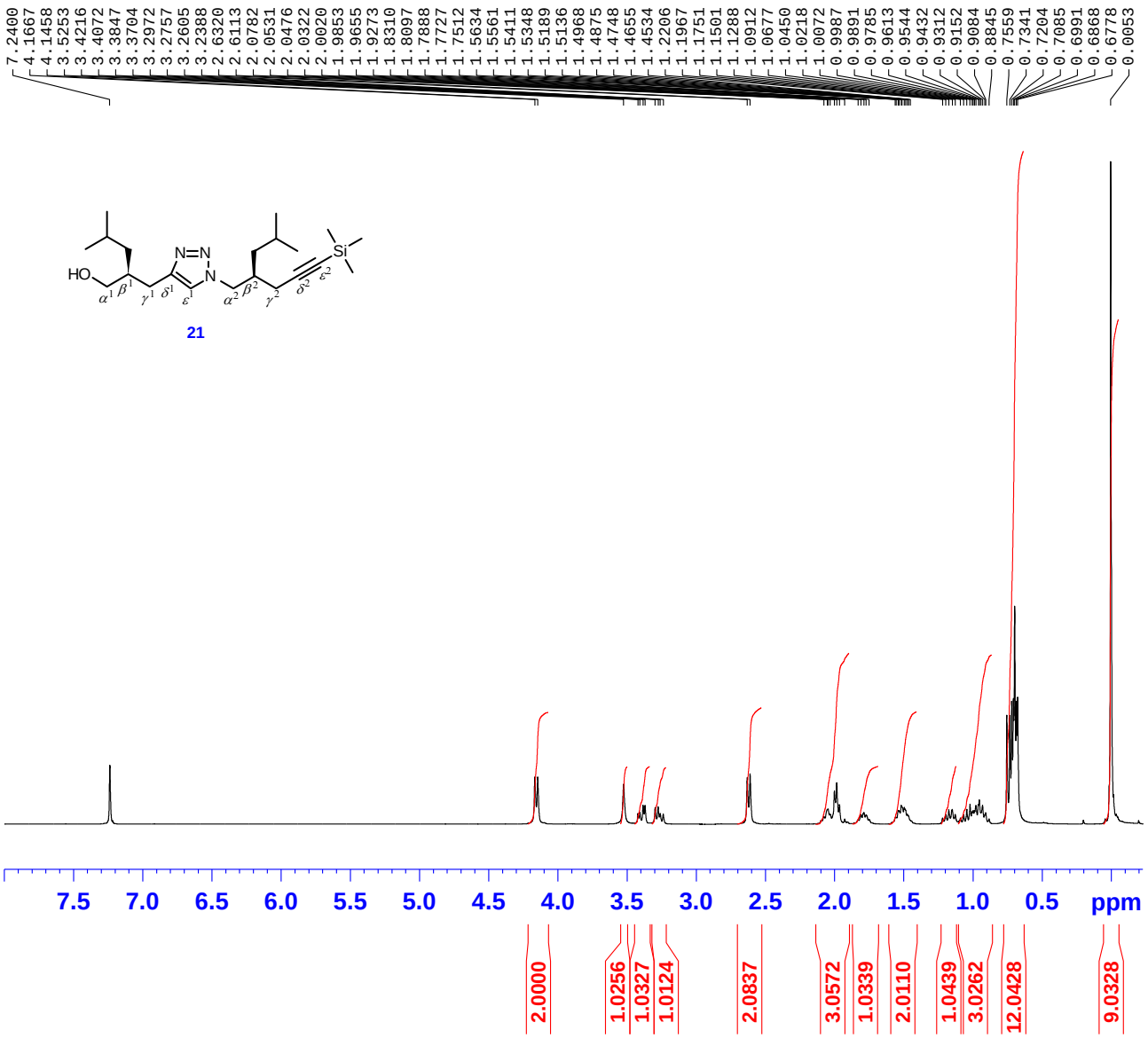
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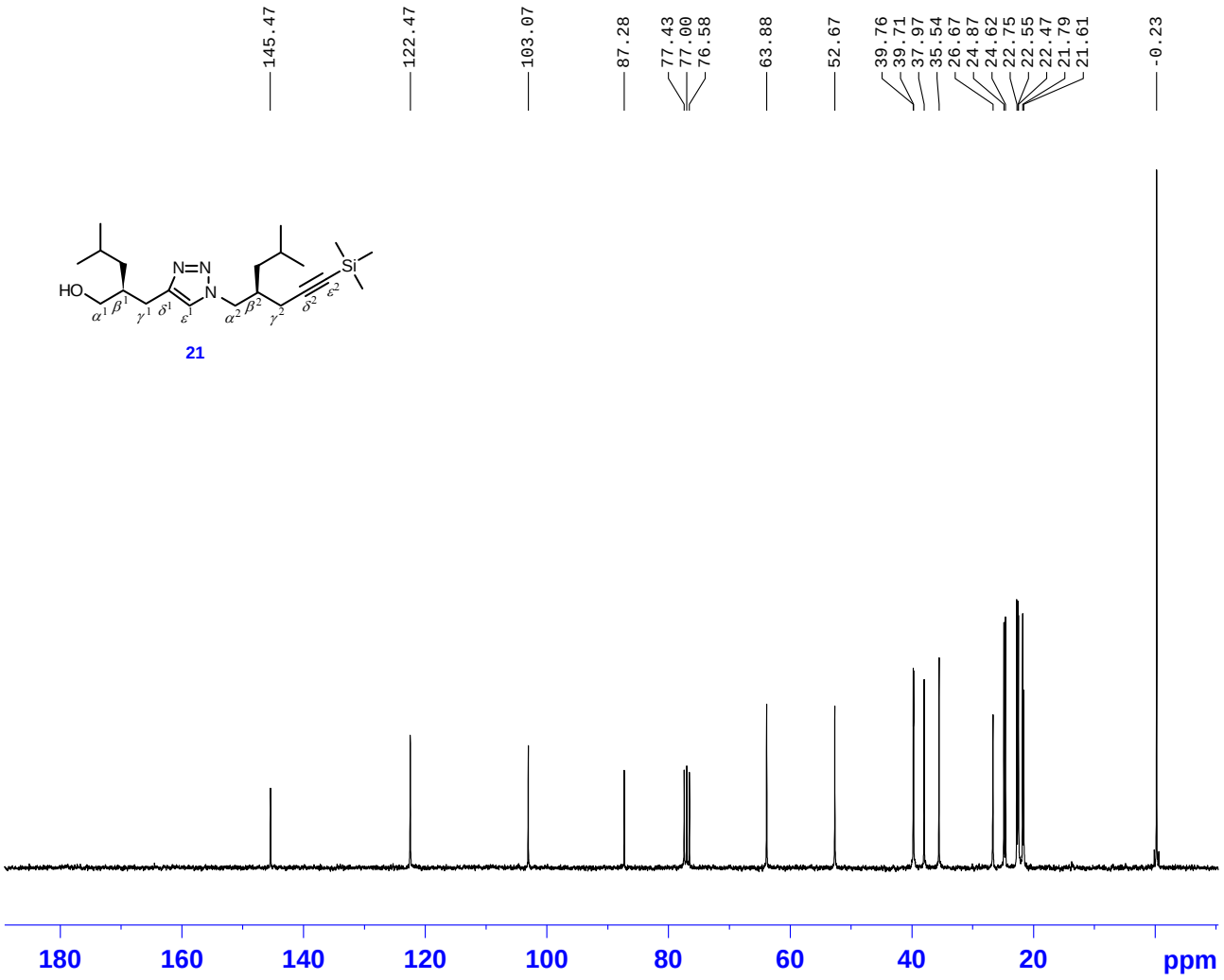
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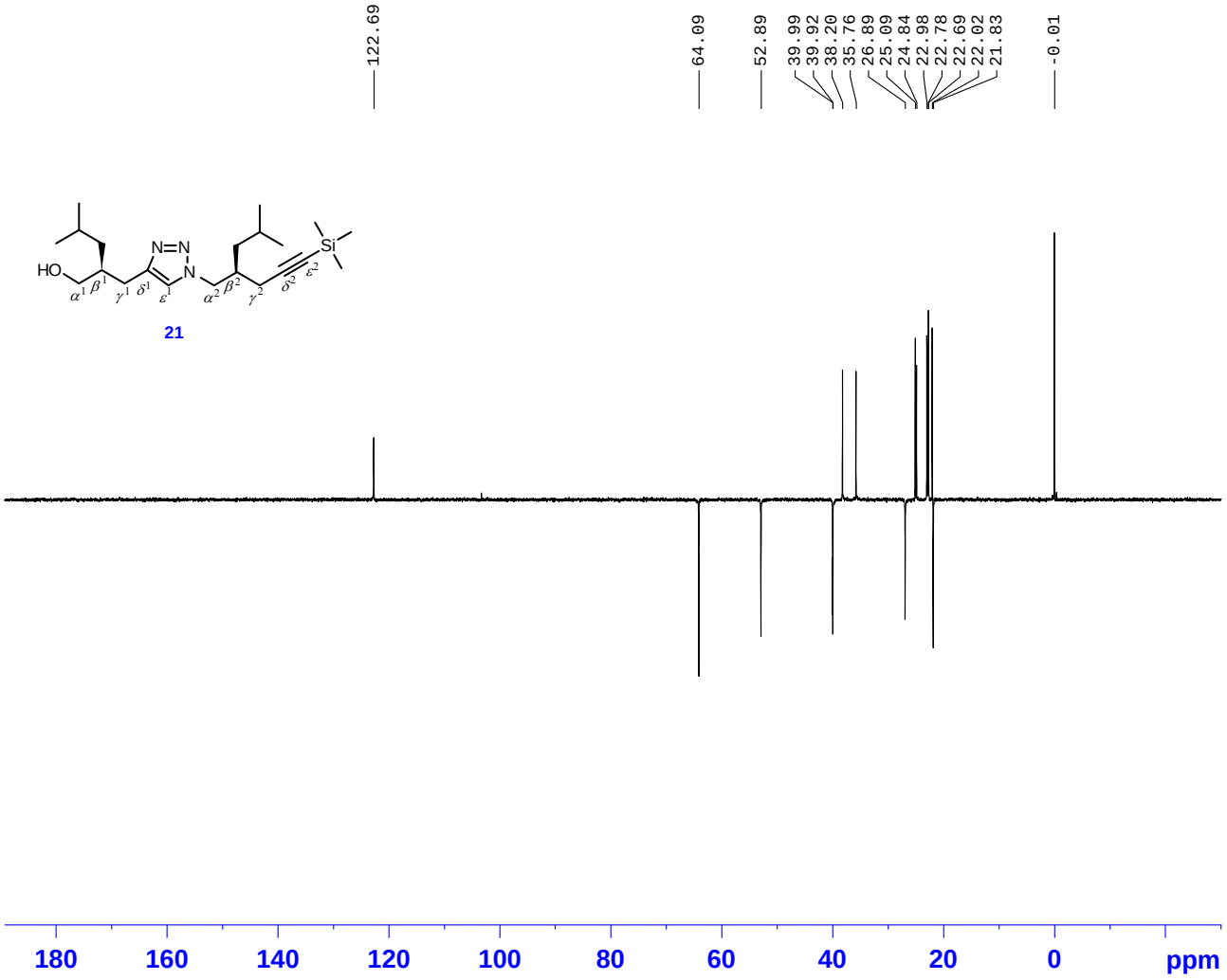
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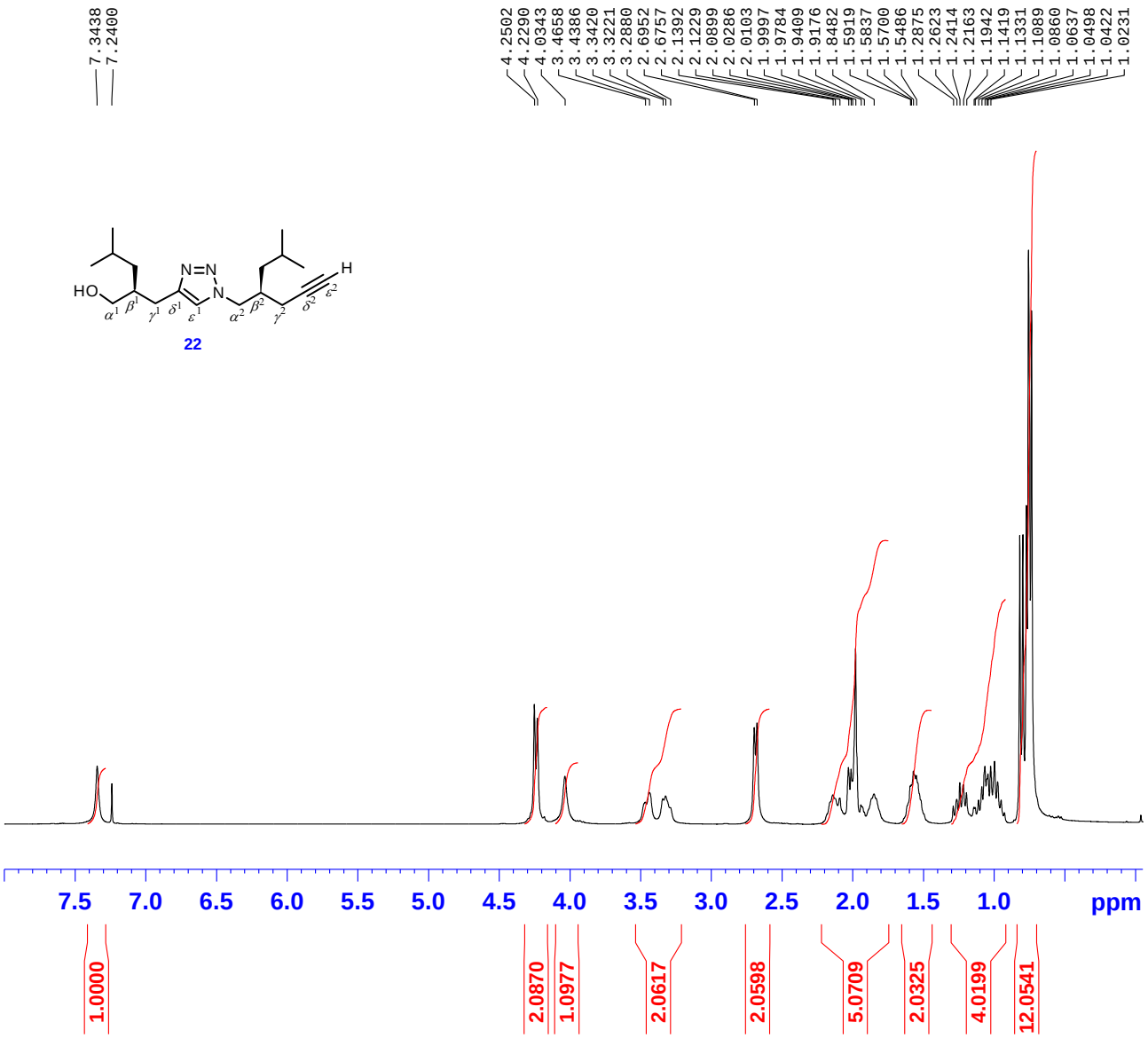
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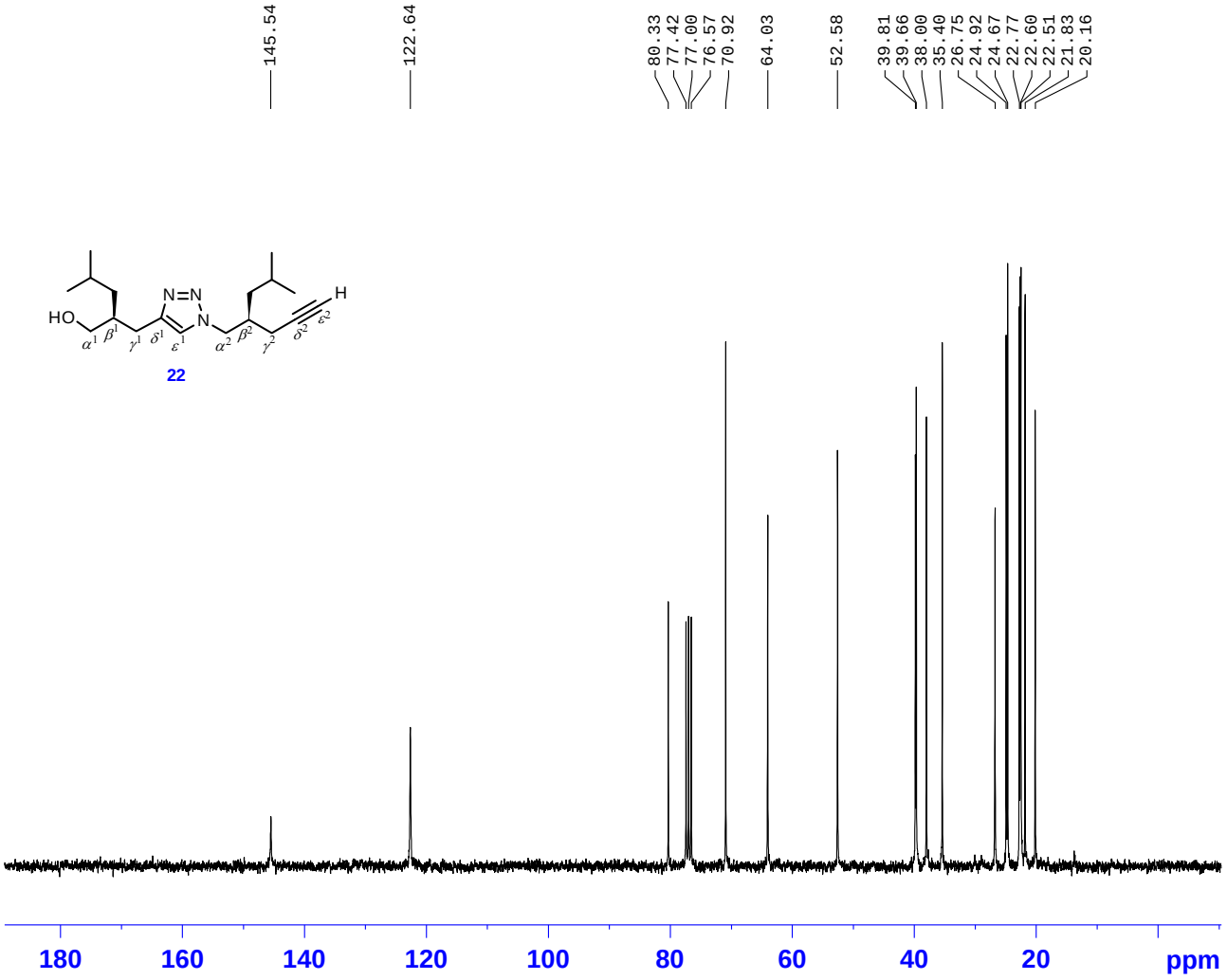
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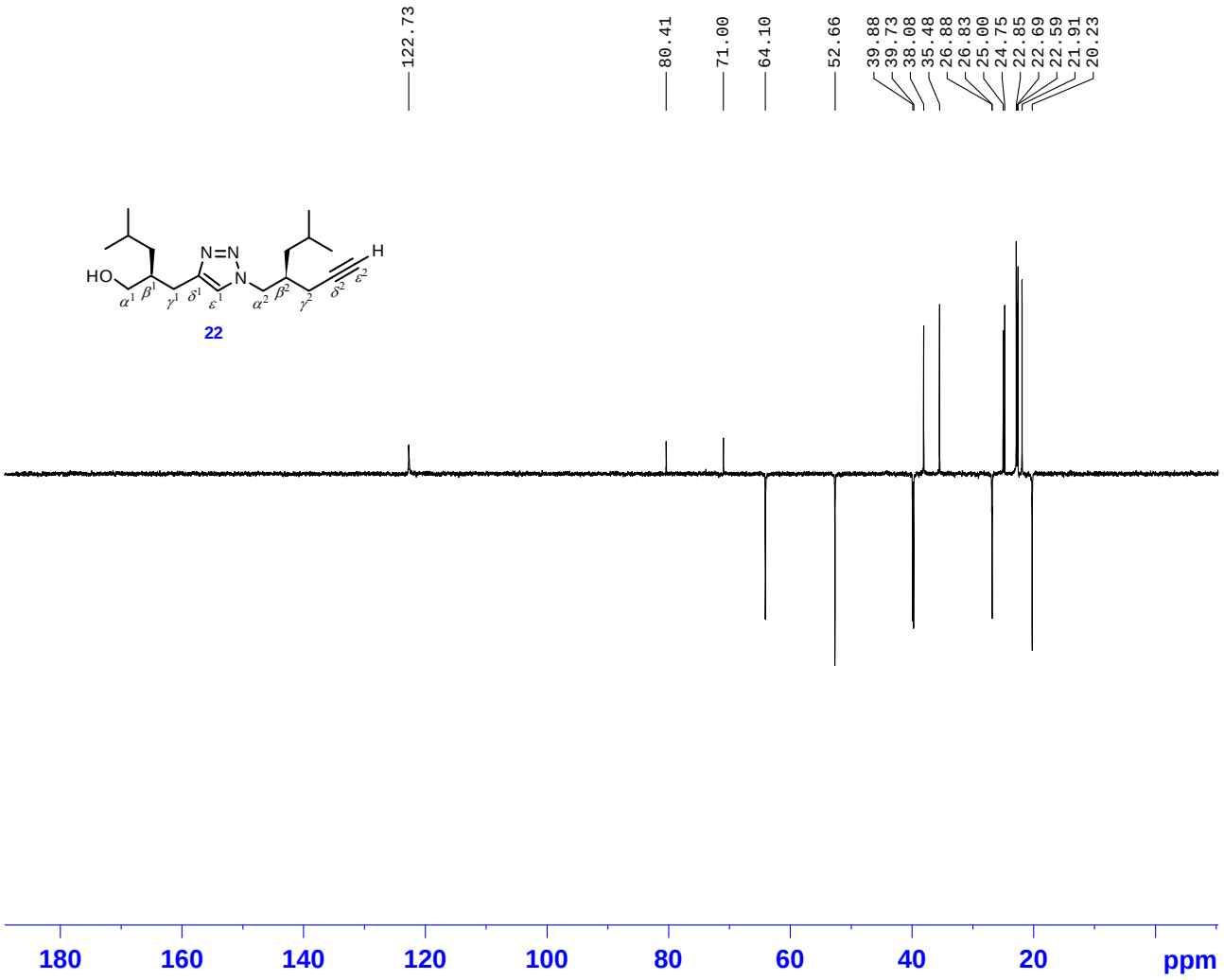
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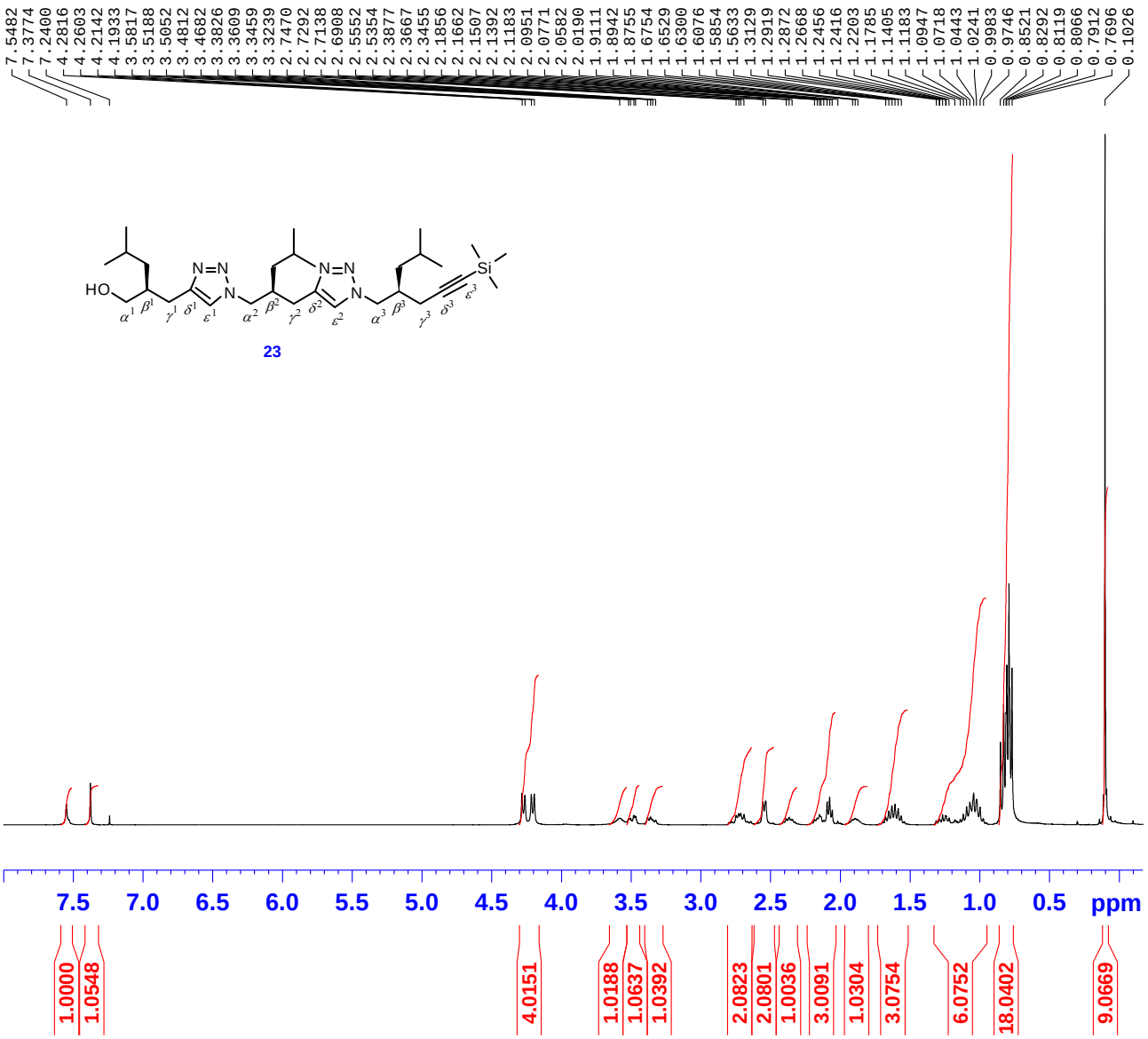
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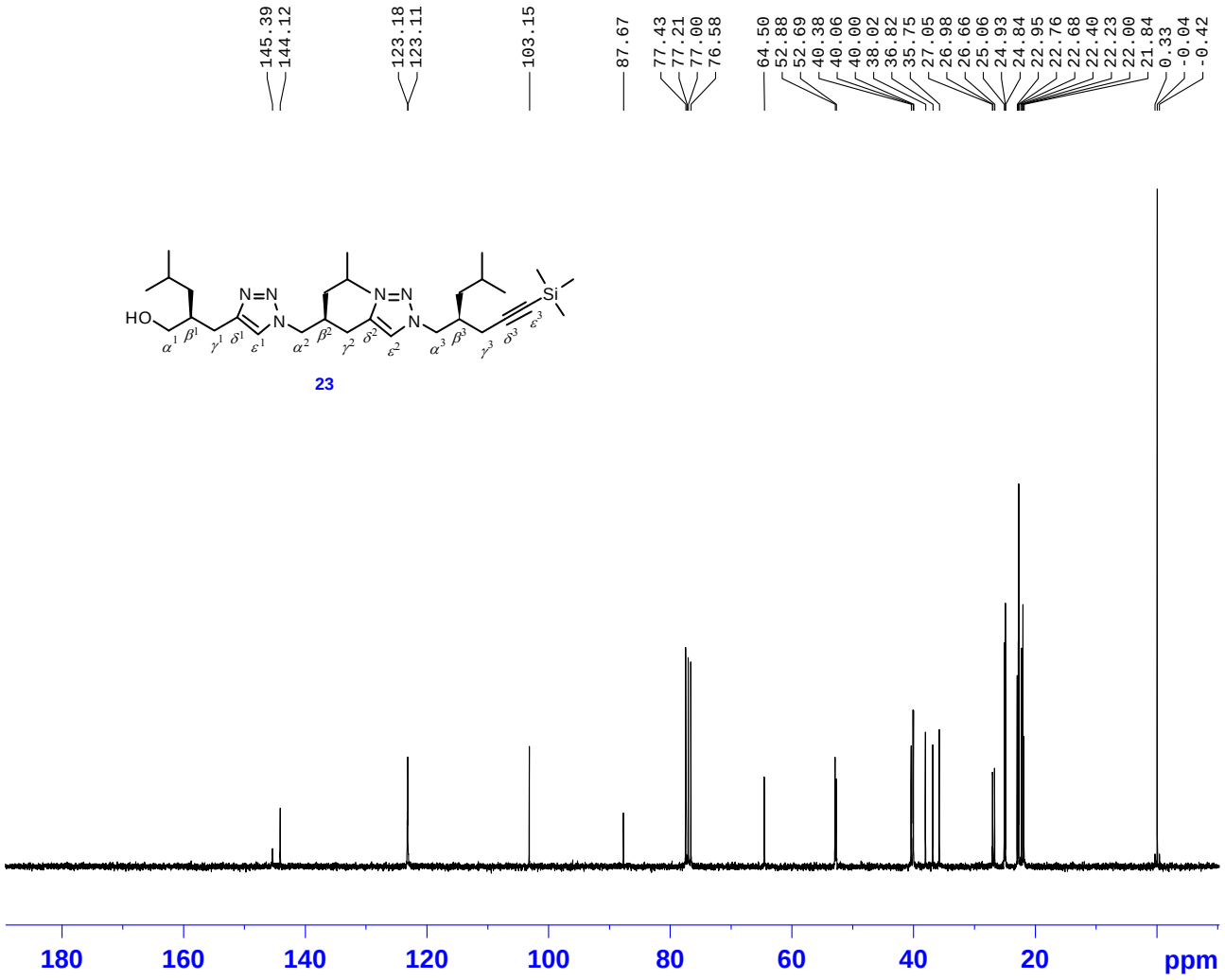
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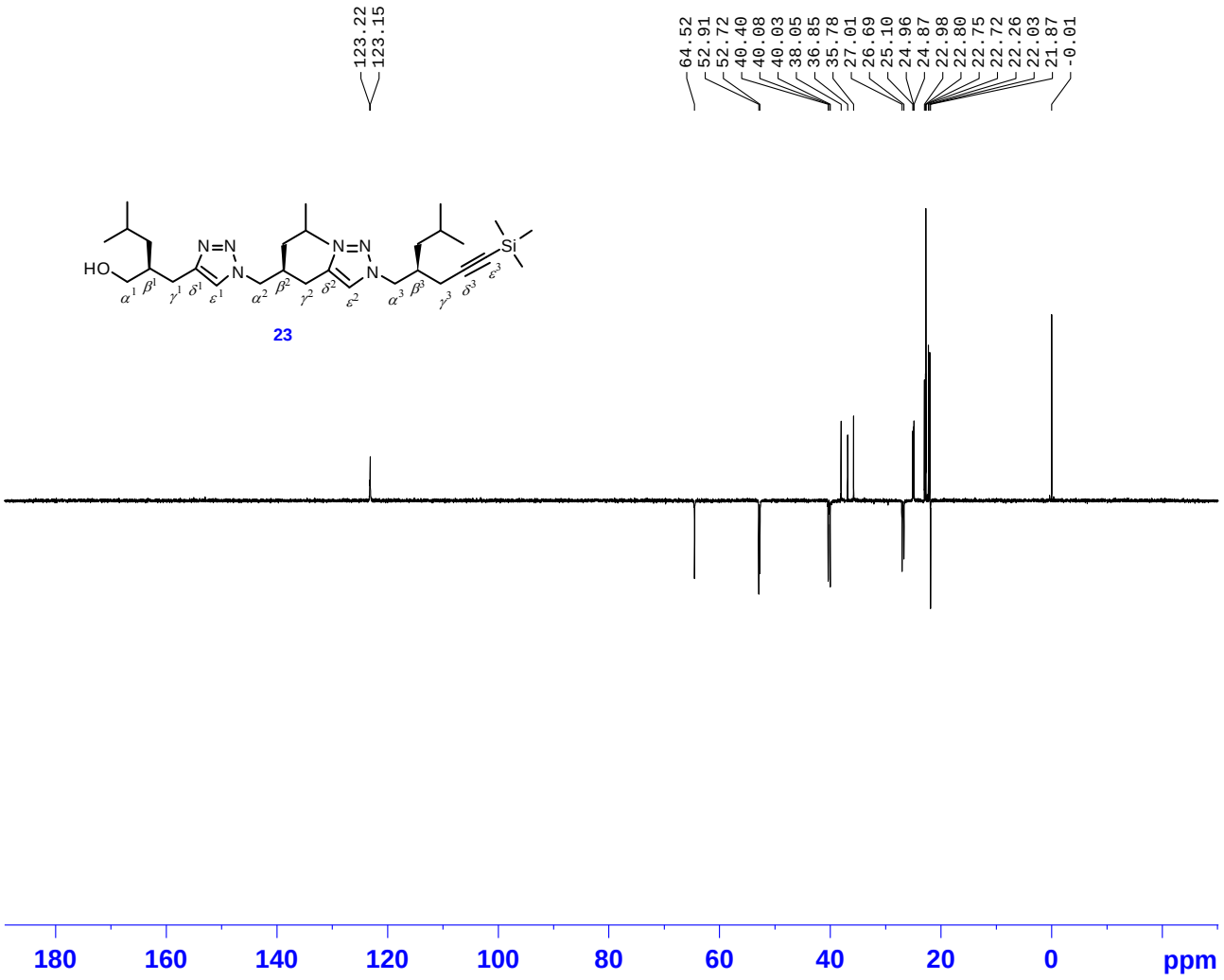
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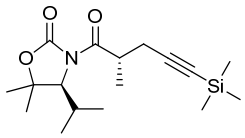
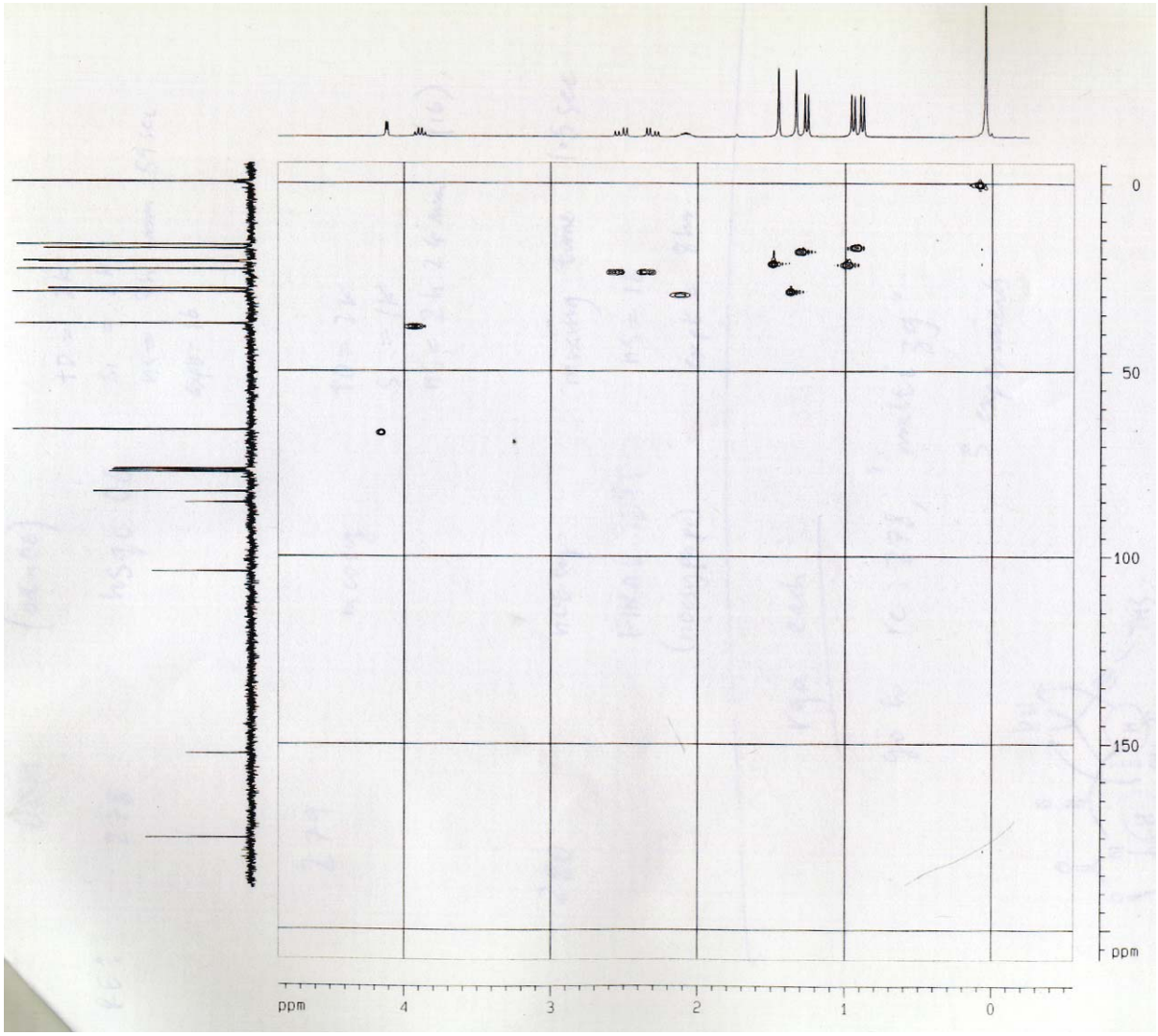
$^{1}H/^{1}H$-mCOSY and $^{1}H/^{13}C$-HSQC NMR spectra of selected compounds

$^{1}H/^{13}C$-HSQC – Compound 8d



8d



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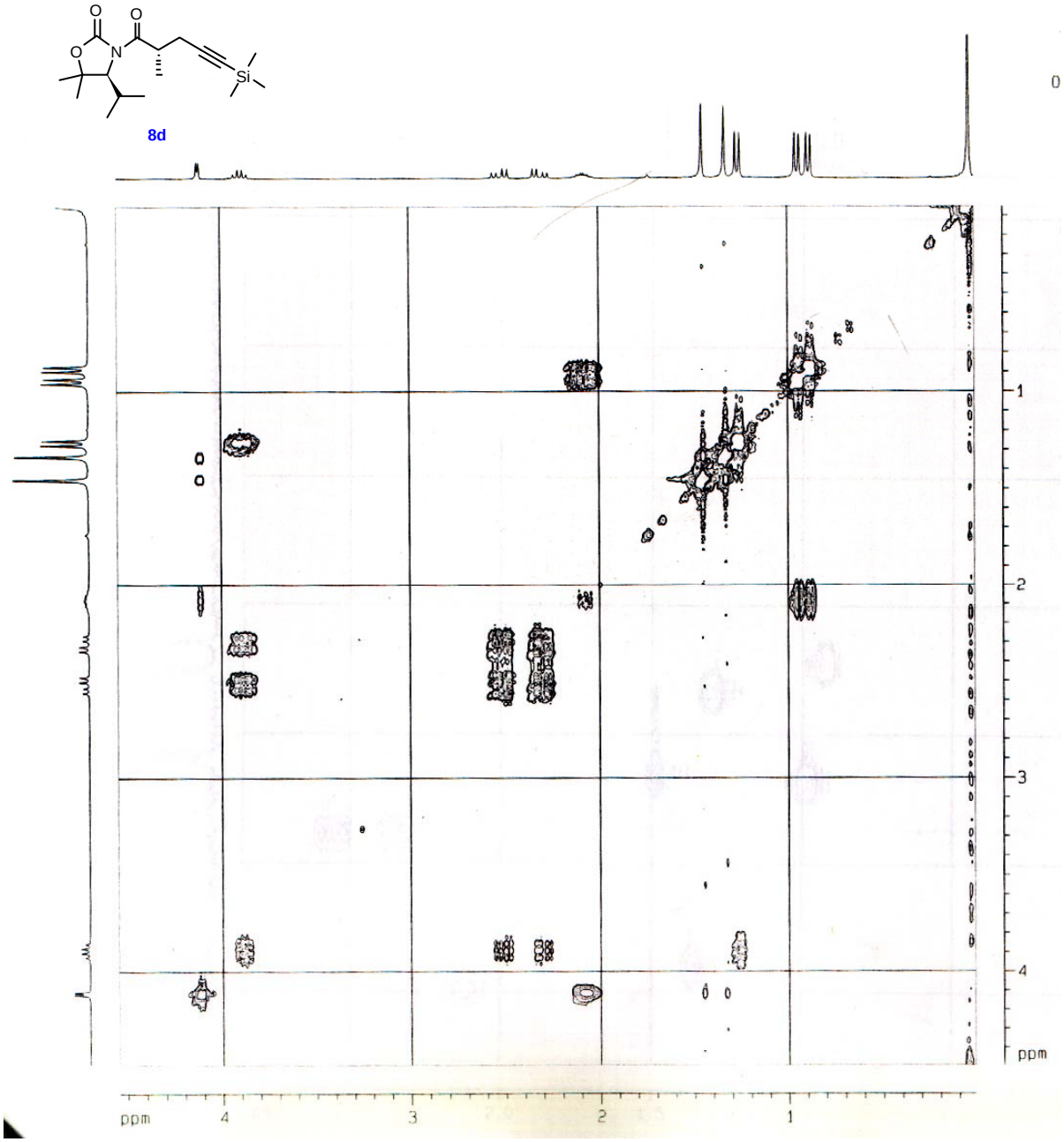

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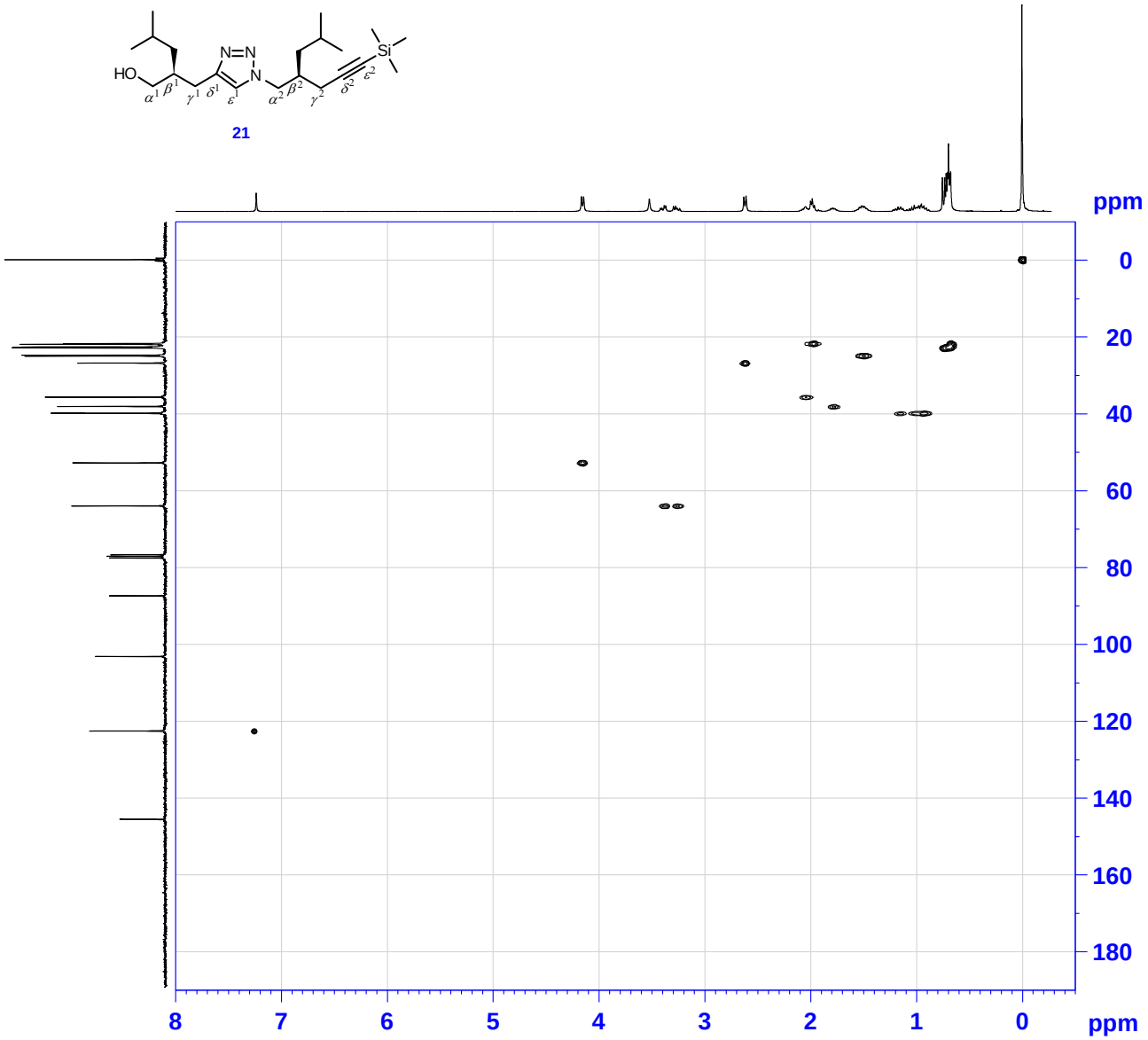

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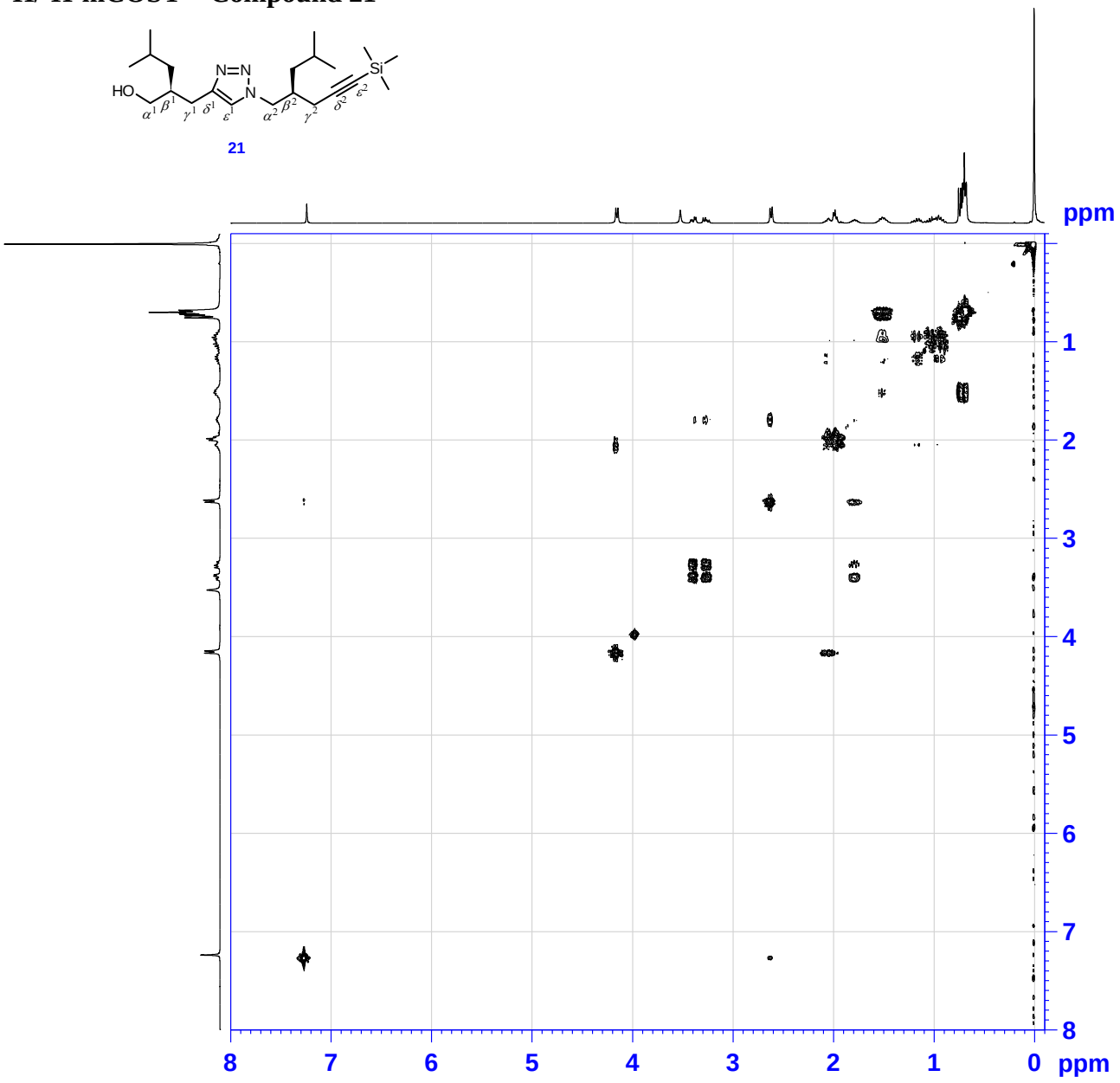

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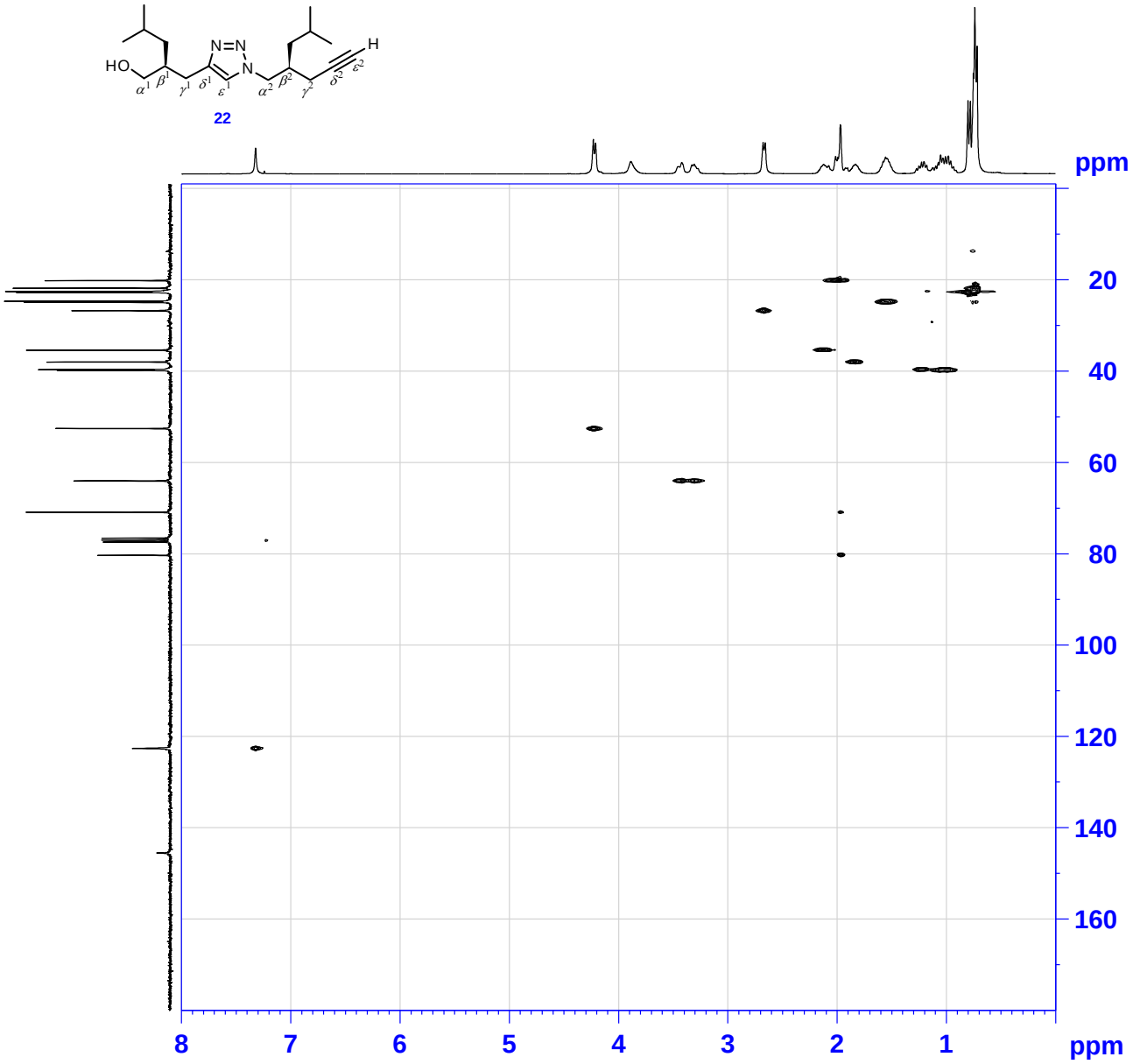

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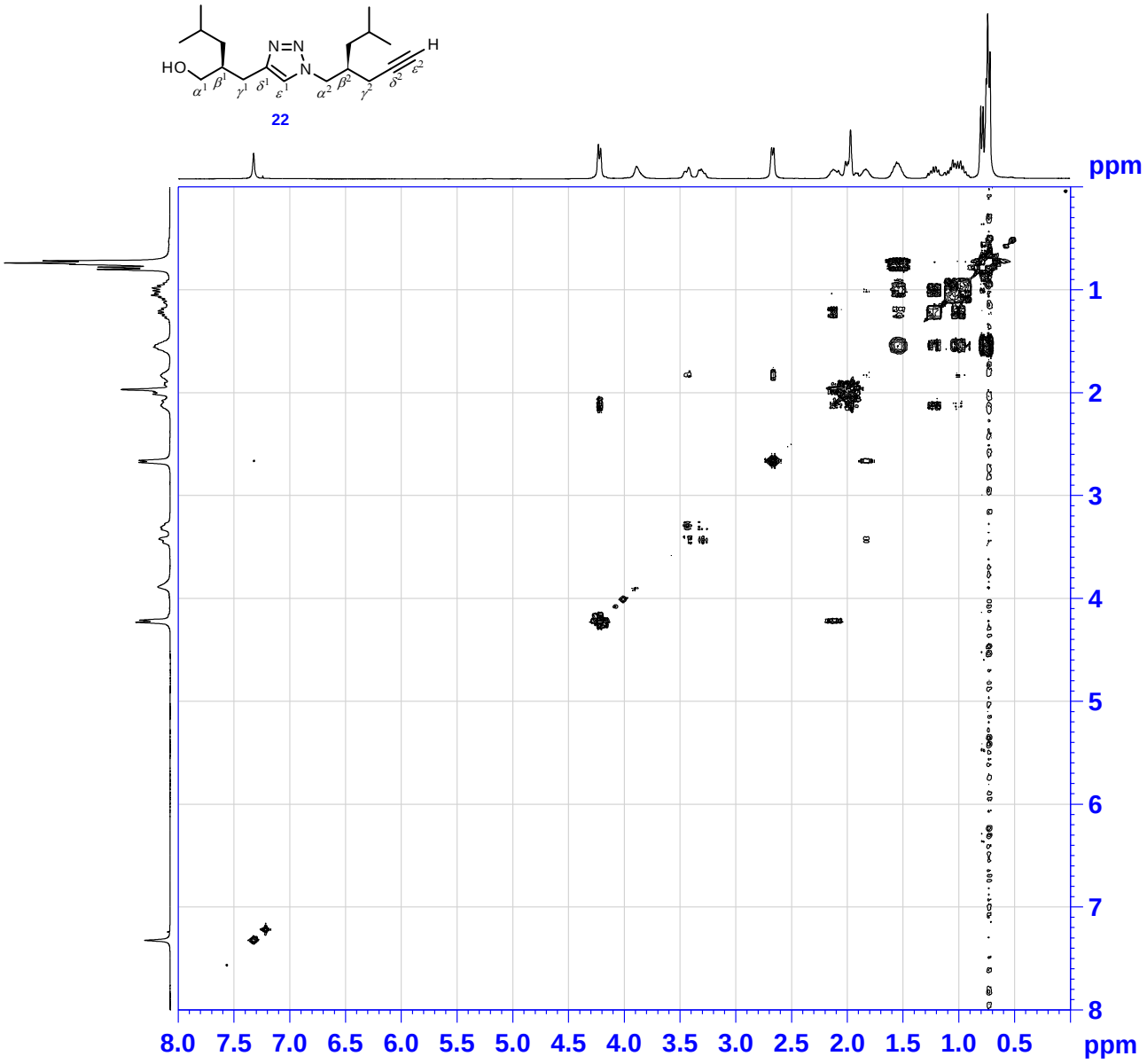

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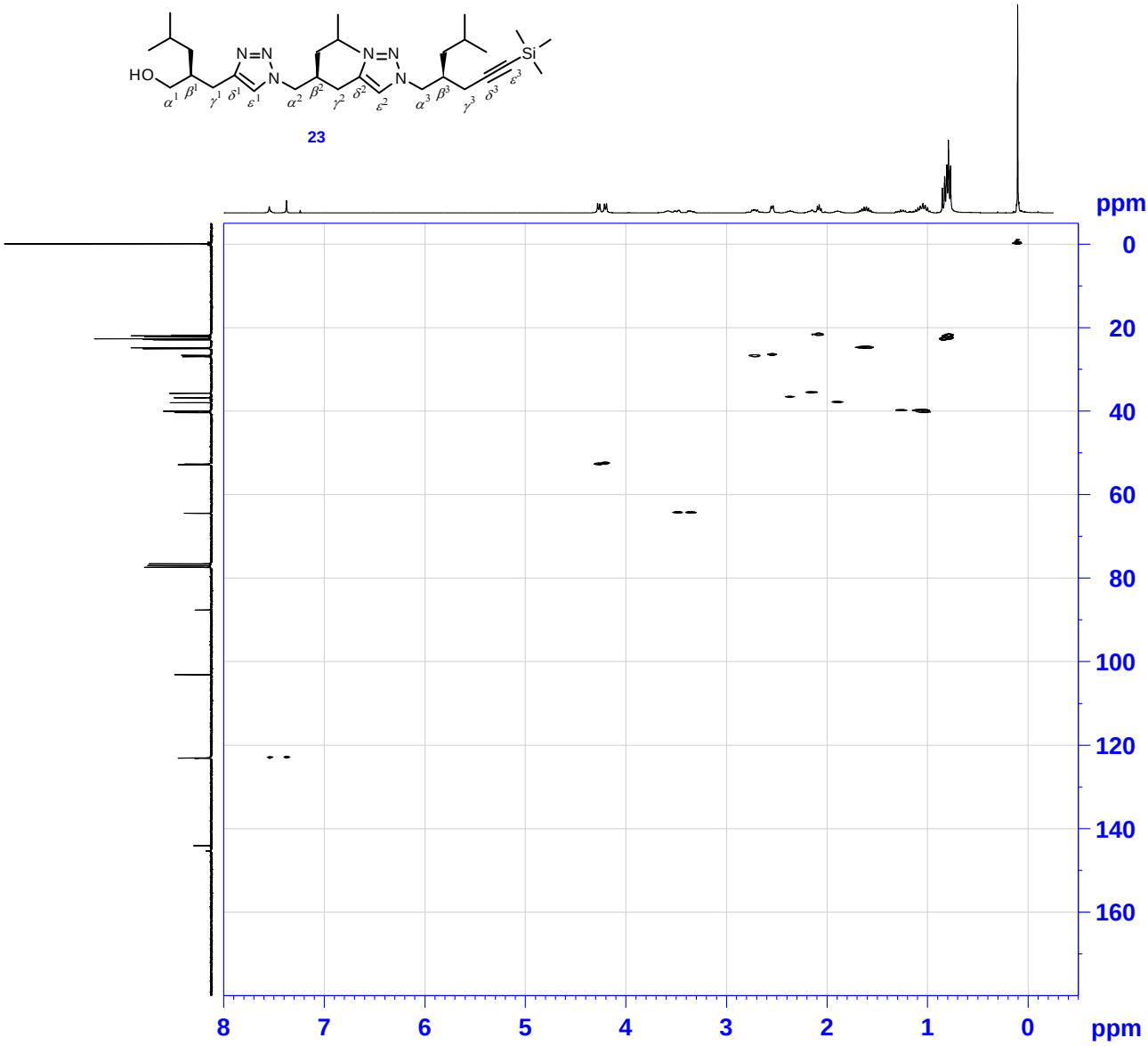
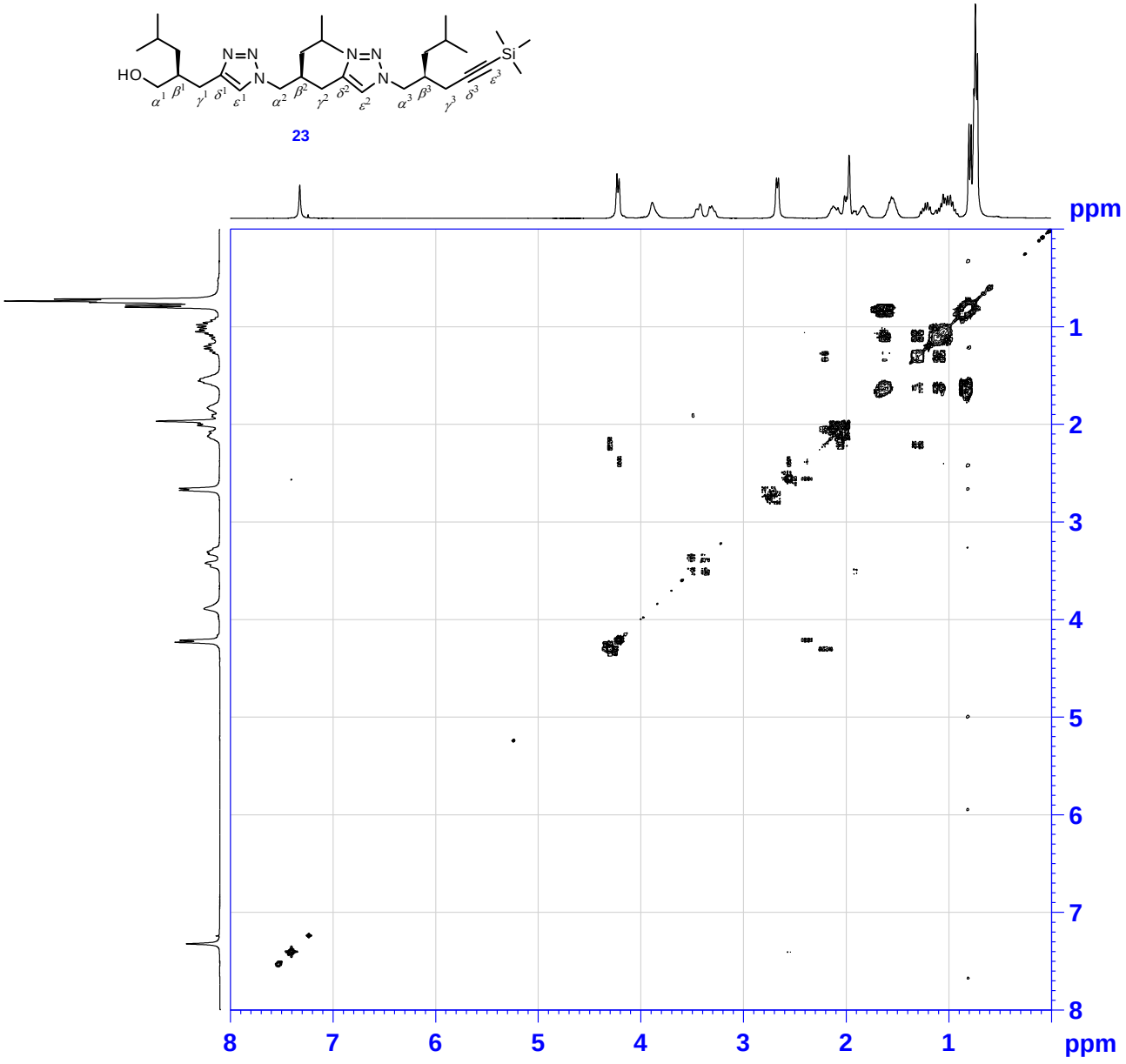


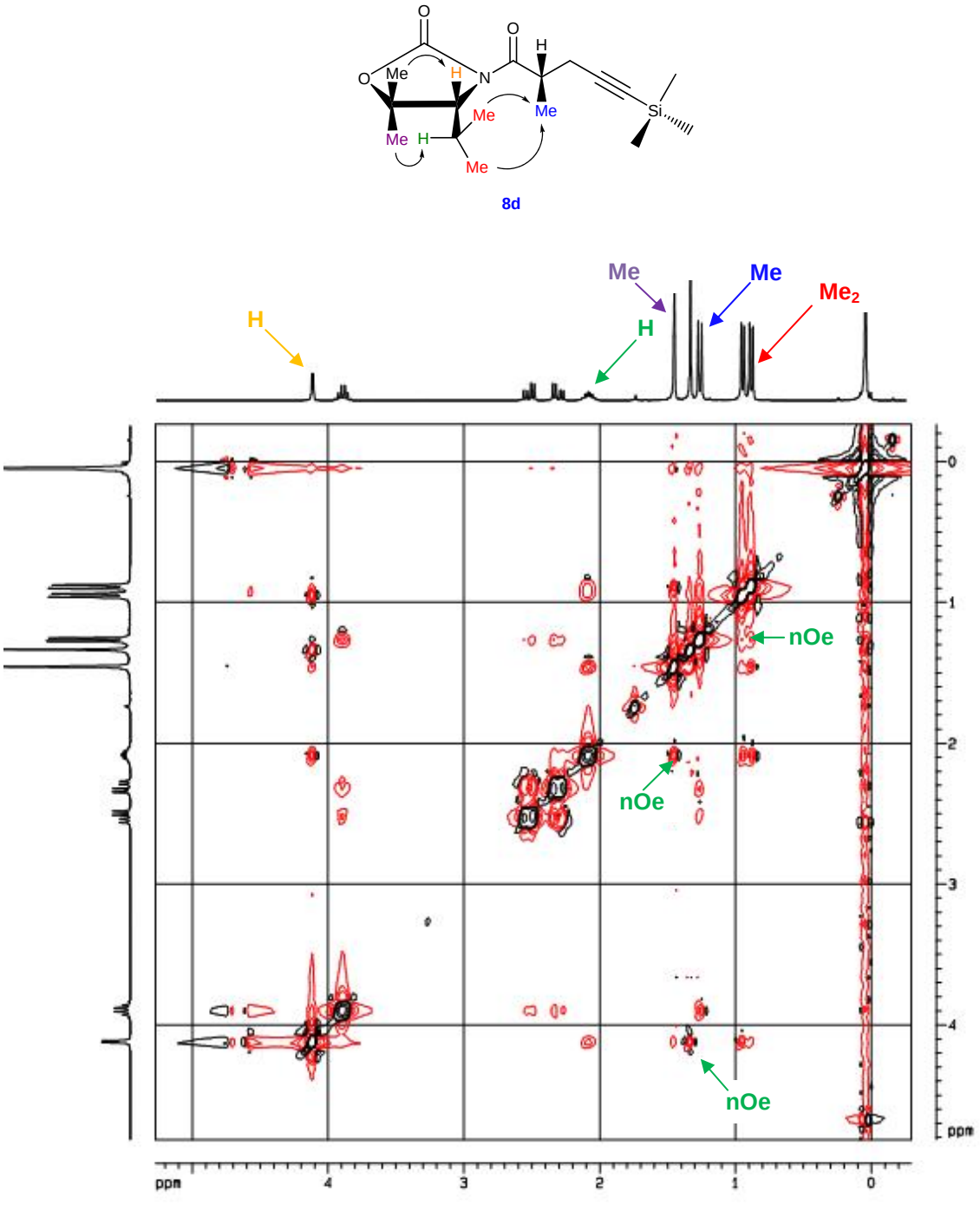
$^{1}H/^{1}H$-mCOSY – Compound 23



^{1}H/^{1}H-NOESY spectra of alkylated SQ adduct 8d

^{1}H/^{1}H-NOESY spectroscopic analysis (400 MHz, $CDCl_3$) was conducted on the major diastereoisomer, the *suspected* (2*R*)-Me-(4*S*)-^{i}Pr SQ adduct **8d** (**Figure 1**).

Figure 1. ^{1}H/^{1}H-NOESY spectra of **8d** showing NOE enhancement (green arrows).



Three strong NOE enhancements were seen:

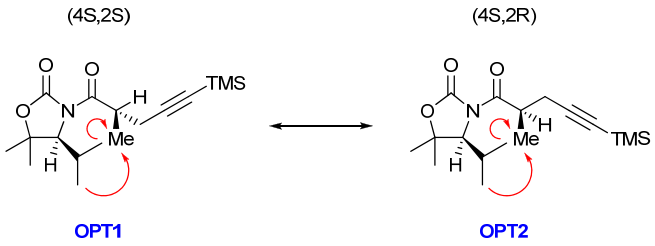
1. Between the *iso*-propyl CH(**Me**)$_2$ methyl groups (**red**) and the 2'-methyl hydrogens (**blue**).

2. Between the *iso*-propyl C**H**(Me)$_2$ proton (**green**) and one CH(Me)$_2$ methyl group (**black**).

3. Between the ^{i}Pr C**H**CH(Me)$_2$ proton (**yellow**) and the other CH(Me)$_2$ methyl group proton (**purple**).

These NOE enhancements are entirely consistent with limited rotation around the carbonyl-C-2' bond, suggesting that out of 6 possible conformations for the 2 diastereoisomers, only two of these conformations are likely; **OPT1** and **OPT2** (**Figure 2**).

Figure 2. 2D representations of two potential conformations of (4*S*, 2*S*)/(4*S*, 2*R*) ^{i}Pr-SQ-Me-adducts **8d** and **8i**. Red arrows indicate potential NOE's from the ^{i}Pr methyls and the 2'-chiral centre.



The two potential conformations are as follows:

1. The (4*S*,2*S*)-diastereomer; with the 2'-methyl group oriented *towards* the ^{i}Pr CH(**Me**)$_2$ groups, the TMS-prop-1-ynyl group oriented *away* from the ^{i}Pr CH(**Me**)$_2$ groups, and the 2'-proton in a *planar arrangement* with the 1'-carbonyl group (**OPT1**).

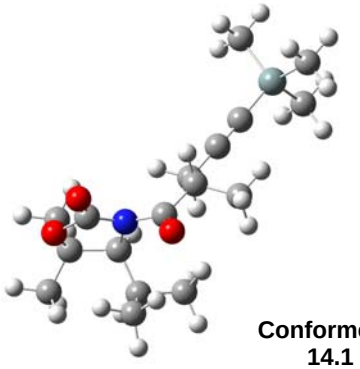
2. The (4*S*,2*R*)-diastereomer, with the 2'-methyl group oriented *towards* the ^{i}Pr CH(**Me**)$_2$ groups, the 2'-proton oriented *away* from the ^{i}Pr CH(**Me**)$_2$ groups, and the TMS-prop-1-ynyl group in a *planar arrangement* with the 1'-carbonyl group (**OPT2**).

Energy minimisation calculations were used to determine which out of these two conformers were more thermodynamically stable.

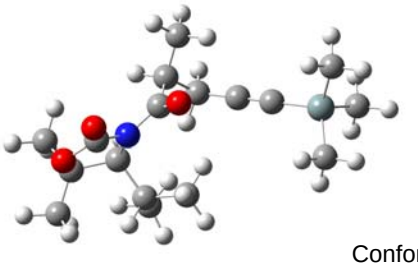
Energy minimisation calculations of alkylated SQ adduct 8d

Studies were performed using semi-empirical quantum mechanics (AM1, Gaussian 03) energy minimization calculations on all 6 possible conformers for the 2 diastereoisomers **8d** and **8i** to provide an initial geometry optimization. This was followed by *ab initio* quantum mechanics (Hartree-Fock/6-31G(d), Gaussian 03) single point energy calculations to provide an accurate estimation of the relative minimum energy for each conformer (**Figure 3**).

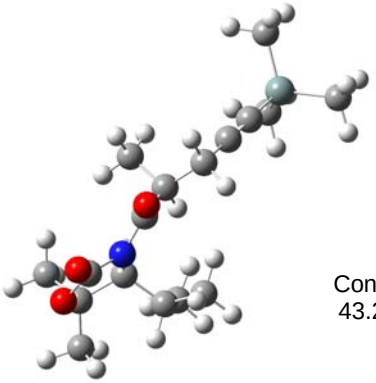
Figure 3. 3D molecular models of 6 conformations for ^{i}Pr-SQ-Me-adduct **8d** and their relative energies (The desired optimizations has been shown in bold).



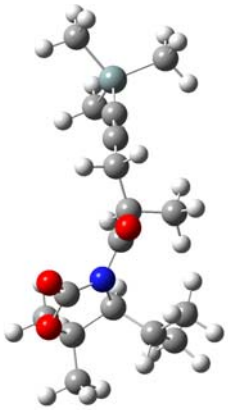
Conformer 1 (OPT1)
14.1 kJ/mol



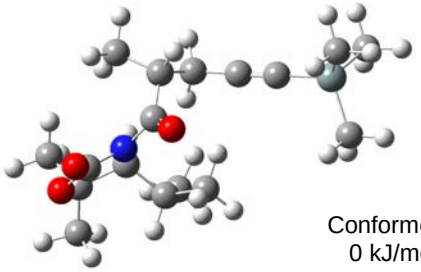
Conformer 2
15.2 kJ/mol



Conformer 3
43.2 kJ/mol



Conformer 4 (OPT2)
26.6 kJ/mol



Conformer 5
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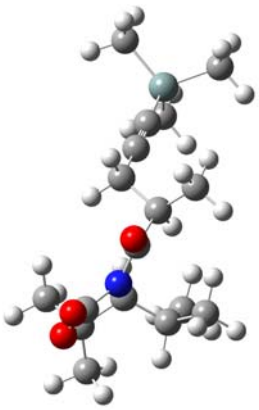

Conformer 6
39.1 kJ/mol

The results showed that of the 6 conformers (Figure 3), conformer 5 was found to have the lowest relative energy. However, this conformation was discounted on the basis of observed NOE enhancements. Of the 2 potential conformers possible from observed NOE enhancements (conformer 1 (**OPT1**) and conformer 4 (**OPT2**)), conformer 1 was found to exist as the lowest energy conformation, and was found to be lower in energy relative to conformer 4 by 12.5 kJ/mol. These results are consistent with literature reports[15-17] that show asymmetric alkylation in the presence of an (*S*)-^{i}Pr SQ auxiliary provides a new (*S*)-alkyl chiral centre in excellent diastereomeric excess.