International Research Journal of Natural and Applied Sciences
Vol. 2, Issue 8, August 2015 IF- 2.818 ISSN: (2349-4077)
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Website: www.aarf.asia Email : editor@aarf.asia , editoraarf@gmail.com

AN EFFICIENT AND CONVENIENT ROUTE TO ENANTIOENRICHED 1,4-SULFANYLALCOHOLS

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ABSTRACT

Enantiomerically pure benzylic 1,4-sulfanylalcohols have been prepared from 4 chlorobutyrophenones in a new three step reaction sequence. A protected thiol has been introduced in the first step. Asymmetric reduction of the pro-chiral ketone followed by deprotection of the thiol generates the enantio-enriched 1,4-sulfanylalcohols. All steps proceed with moderate to excellent yields (64–98%) and the products are obtained with high enantiomeric excess (80–91%). Significant reactivity differences in terms of thiolation and asymmetric reduction was observed for substrate having phenylpropargyl substituent. An alternate strategy was applied for this substrate to furnish the product with 72% *ee*.

Sulfanylalcohols belong to a class of compounds having importance in the flavor and fragrance chemistry.[1] They are naturally occurring in fruit and vegetables and are believed to contribute to the flavor and aroma even when present in very low concentrations (Figure 1, **A** and **B**).[2] Sulfanylalcohols have also been found to contribute to the taste of beers and wines.[3] This family of compounds can be regarded as precursors to the corresponding thiolanes, another family of compounds important for their olfactory properties.[4] It has been shown that the enantiomers of volatile sulfur compounds often have different sensory properties.[5] A variety of thio-substituted alcohols and their esters have been found, one enantiomer of which have a strong smell of burnt sulfur while the other enantiomer have a

typical fruity aroma (Figure 1, **C**–**F**).[6] It is therefore of great interest to find ways to prepare these compounds in their enantiomerically pure form.[7] Although, 1,3-sulfanylalcohols have been studied extensively,[8] no significant investigations have been carried out with the homologous 1,4-sulfenylalcohols. There are few reports of stereoselective synthesis of 1,4-sulfanylalcohols. Schellenberg et al.[9] prepared the enantiomerically pure 1,4-sulfanylalcohols by means of chiral resolution. In this method, the racemic compounds obtained by reduction of γ-thiolactones were functionalize by using stoichiometric amount of chiral auxiliaries in order to diastereomeric seperation through semi-preparative HPLC. Filippi et al.[10] reported synthesis of 1,4-sulfanylalcohols from enantiomerically pure γ-lactones (Scheme 1). The first step of the reported reaction sequences consisted of enzymatic resolution of racemic γ-lactones which required water-based buffers with low solubility of small organic molecules. Moreover, the reaction was very sluggish requiring long reaction time ranging from 2 to 9 days to achieve 26–91% *ee* of the desired products. Morover, only aliphatic sulfanylalcohols were synthesized by this reported method. Considering the limitations associated with the previously reported methods, such as, use of stoichiometric amount of chiral auxiliaries, long reaction times, low solubility of organic molecules in aqueous buffer, and poor enantioselectivily, an improved and efficient alternative protocol is desirable.

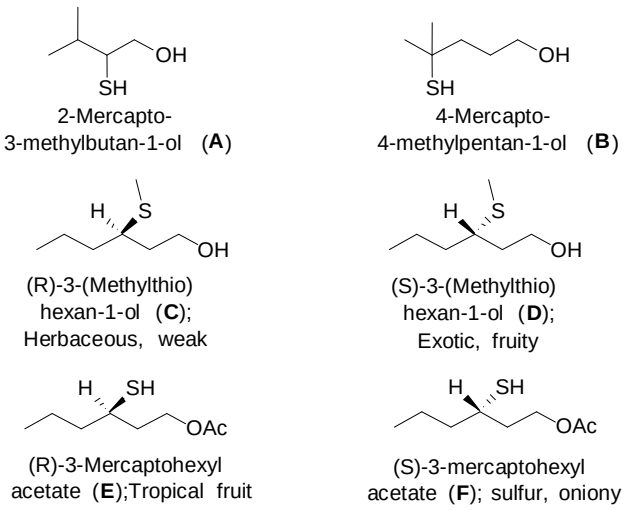
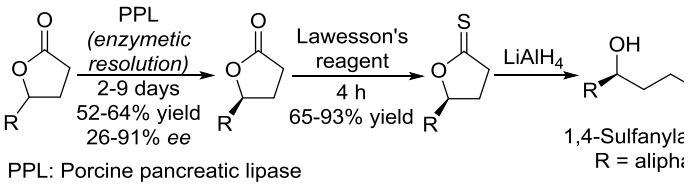


Figure 1. Representative examples of some simple and naturally occurring sulfanylalcohols in foods and beverages (**A**, **B**).[1,2a] and odors of some enantiomeric sulfanylalcohols and their esters (**C**, **D**).

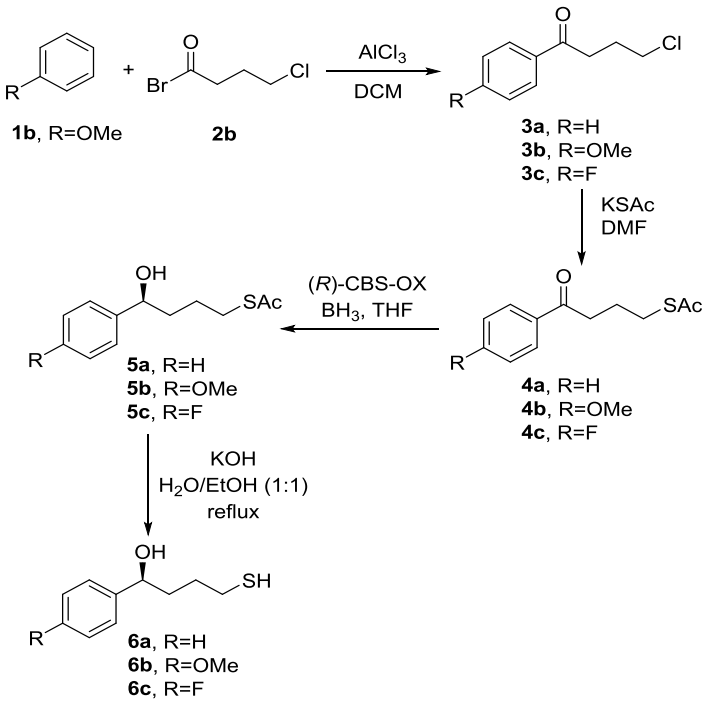
In this paper we describe a fast and efficient synthetic route to enantiomerically pure benzylic 1,4-sulfanylalcohols with higher enantiomeric excess (80–91%). The overall reaction

sequence consists of only 3 to 4 rapid, moderate to high yielding, and straight forward reaction steps from readily available precursors.



Scheme 1. Previous report of enantioselective synthesis of 1,4-sulfanylalcohols.[9]

4-chlorobutyrophenone **3b** was synthesized *via* a standard Fridel-Craft reaction (Scheme 2).[11] Anhydrous $AlCl_3$ was suspended in a dichloromethane solution of anisole **1b** and cooled to **0** °C. 1-Bromobutyrylchloride **2b** was added to it to produce 4-chlorobutyrophenone **3b** in a near quantitative yield (98%).[12] We intended to protect the ketones (**3**) with ethylene glycol and introduce the thiol thereafter. However, this approach gave poor yields of the desired products. Also, the keto-protected species were found to be

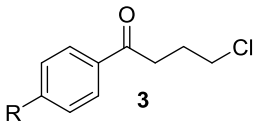
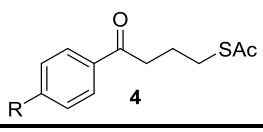


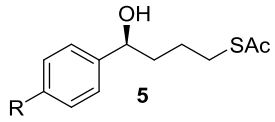
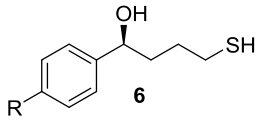
Scheme 2. Enantioselective synthesis of 1,4-sulfanylalcohols.

very unstable, especially for substituents other than hydrogen at the R-position of **3**.[13] Other protecting groups attempted were found equally inefficient. Thus, to avoid protection of the reactive ketone, another strategy was applied. We envisioned to introduce a protected thiol directy to the 1,3-chloroketones (**3**). Potassium thioacetate presented a convenient route to obtain the protected thiols in high yields. An advantage with the acetate-protection on sulfur

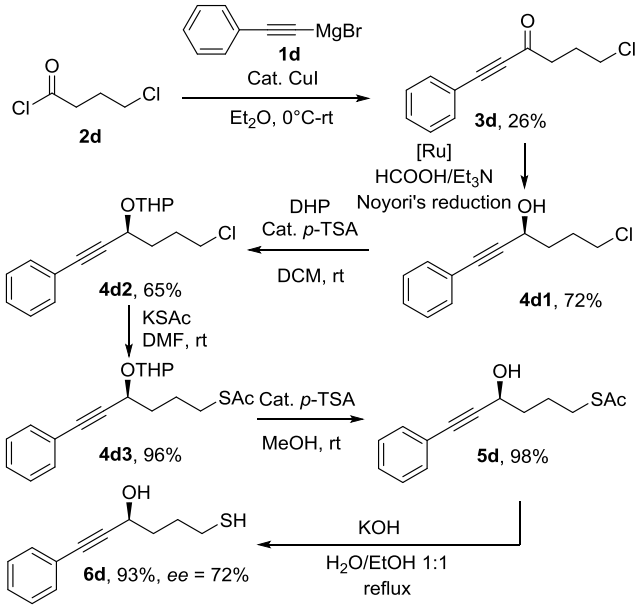
was the subsequent de-protection to yield the free thiols in the final step (*vide infra*). Thus, 4-chlorobutyrophenones **3a–c**[12,14] were treated with potassium thioacetate to introduce the protected thiols. The introduction of the protected thiol was carried out in DMF, at room temperature; using 1.5 equivalents of KSAc. The products **4a–c** were formed in excellent yields (90–98%). The pro-chiral keto groups in **4a–c** were asymmetrically reduced through a Corey-Bakshi-Shibata reduction,[15] producing compounds **5a–c**. Attempt to asymmetrically reduce **4a–c** by Noyori's transfer hydrogenation method[16] did not work for these types of substrates. Corey-Bakshi-Shibata reduction of **4a–c** was performed using (*R*)-(+)-2-Methyl-CBS-oxazaborolidine (10 mol%, 1 M in toluene) as catalyst and BH_3 (0.6 eqv., as THF-complex) to obtain the (*S*)-enantiomers of **5a–c** in moderate to excellent yields (64–96%) and moderate to high *ee* (80–91%), which is an improvement to the previous reports.[9,10] Importantly, to the best of our knowledge, this step represents a novel synthetic route where it is evident for the first time that enantioselective reduction of keto group by CBS-reduction could be performed in presence of thio-ester functionality. Besides having better *ee* of the products compared to the previous methods, another synthetic advantage of this CBS-reduction is that either of the enantiomers of **5** can be prepared as the catalyst is available both in (*R*) and (*S*) forms. In the final step, the protecting acetate group was removed from the sulfur of **5a–c** by reflux in a solution of potassium hydroxide in ethanol:water (1:1), which provided the desired products **6a-c** in 70–83% yields. To emphasize the electronic effects, we used neutral substrate as well as substrates with strong electron donating –OMe and withdrawing –F substituents. The yields and enantiomeric excess (*ee*) of all the synthesized compounds are shown in Table 1.

Table 1. Yields and enantiomeric excess of all compounds.

Entry	Compound		Yield (%)[a]	*ee* (%)[b]
1	 3	R=H, **3a**	CA[c]	–
2		R=OMe, **3b**	98	–
3		R=F, **3c**	CA[c]	–
4	 4	R=H, **4a**	98	–

5		R=OMe, **4b**	91	–
6		R=F, **4c**	90	–
7	 **5**	R=H, **5a**	96	90
8		R=OMe, **5b**	64	87
9		R=F, **5c**	66	80
10	 **6**	R=H, **6a**	83	90
11		R=OMe, **6b**	94	87
12		R=F, **6c**	70	80

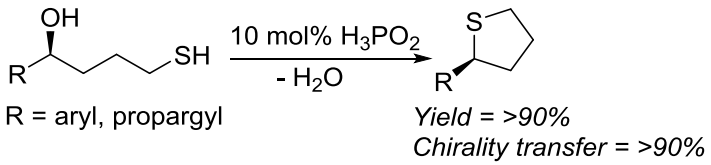
[a] Yields refer to pure and isolated products. [b] *ee* were determined by chiral HPLC analysis. [c] CA refers to *Commercially Available*.



Scheme 3. Enantioselective synthesis of propargylic substituted 1,4-sulfanylalcohol **6d**.

The thiolation and asymmetric reduction by CBS method were found to be substrate selective. Thus, an alternative strategy was needed to synthesize propargyl-substituted 1,4-sulfanylalcohol **6d** from 4-chlorobutanoyl chloride (**2d**) and (phenylethynyl)magnesium bromide (**1d**) through subsequent protection / deprotection sequences (Scheme 3). **3d** was synthesized by a controlled Grignard reaction in 26% yield. Attempt to perform thiolation reaction on **3d** was unsuccessful. Moreover, the CBS reduction also did not work and starting material was recovered even after prolonged reaction time. In an alternative strategy, **3d** was first reduced to enriched alcohol **4d1** through Noyori's transfer hydrogenation[16] followed by DHP protection of the hydroxy group to synthesize **4d2** in 65% yield. **4d2** successfully underwent thiolation to generate **4d3** which upon deprotection and subsequent hydrolysis generated the desired product **6d** in 93% yield and with 72% *ee* (see SI for detail experimental procedures). Although, the overall yield is poor for this six step synthetic route, the low yielding steps are fortunately in the beginning of the synthesis. The last three steps have an overall yield of 96% (isolated yield).

We have successfully used these 1,4-sulfanylalcohols in stereospecific substitution reactions in which phosphinic acid promotes the substitution of the hydroxyl group without prior derivatization (Scheme 4).[8] The resulting thiolane derivatives were generated in good yields and high degree of chirality transfer with water as the only side-product.



Scheme 4. 1,4 sulfanylalcohols were used in the synthesis of enantioenriched thiolanes.

In conclusion, a fast and efficient synthesis of 1,4-sulfanylalcohols in moderate to excellent yields with high enantiomeric excess (80–91%) has been developed. Strategic The described pathway allows the synthesis of both the enantiomers of the targeted 1,4-sulfanylalcohols having olfactory properties that identify them as valuable chemical entities in flavor and fragrance chemistry. An alteration of the present strategy was required in order to prepare enantiomerically enriched propargyl substituted 1,4 sulfanylalcohol with 72% *ee*.

Experimental Section

Representative experimental procedure of the synthesis of 5a: All experiments were carried out under argon atmosphere.

Synthesis of S-(4-oxo-4-phenylbutyl) ethanethioate **4a**: To a solution of KSAc (1.91 g, 16.7 mmol) in DMF (35 ml) was added 4-chloro-1-phenylbutan-1-one 3a (1.8 ml, 11.0 mmol) dropwise at 0 °C. The reaction was run at RT overnight. After the completion of the reaction

(TLC), the solvent was evaporated; the residue was extracted with EtOAc (3 × 50 mL) and washed with water and brine. The combined organic phase was dried over $MgSO_4$ and the solvent removed in reduced pressure to obtain pure S-(4-oxo-4-phenylbutyl) ethanethioate **4a** (2.40 g, 10.8 mmol, 98%). No further purification was needed in this step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.94–7.96 (m, 2 H, H-aromatic), 7.54–7.56 (m, 1 H, H-aromatic), 7.44–7.48 (m, 2 H, H-aromatic), 3.06 (at, J = 7.2 Hz, 2 H, H-3), 2.99 (at, J = 7.2 Hz, 2 H, H-1), 2.33 (s, 3 H, H-COC$\underline{H}_3$), 2.04 (dddd, J = 7.2 Hz, 7.2 Hz, 7.2 Hz, 7.2Hz, 2 H, H-2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 198.9, 195.5, 136.7, 133.0, 128.7, 128.5, 127.9, 37.0, 30.5, 28.5, 24.0 ppm.

Synthesis of (*S*)-S-(4-hydroxy-4-phenylbutyl) ethanethioate **5a** by Corey-Bakshi-Shibata reduction of **4a:** To a 1 M solution of BH_3 in THF (4.5 mmol) at 0 °C was added 1 M solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine catalyst in toluene (0.9 mmol) dropwise. Compound **4a** (2.00 g, 9.0 mmol) was dissolved in THF (15 mL) and added dropwise. The reaction was completed after 3 h stirring at the same temperature (TLC). A saturated solution of NH_4Cl (25 mL) was added and solution was stirred for 15 min. The reaction mixture was extracted with EtOAc (3 × 50 mL), washed with brine, dried over $MgSO_4$. The combined organic layer was concentrated under reduced pressure and purified by silica gel (100-200 mess) column chromatography to obtain (*S*)-S-(4-hydroxy-4-phenylbutyl) ethanethioate **5a** (1.94 g, 8.6 mmol, 96% yield, 91% *ee*). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.37 (m, 5 H, H-aromatic), 4.70 (m, 1 H, H-4), 2.90 (dd, J = 6.9 Hz, 6.9 Hz, 2 H, H-1), 2.31 (s, 3 H, H-COC$\underline{H}_3$), 1.58–1.87 (m, 4 H, H-2 and H-3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 196.0, 144.6, 128.6, 127.8, 125.9, 74.1, 38.0, 30.8, 29.0, 26.1 ppm.

Synthesis of (*S*)-4-mercapto-1-phenylbutan-1-ol **6a** by alkaline hydrolysis of **5a:** A solution of KOH (22.5 mmol) in 1:1 EtOH/H_2O (25 mL) was added to **5a** (1 g, 4.5 mmol) and the reaction mixture was refluxed for 2 h. After completion of the reaction (TLC), the reaction mixture was allowed to attain room temperature; saturated NH_4Cl solution (20 mL) was added to it and extracted three times with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by silica gel (100-200 mess) column chromatography to obtain **6a** (682 mg, 3.74 mmol, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.28 (m, 5 H), 4.72 (m, 1 H), 2.58 (dddd, J = 7.2 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, 2 H) 1.77–1.93 (m, 4 H), 1.58–1.69 (m, 1 H), 1.35 (dd, J = 7.7 Hz, 7.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 144.7, 128.8, 127.9, 126.1, 74.4, 37.9, 30.5, 24.8 ppm.

Acknowledgements

We thank the Swedish Research Council, Stiftelsen Olle Engkvist Byggmästare, and Wenner Gren Foundations for financial support. SB thanks Department of Science and Technology, Govt. of India for INSPIRE Faculty award (DST/INSPIRE/04/2013/000017).

Keywords: Sulfanylalcohol • Asymmetric Synthesis • Flavor and fragrance chemistry • CBS-Reduction

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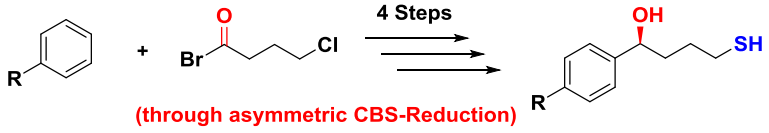


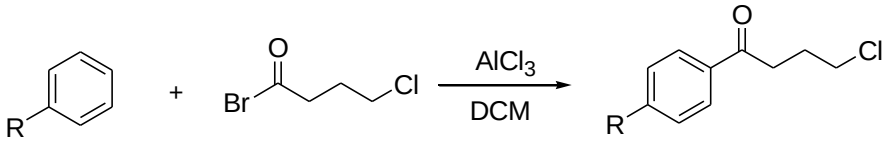
Enantiomerically pure 1,4-sulfanylalcohols have been prepared from 4-chlorobutyrophenones in a new three step reaction sequence to generate the products in 64–98% yields and 80–91% *ee*.

Supporting information

1. General Considerations:

Unless stated differently, all the reactions were carried out at room temperature, under atmospheric pressure and with argon atmosphere. The starting materials, solvents and reagents were commercially available and used as supplied. Solvents were distilled and dried prior to use. Flash chromatography was done over Merck silica gel (100–200 mess). Thin layer chromatography analyses were performed using Fluka pre-coated silica gel (60 F_{254}) plates and visualized with UV light and / or iodine. NMR analyses were carried out on a Varian Mercury 300 MHz, Varian Unity 400 MHz or Varian Inova 500 MHz NMR spectrometer as a solution of $CDCl_3$. Chemical shifts are given in ppm (δ) using residual $CHCl_3$ peaks as internal standard. Enantiomeric excess (*ee*) were determined by chiral HPLC using aYoung Lin 9100 instrument with a Daicel Chiracel OD-H column and a UV-detector (225 nm and 250 nm).

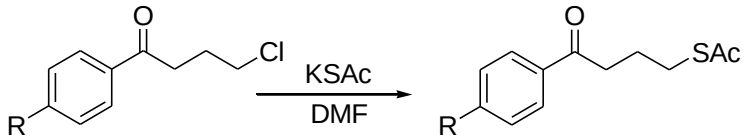
2. Synthesis of 4-Chloro-1-(4-methoxyphenyl)butan-1-one (3b):



1b, R=OMe **2** **3b,** R=OMe

$AlCl_3$ (2.2 g, 16.2 mmol) was suspended in DCM under argon atmosphere. The suspension was cooled to 0°C and anisol (0.81 ml, 7.4 mmol) added dropwise. 1-Bromobutyrylchloride (0.94 ml, 8.1 mmol) was added dropwise. The reaction was stirred for 10 min. EtOH (3 ml) and HCl (5 M, 10 ml) was slowly added successively. The mixture was stirred for 1h. The phases were separated and the water phase extracted with DCM. The combined organic phases were washed with $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated. The crude product was purified by silica gel column chromatography (EtOAc/pentane 1:9) to obtain **3b** (2.1 g, 98%) as a yellow oil . ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.94 (d, J = 7.1 Hz), 6.92 (d, J = 6.9 Hz, 2 H), 3.86 (s, 3 H), 3.63 (t, J = 6.2 Hz, 2 H), 3.10 (t, J = 7.2 Hz, 2 H), 2.18–2.22 (m, 2 H) ppm which is in agreement with the literature (Rao; M. L. N., Venkatesh; V., Banerjee; D. *Tetrahedron*, **2007**, *63*, 12917).

3. General Procedure A (Thiolation):

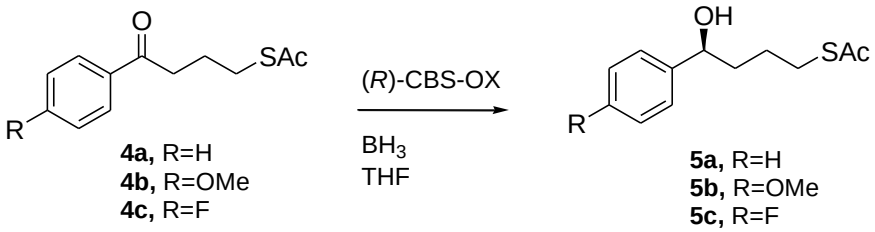


3a, R=H
3b, R=OMe
3c, R=F

4a, R=H
4b, R=OMe
4c, R=F

To a solution of KSAc (16.7 mmol) in DMF (35 ml) was added 4-chloro-1-phenylbutan-1-one **3a–3c** (11.0 mmol) dropwise at 0 °C. The reaction was run at RT overnight. After the completion of the reaction (TLC), the solvent was evaporated; the residue was extracted with EtOAc (3 × 50 mL) and washed with water and brine. The combined organic phase was dried over $MgSO_4$ and the solvent removed in reduced pressure to obtain pure **4a–4c** in analytically pure forms which were used directly for the next synthetic steps without further purifications.

4. General Procedure B (Corey-Bakshi-Shibata Reduction):

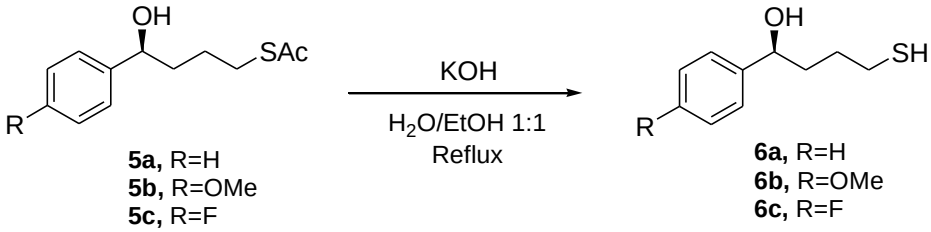


4a, R=H
4b, R=OMe
4c, R=F

5a, R=H
5b, R=OMe
5c, R=F

To a 1 M solution of BH_3 in THF (4.5 mmol) at 0 °C was added 1 M solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine catalyst in toluene (0.9 mmol) dropwise. Compound **4a–4c** (9.0 mmol) was dissolved in THF (15 mL) and added dropwise. The reaction was completed after 3 h stirring at the same temperature (TLC). A saturated solution of NH_4Cl (25 mL) was added and solution was stirred for 15 min. The reaction mixture was extracted with EtOAc (3 × 50 mL), washed with brine, dried over $MgSO_4$. The combined organic layer was concentrated under reduced pressure and purified by silica gel (100-200 mess) column chromatography to obtain **5a–5c.**

5. General Procedure C (Deprotection of Thiol):

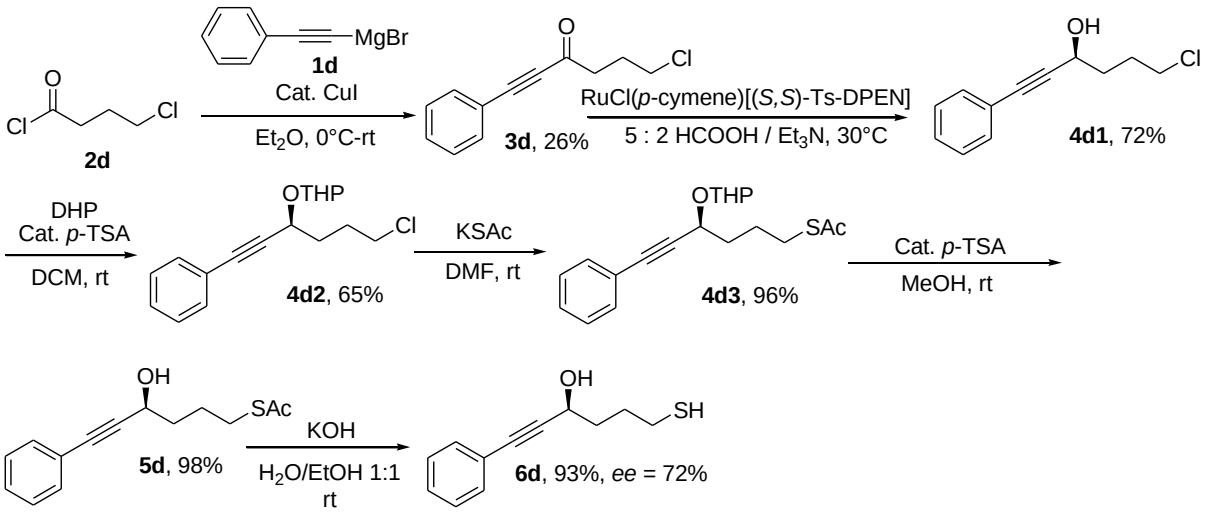


5a, R=H
5b, R=OMe
5c, R=F

6a, R=H
6b, R=OMe
6c, R=F

A solution of KOH (22.5 mmol) in 1:1 EtOH/H_2O (25 mL) was added to **5a–5c** (4.5 mmol) and the reaction mixture was refluxed for 2 h. After completion of the reaction (TLC), the reaction mixture was allowed to attain room temperature; saturated NH_4Cl solution (20 mL) was added to it and extracted three times with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by silica gel (100-200 mess) column chromatography to obtain **6a–6c.**

6. Specific procedure D to synthesize 6d:



To a stirred solution of CuI (10 mol%) in 30 mL dry Et_2O, was added 4-chlorobutyryl chloride **2d** (30 mmol) at 0°C and stirred for 15 mint. Phenylethynylmagnesium bromide solution **1d** (1 equiv.) was added very slowly over the period of 1 h and the reaction mixture was stirred for another 1 h and then allowed to attain room temperature. Saturated NH_4Cl solution (50 mL) was added and extracted by Et_2O (3×50 mL). The combined organic layers were washed with water (1×50 mL) and Brine (1×50 mL) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain **3d** in 26% yield.

Ketone **3d** (4.8 mmol) was added to a solution of RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN (1 mol%) in 5 : 2 formic acid / triethylamine (10 mL) under argon and stirred for 12 h at rt. After completion of the reaction, saturated $NaHCO_3$ solution (20 mL) was added and the reaction mixture was extracted by DCM (3×50 mL). The combined organic layers were washed with water (2×50 mL) and Brine (1×50 mL); dried on anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to obtain alcohol (**4d1**) in 72% yield.

To a solution of alcohol **4d1** (2.4 mmol.) in DCM (10 ml) was added *p*-TSA (10 mol%) and dihydropyran (1.2 equiv.) dropwise at rt. The reaction was run at rt for 12 h. After completion of the reaction (TLC), the reaction mixture was worked-up with water (50 mL) and extracted by DCM (3×50 mL). The combined organic layers were washed with Brine (1×50 mL); dried on anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to obtain a ether (**4d2**) in 65% yield.

To a solution of ether **4d2** (4.5 mmol) in DMF (10 ml) was added KSAc (1.2 equiv.) at 0 °C. The reaction was warmed up and run at rt for 10 h. After completion of the reaction (TLC), the reaction mixture was worked up with water (50 mL) and extracted by DCM (3×50 mL). The combined organic layers were washed with water (2x50 mL) and Brine (1×50 mL); dried on anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to obtain a thioacetate (**4d3**) in 96% yield.

To a solution of thioacetate **4d3** (1.8 mmol) in MeOH (5 ml) was added *p*-TSA (10 mol%) at rt. The reaction was run at rt for 4 h. After completion of the reaction (TLC), the reaction mixture was worked up with water (50 mL) and extracted by DCM (3×50 mL). The combined organic layers were washed with Brine (1×50 mL); dried on anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain pure **5d** (98% yield) in analytically pure forms which were used directly for the next synthetic steps without further purifications.

A solution of KOH (5 equiv.) in 1:1 EtOH/H_2O (5 mL) was added to **5d** (2.2 mmol) and the reaction mixture was stirred at rt for 4 h. After completion of the reaction (TLC), the reaction mixture was worked up with water (50 mL) and extracted by DCM (3×50 mL). The combined organic layers were washed with Brine (1×50 mL); dried on anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to obtain the desired sulfanylalcohol (**6d**) in 93% yield and 72% *ee*.

7. Synthesis and characterization data of all compounds:

(i) S-4-Oxo-4-phenylbutyl ethanethioate **4a**:[11]

The synthesis followed General Procedure A to obtain **4a** (2.46 g, 98% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.94–7.96 (m, 2 H), 7.54–7.56 (m, 1 H), 7.44–7.48 (m, 2 H), 3.06 (at, J = 7.2 Hz, 2 H), 2.99 (at, J = 7.2 Hz, 2 H), 2.33 (s, 3 H), 2.04 (dddd, J = 7.2 Hz, 7.2 Hz, 7.2 Hz, 7.2Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 198.9, 195.5, 136.7, 133.0, 128.7, 128.5, 127.9, 37.0, 30.5, 28.5, 24.0 ppm.

(ii) S-4-(4-Methoxyphenyl)-4-oxobutyl ethanethioate **4b**:

The synthesis followed General Procedure A to obtain **4b** (2.52 g, 91% yield) as a reddish brown solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.93 (m, 2 H), 6.93 (m, 2 H), 3.87 (s, 3 H), 3.01 (dd, J = 7.2 Hz, 7.2 Hz, 2 H), 2.98 (dd, J = 7.2 Hz, 7.2 Hz, 2 H), 2.33 (s, 3 H), 2.02 (dddd, J = 7.2 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.8, 195.9, 163.6, 130.4, 130.1, 113.9, 55.6, 36.9, 30.8, 28.8, 24.4 ppm.

(iii) S-4-(4-Fluorophenyl)-4-oxobutyl ethanethioate **4c**:[1]

The synthesis followed General Procedure A to obtain **4c** (2.42 g, 90% yield) as a brown oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.96–7.99 (m, 2 H), 7.11–7.14 (m, 2 H), 3.02 (dd, J = 7.2 Hz, 7.2 Hz, 2 H), 2.98 (dd, J = 7.2 Hz, 7.2 Hz, 2 H), 2.33 (s, 3 H), 2.08 (dddd, J = 7.2 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.6, 195.8, 167.5, 164.2, 133.4, 133.3, 130.8, 130.7, 115.9, 115.7, 37.1, 30.7, 28.6, 24.1 ppm.

(iv) (*S*)-S-4-Hydroxy-4-phenylbutyl ethanethioate **5a**:[1]

The synthesis followed General Procedure B to obtain **5a** (1.94 g, 96% yield, 90% *ee*) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.26 (m, 5 H), 4.70 (m, 1 H), 2.90 (dd, J = 6.9 Hz, 6.9 Hz, 2 H), 2.31 (s, 3 H), 1.69–1.91 (m, 4 H), 1.60 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 196.0, 144.6, 128.6, 127.8, 125.9, 74.1, 38.0, 30.8, 29.0, 26.1 ppm.

(v) (*S*)-S-4-hydroxy-4-(4-methoxyphenyl)butylethanethioate **5b**:[1]

The synthesis followed General Procedure B to obtain **5b** (1.46 g, 64% yield, 87% *ee*) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.28 (m, 2 H), 6.87–6.90 (m, 2 H), 4.65 (m, 1 H), 3.82 (s, 3 H), 2.91 (dd, J = 7.1 Hz, 7.1 Hz, 2 H), 2.32 (s, 3 H), 1.69–1.88 (m, 4 H), 1.58–1.60 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 196.2, 159.1, 136.7, 127.1, 113.9, 73.5, 55.3, 37.8, 30.6, 28.9, 26.0 ppm.

(vi) (*S*)-S-4-(4-fluorophenyl)-4-hydroxybutyl ethanethioate **5c**:[1]

The synthesis followed General Procedure B to obtain **5c** (1.45 g, 66% yield, 80% *ee*) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.29–7.32 (m, 2 H), 7.01–7.04 (m, 2 H), 4.74 (dd, J = 5.4 Hz, 7.4 Hz, 1 H), 2.94 (dd, J = 7.4 Hz, 7.4 Hz, 2 H), 2.33 (s, 3 H), 1.95 (bs, 1 H), 1.80–1.84 (m, 1 H), 1.69–1.76 (m, 2 H), 1.58–1.60 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 163.9, 160.7, 140.4, 127.6, 127.5, 115.6, 115.3, 73.4, 38.1, 30.7, 28.9, 26.0 ppm.

(vii) (*S*)-4-mercapto-1-phenylbutan-1-ol **6a**:[1]

The synthesis followed General Procedure C to obtain **6a** (681 mg, 83% yield, 90% *ee*) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.28 (m, 5 H), 4.72 (m, 1 H), 2.58 (dddd, J = 7.2 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, 2 H) 1.77–1.93 (m, 4 H), 1.58–1.69 (m, 1 H), 1.35 (dd, J = 7.7 Hz, 7.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 144.7, 128.8, 127.9, 126.1, 74.4, 37.9, 30.5, 24.8 ppm.

(viii) (*S*)-4-mercapto-1-(4-methoxyphenyl)butan-1-ol **6b**:[2]

The synthesis followed General Procedure C to obtain **6b** (898 mg, 94% yield, 87% *ee*) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.28 (m, 2 H), 6.87–6.90 (m, 2 H), 4.61–4.65 (m, 1 H), 3.81 (s, 3 H), 2.56 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 2.52 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 1.70–1.92 (m, 4 H), 1.59 (m, 1 H), 1.33 (dd, J = 7.8 Hz, 7.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 159.4, 136.9, 127.3, 114.2, 74.0, 55.5, 37.8, 30.6, 24.8 ppm.

(ix) Synthesis of (S)-1-(4-fluorophenyl)-4-mercaptobutan-1-ol **6c**:[1]

The synthesis followed General Procedure C to obtain **6c** (631 mg, 70% yield, 80% *ee*) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.33 (m, 2 H), 7.01–7.06 (m, 2 H), 4.68 (m, 1 H), 2.56 (dd, J = 7.2 Hz, 7.2 Hz, 1 H), 2.53 (dd, J = 7.2 Hz, 7.2 Hz, 1 H), 1.70–1.90 (m, 4 H), 1.58–1.62 (m, 1 H), 1.33 (dd, J = 7.9 Hz, 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 163.7, 161.2, 140.5, 140.4, 127.7, 127.7, 115.7, 115.5, 73.7, 37.9, 30.4, 24.7 ppm.

(x) 6-chloro-1-phenylhex-1-yn-3-one **3d**:[1]

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.57 (d, J = 7.2 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 3.63 (t, J = 6.4 Hz, 2 H), 2.89 (t, J = 7.2 Hz, 2 H), 2.19 (quin, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.3, 133.1, 130.8, 128.6, 119.7, 91.2, 87.6, 43.9, 42.3, 26.6 ppm.

(xi) (*S*)-6-chloro-1-phenylhex-1-yn-3-ol **4d1**:[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44-7.30 (m, 5H), 4.66 (t, J = 6.4 Hz, 1H), 3.64 (t, J = 6.0 Hz, 2H), 2.08-1.93 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 131.7, 128.5, 128.3, 122.3, 89.4, 85.3, 62.2, 44.7, 35.0, 28.3 ppm.

(xii) 2-(((*S*)-6-chloro-1-phenylhex-1-yn-3-yl)oxy)tetrahydro-2H-pyran **4d2**:[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44-7.30 (m, 5H), 5.05 (bs, 1H), 4.70 (t, J = 6.4, 1H), 3.83 (t, J = 8.8 Hz, 1H), 3.64 (t, J = 6.0 Hz, 2H), 3.58-3.55 (m, 1H), 2.11-1.97 (m, 4H), 1.84-1.74 (m, 2H), 1.64-1.25 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 131.8, 128.4, 128.2, 122.6, 95.7, 87.5, 85.7, 64.6, 62.4, 44.8, 33.1, 30.5, 25.4, 19.4 ppm.

(xiii) (*S*)-((4S)-6-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)hex-5-yn-1-yl) ethanethioate **4d3**:[1]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.43-7.29 (m, 5H), 5.04 (bs, 1H), 4.65 (t, J = 6.0 Hz, 2H), 3.82 (t, J =8.0 H), 3.57-3.54 (m, 1H), 2.97 (t, J = 6.8 Hz, 2H), 2.33 (s, 3H), 1.95-1.73 (m, 7H), 1.64-1.56 (m, 3H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 195.8, 131.8, 128.3, 128.2, 122.7, 95.6, 87.6, 85.6, 64.8, 62.4, 34.8, 30.6, 30.5, 28.9, 25.6, 25.4, 19.3 ppm.

(xiv) (*S*)-S-(4-hydroxy-6-phenylhex-5-yn-1-yl) ethanethioate **5d**:[1]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.43-7.30 (m, 5H), 4.63 (t, *J* = 5.2 Hz, 1H), 2.96 (t, *J* = 6.8 Hz, 2H), 2.33 (s, 3H), 1.90-1.82 (m, 4H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 195.9, 131.7, 128.5, 128.5, 122.4, 89.6, 85.2, 62.4, 36.6, 30.6, 28.7, 25.3 ppm.

(xv) (*S*)-6-mercapto-1-phenylhex-1-yn-3-ol **6d**:[1]

IR (neat) 3351, 2925, 1705, 1598, 1489, 1442, 1412, 1264, 1143, 1050, 914, 755, 734 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.44–7.27 (m, 5H), 4.63 (t, *J* = 5.6 Hz, 1H), 2.76 (t, *J* = 6.8 Hz, 2H), 2.54 (bs, 1H), 1.98–1.86 (m, 4H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 131.6, 128.4, 128.2, 122.4, 89.7, 85.1, 62.3, 38.5, 36.2, 24.8 ppm. HRMS (ESI) calcd. for $C_{12}H_{14}SO$ $[M]^{\cdot}$ *m/z* 206.0765 found *m/z* 206.0770.

8. Copies of 1H and 13C NMR Spectra of all compounds:

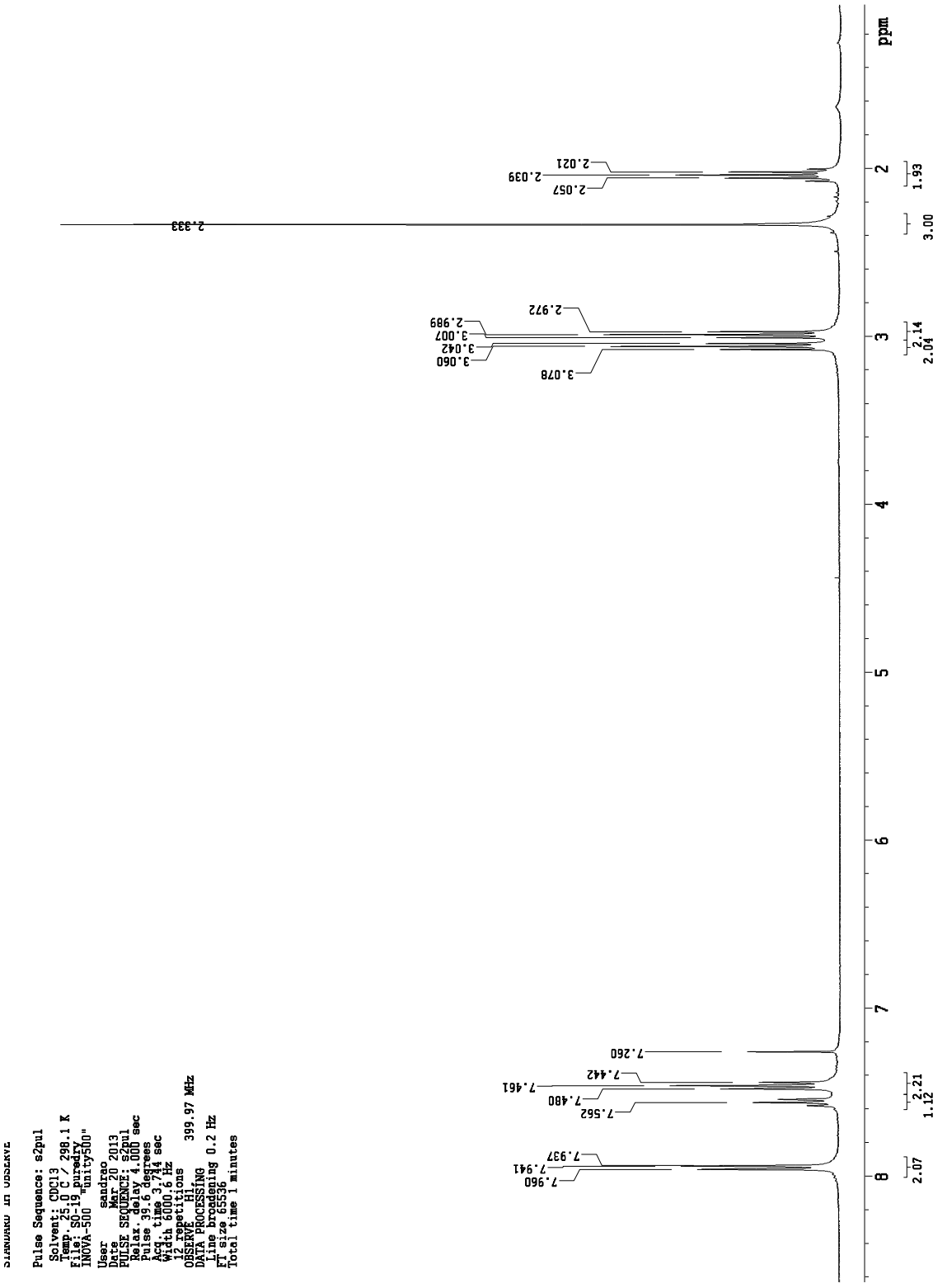


Figure 1. ^{1}H NMR of 4a in $CDCl_3$.

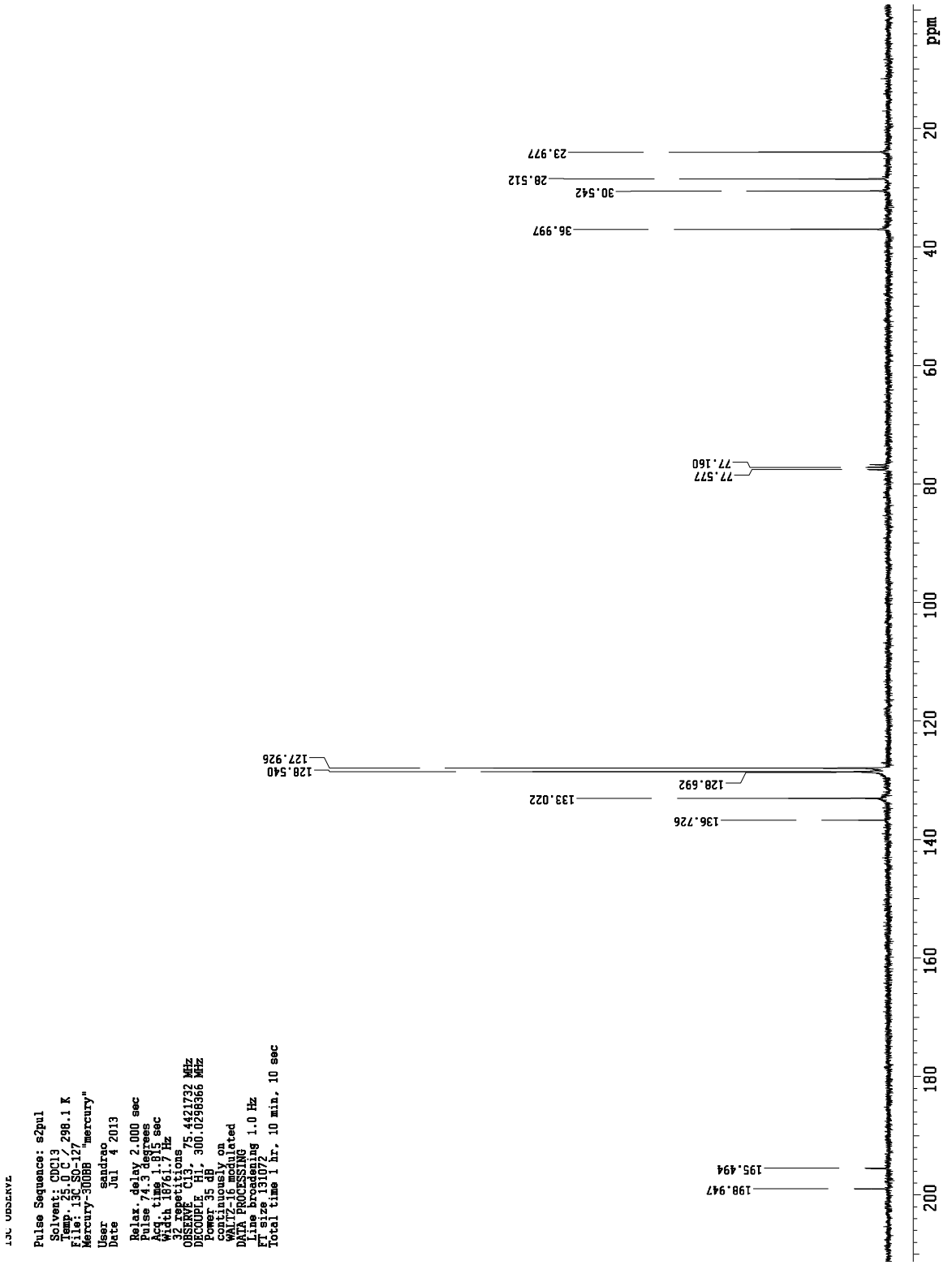


Figure 2. ^{13}C NMR of 4a in $CDCl_3$.

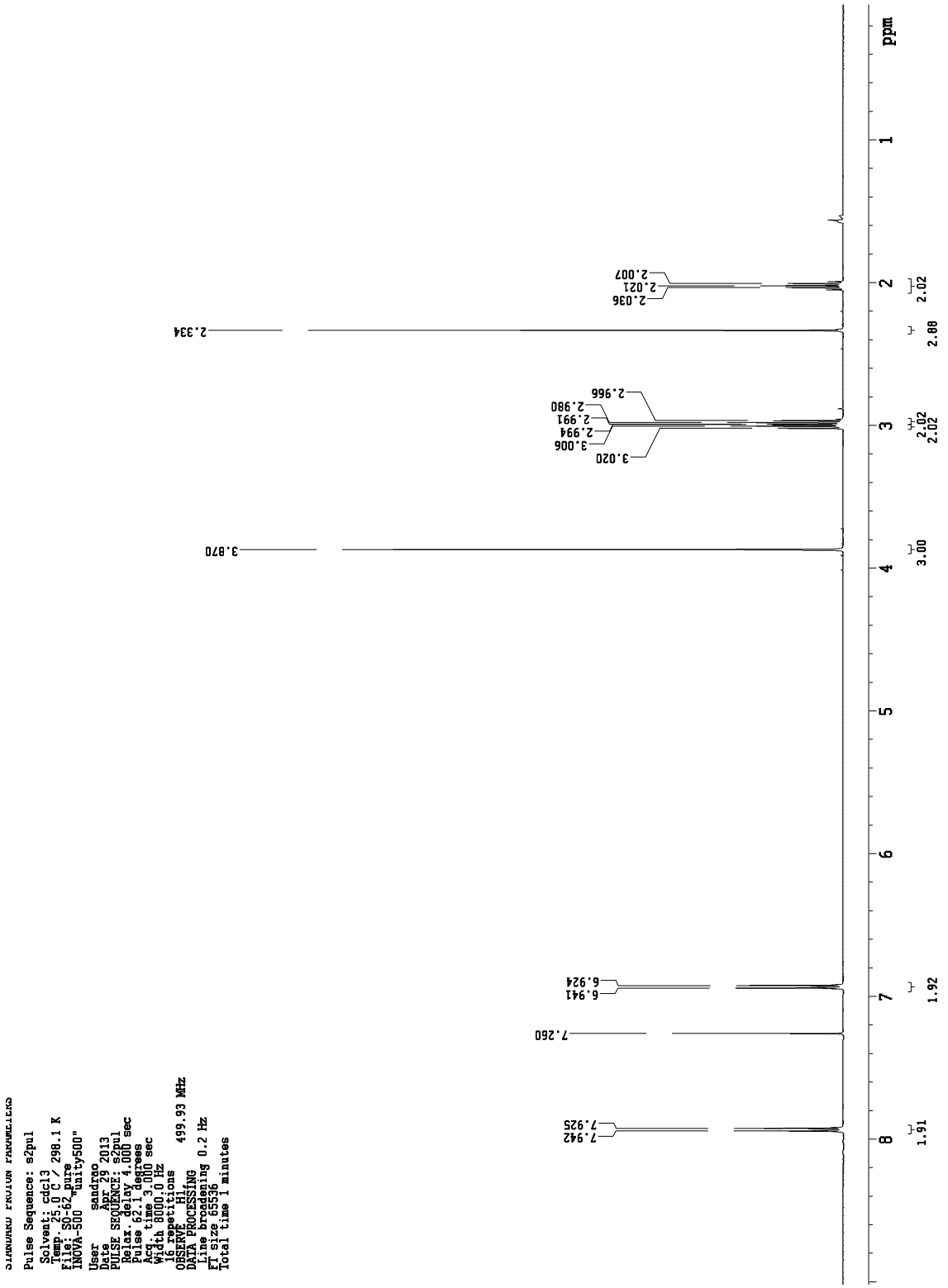


Figure 3, ^{1}H NMR of 4b in $CDCl_3$.

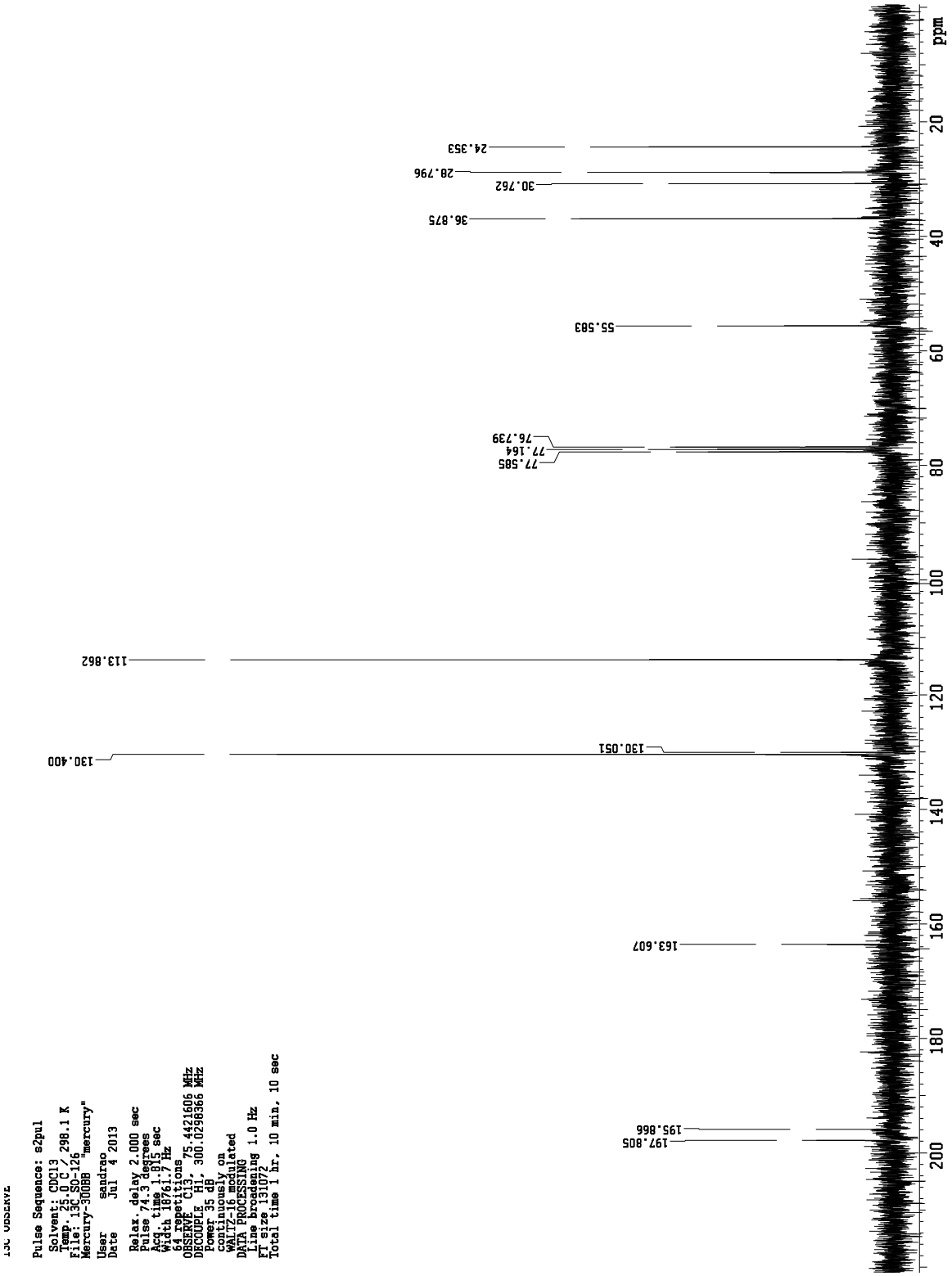


Figure 4. ^{13}C NMR of 4b in $CDCl_3$.

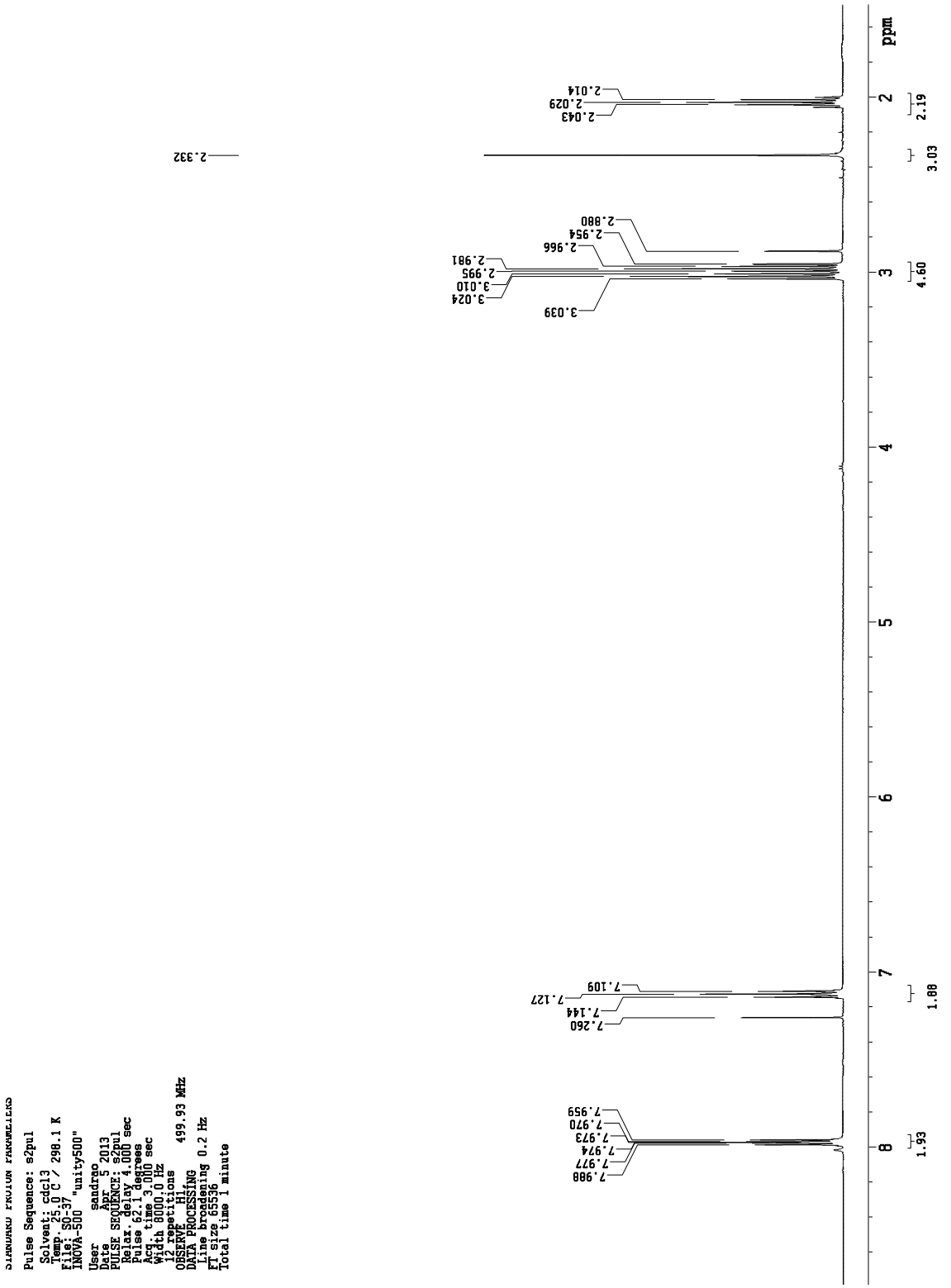


Figure 5. ^{1}H NMR of 4c in $CDCl_3$.

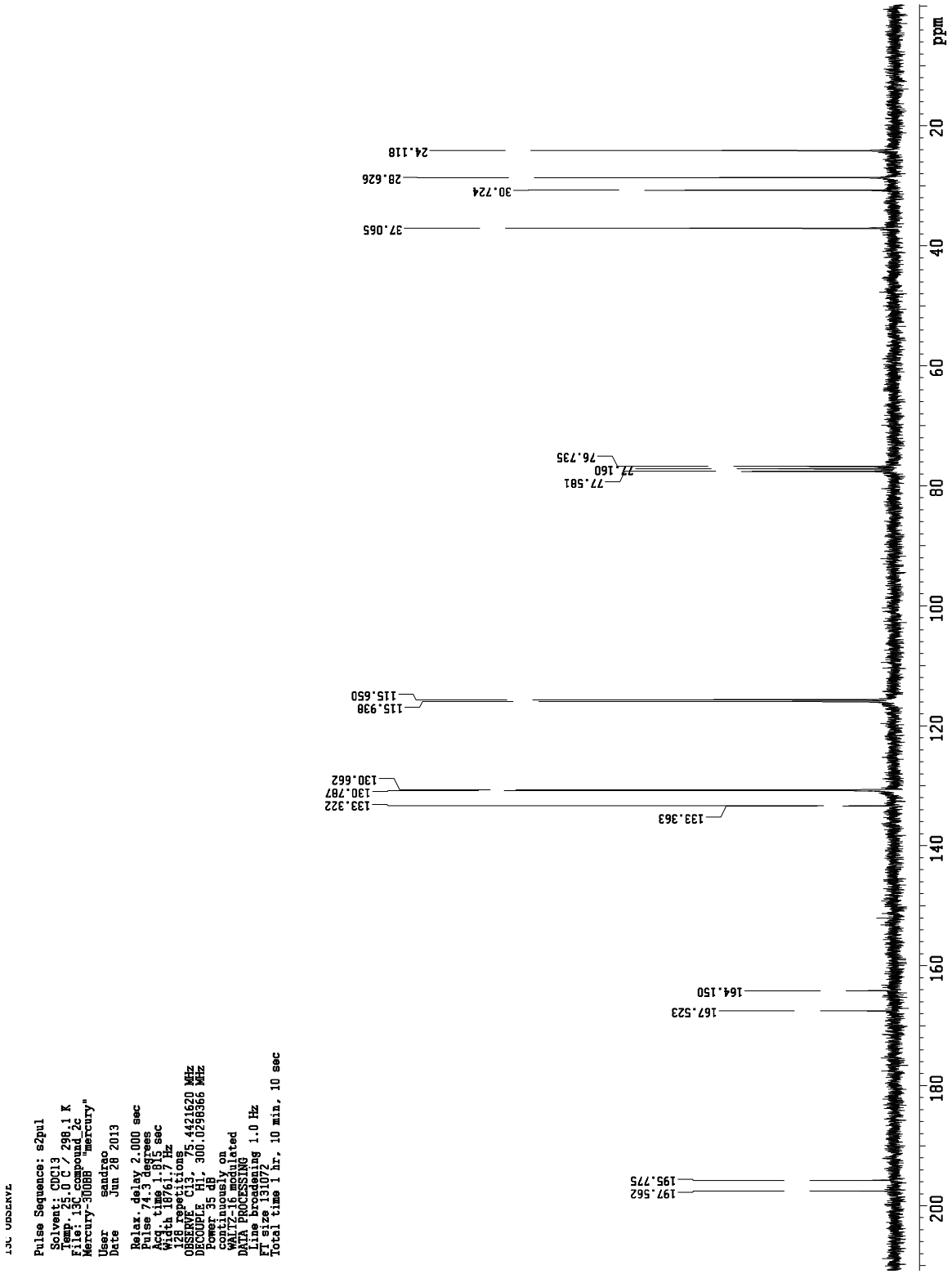


Figure 6. ^{13}C NMR of 4c in $CDCl_3$.

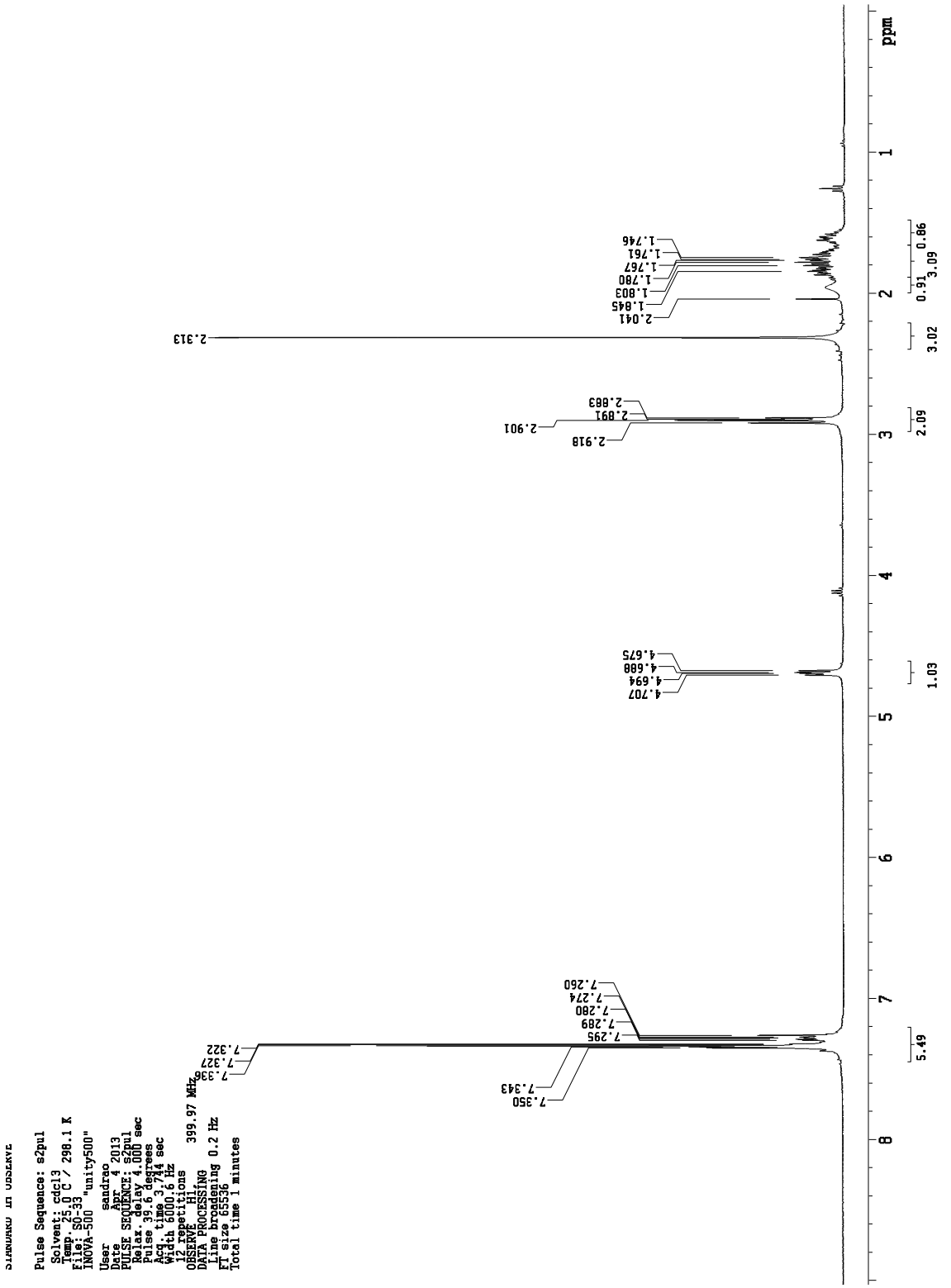


Figure 7. ^{1}H NMR of 5a in $CDCl_3$.

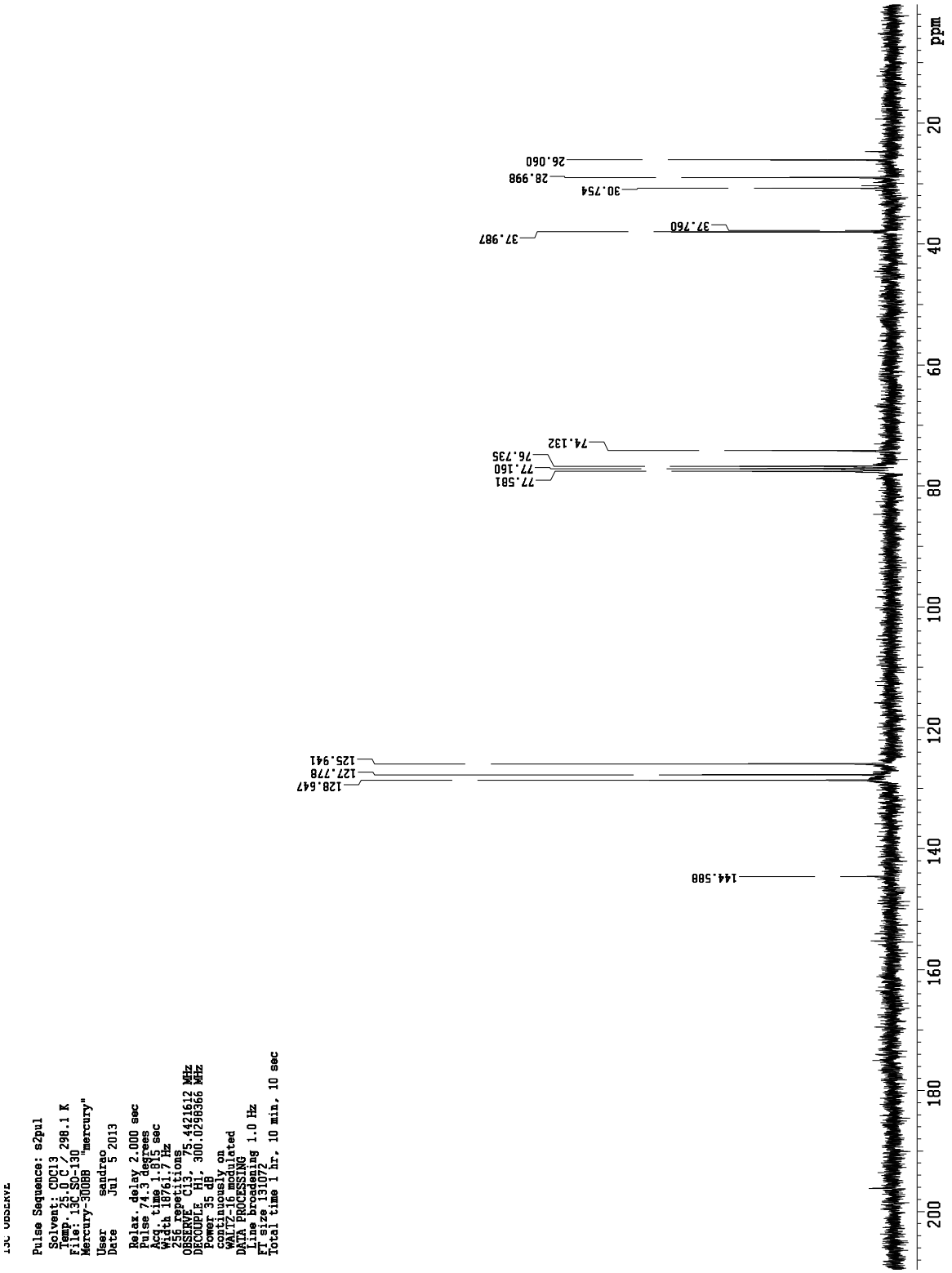


Figure 8. ^{13}C NMR of 5a in $CDCl_3$.

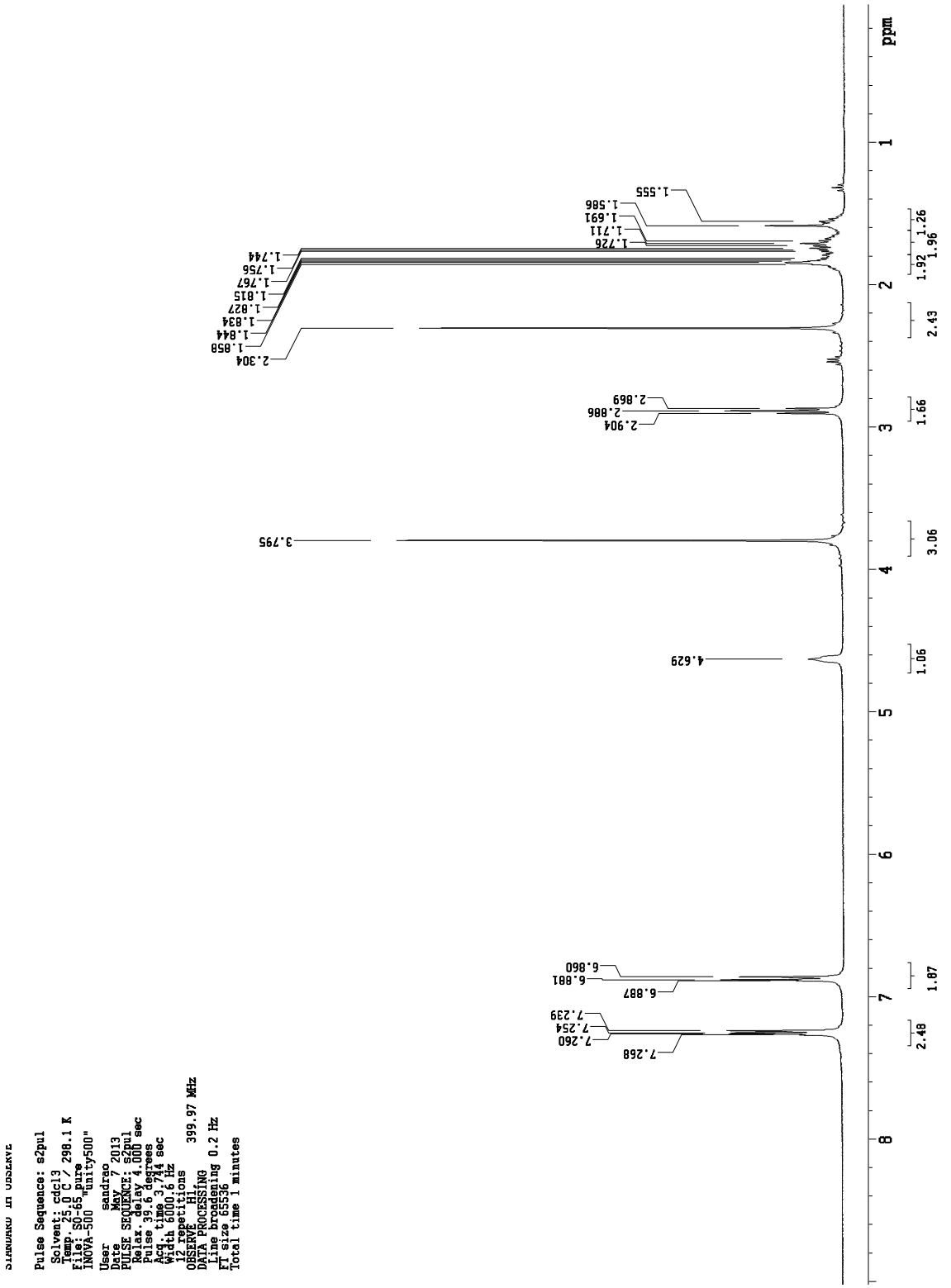


Figure 9. ^{1}H NMR of 5b in $CDCl_3$.

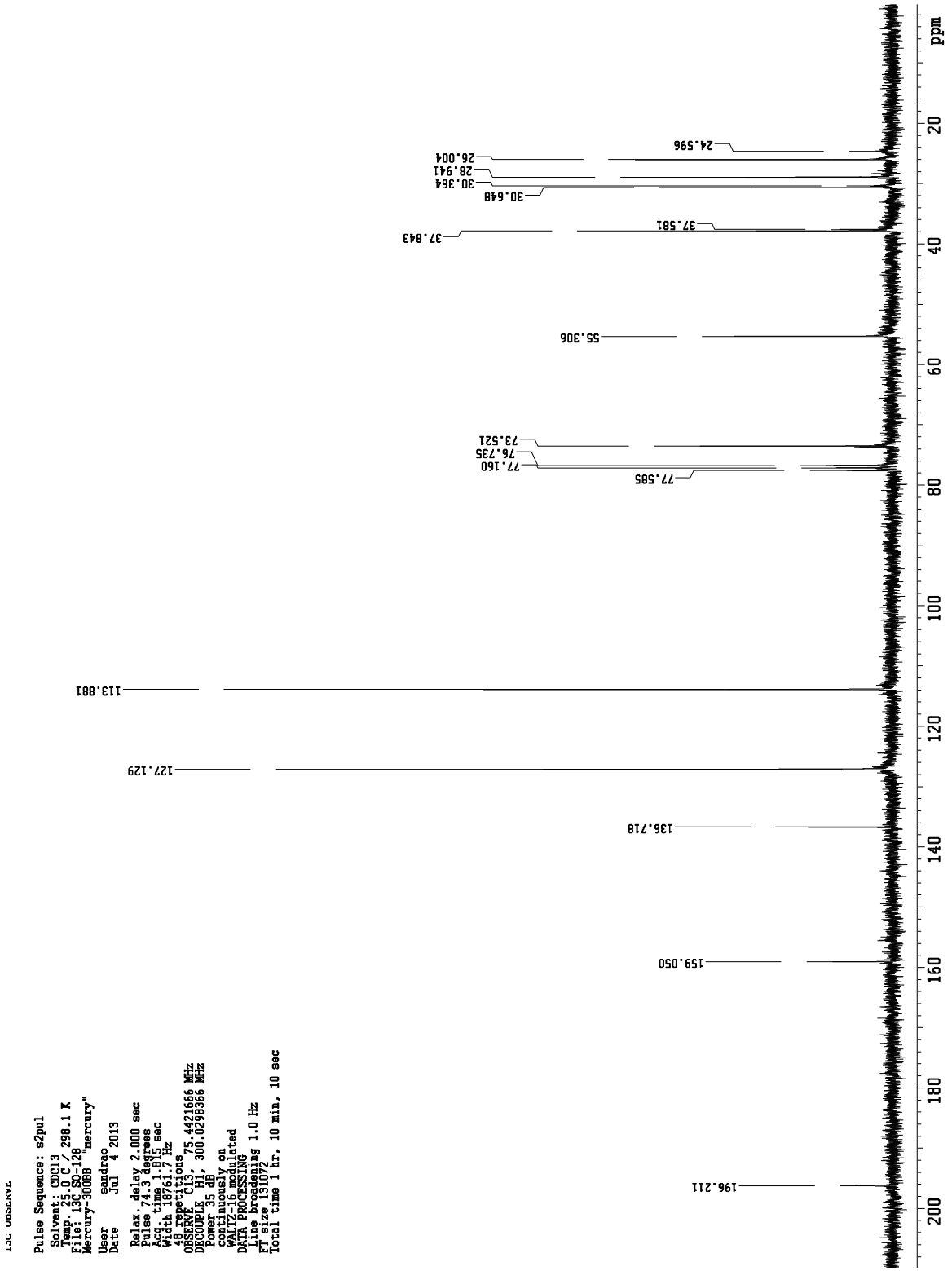


Figure 10. ^{13}C NMR of 5b in $CDCl_3$.

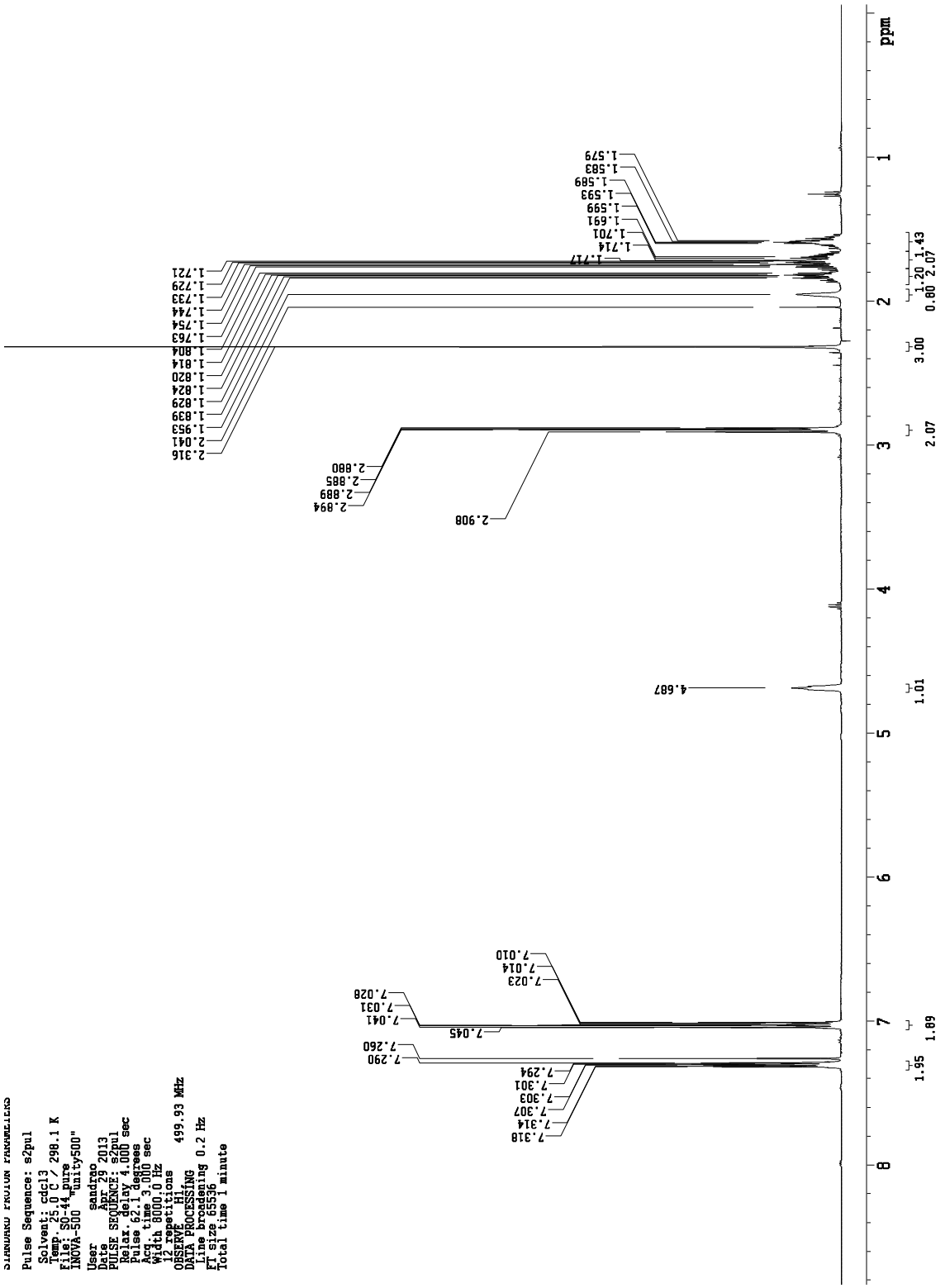


Figure 11. ^{1}H NMR of 5c in $CDCl_3$.

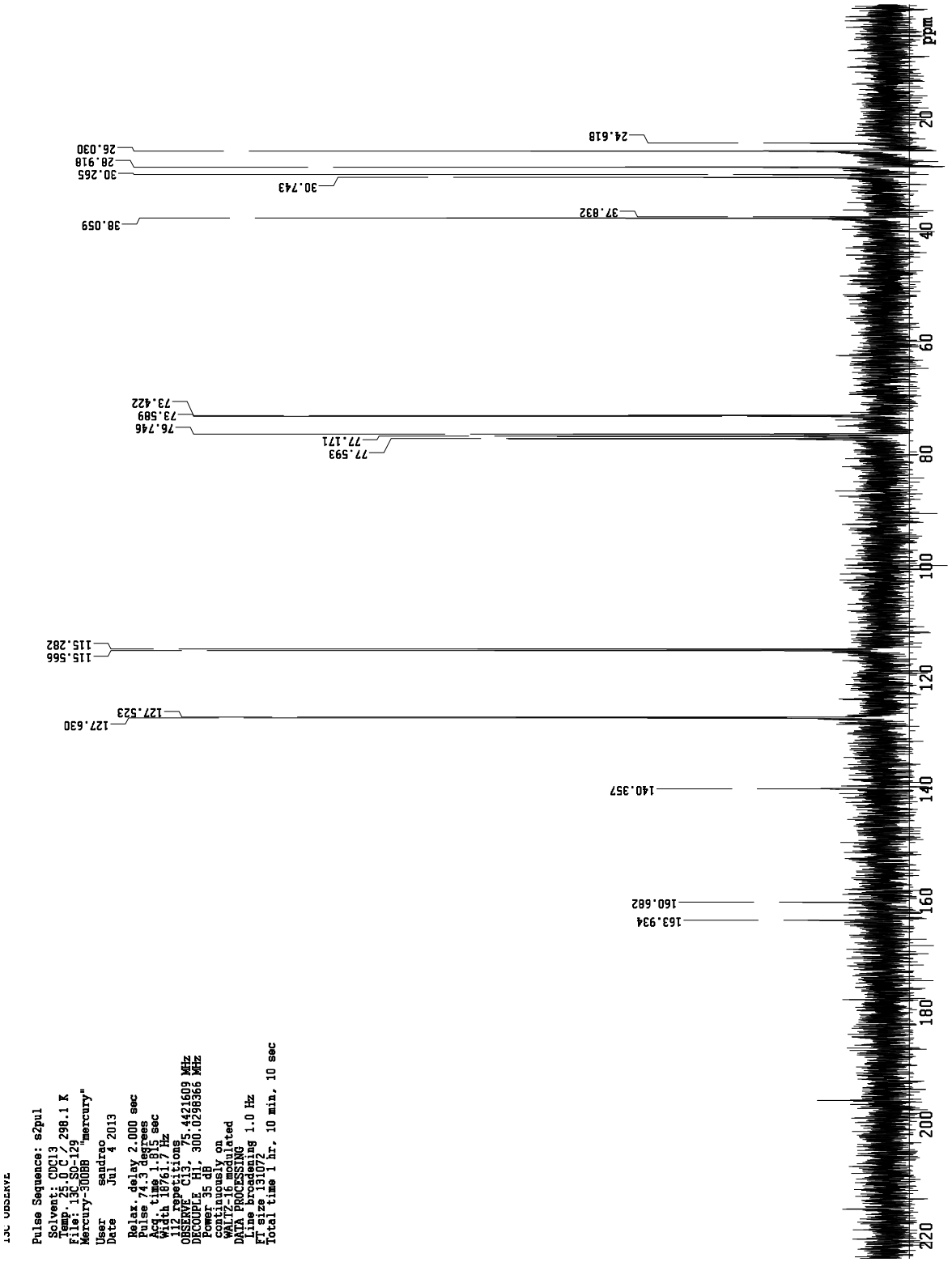


Figure 12. ^{13}C NMR of 5c in $CDCl_3$.

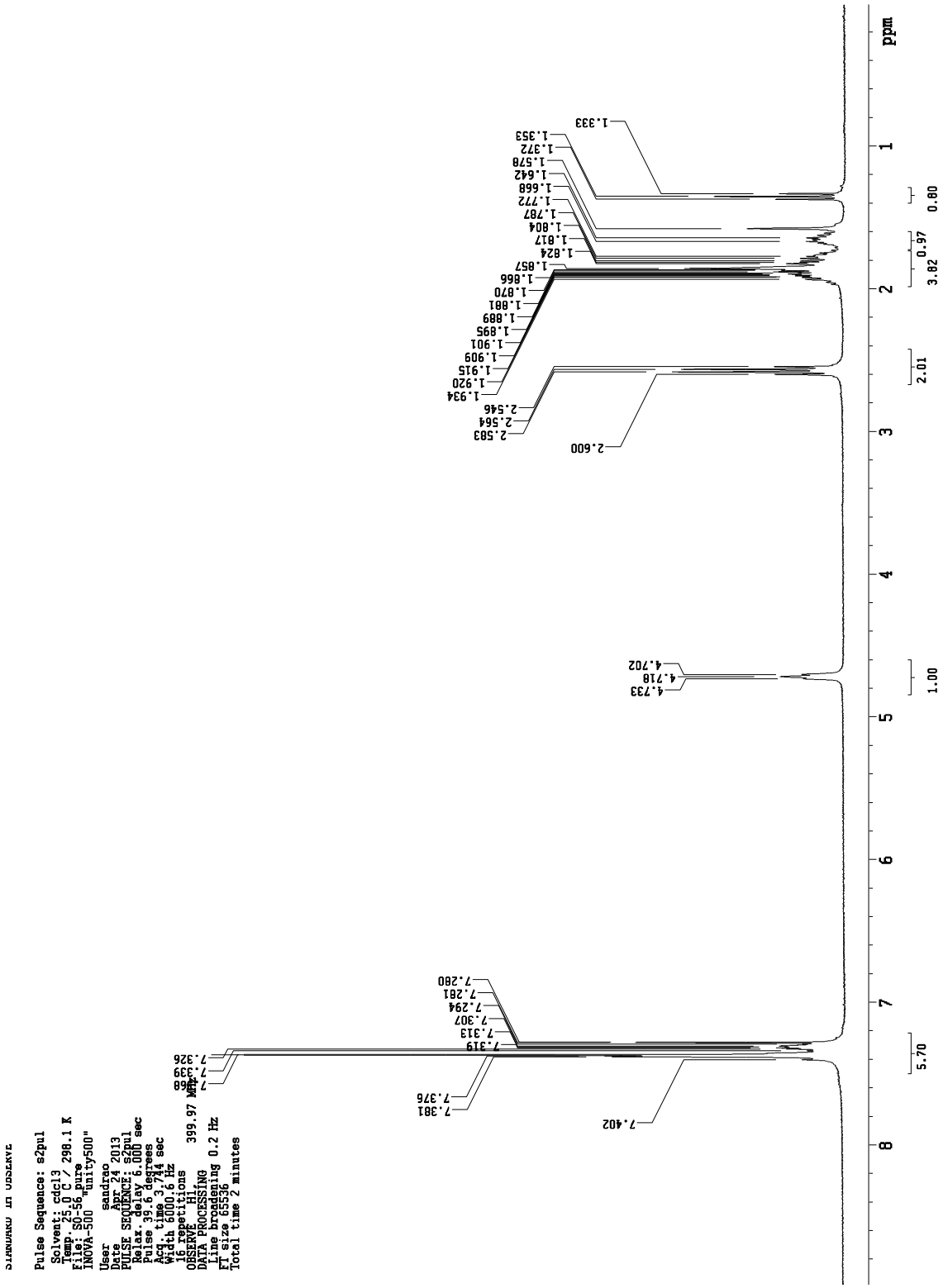


Figure 13. ^{1}H NMR of 6a in $CDCl_3$.

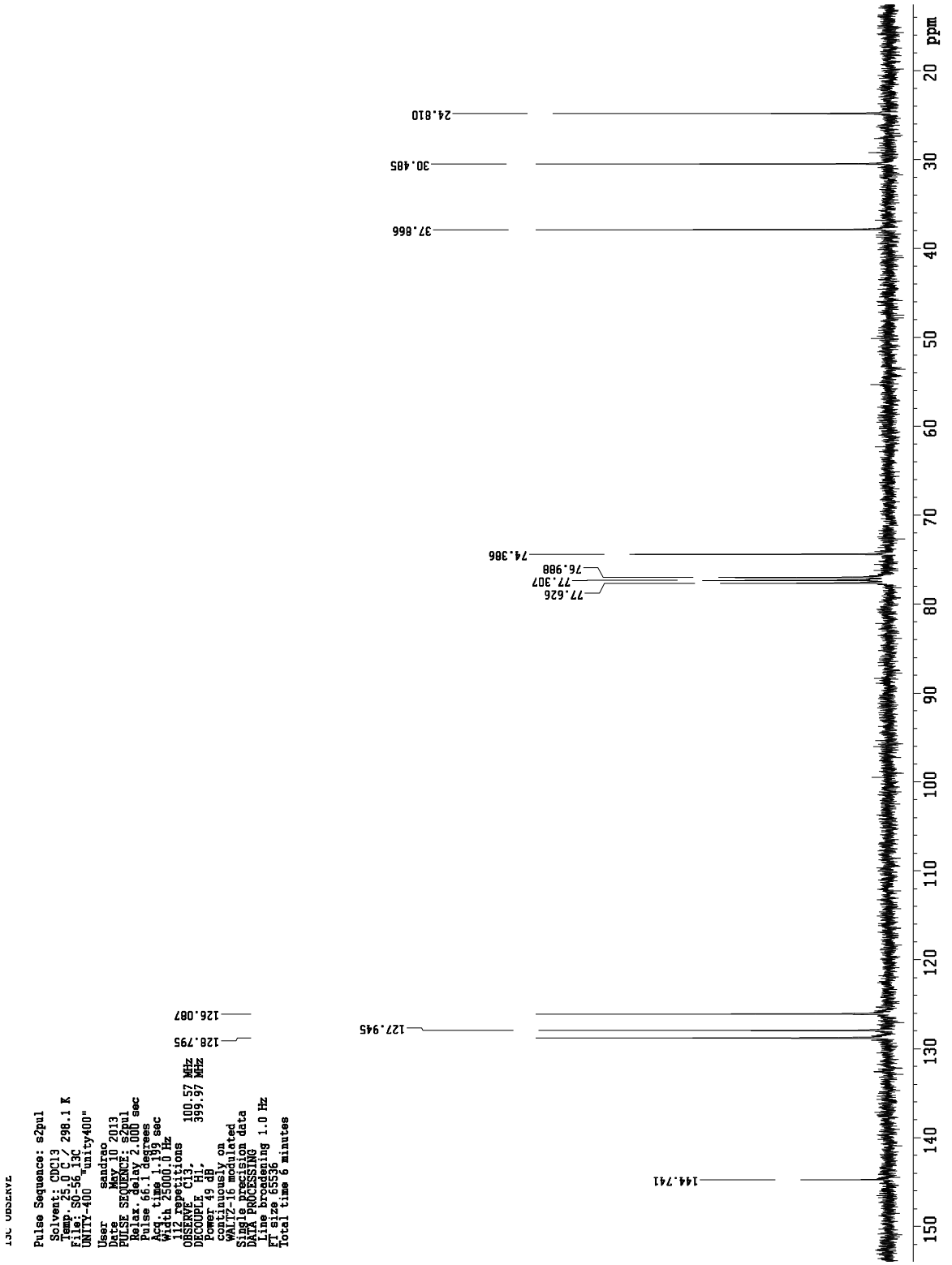


Figure 14. ^{13}C NMR of 6a in $CDCl_3$.

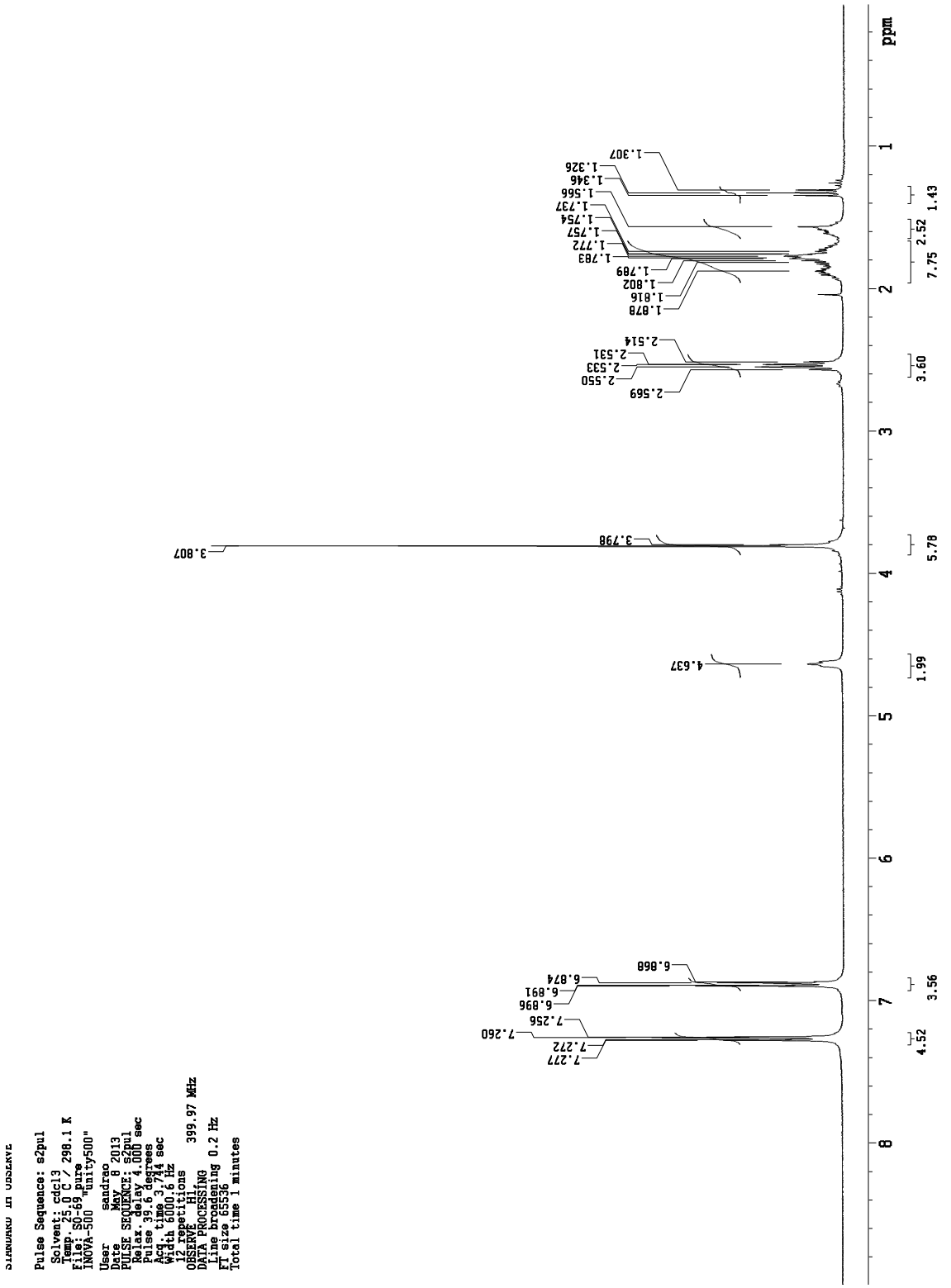


Figure 15. ^{1}H NMR of 6b in $CDCl_3$.

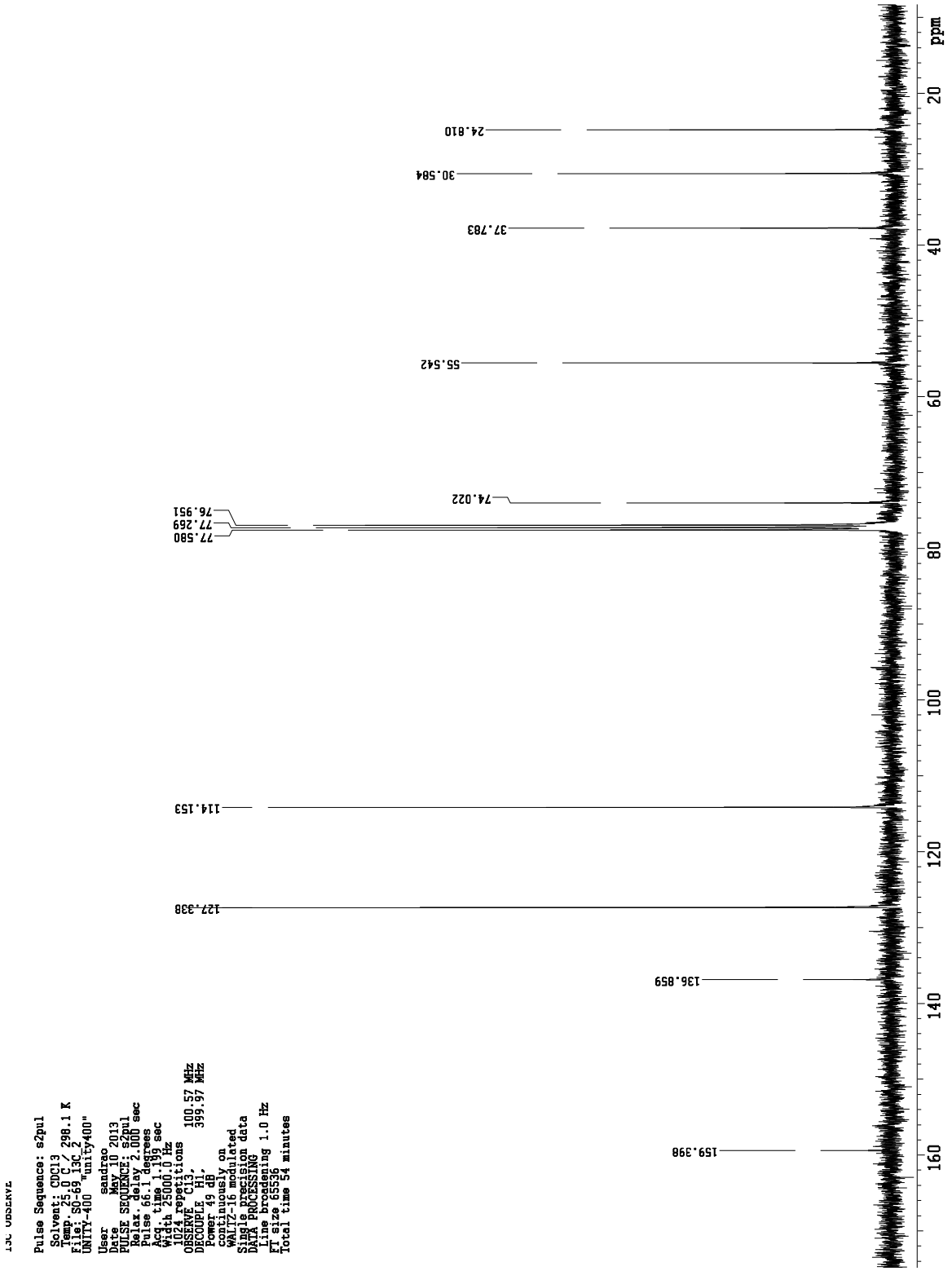


Figure 16. ^{13}C NMR of 6b in $CDCl_3$.

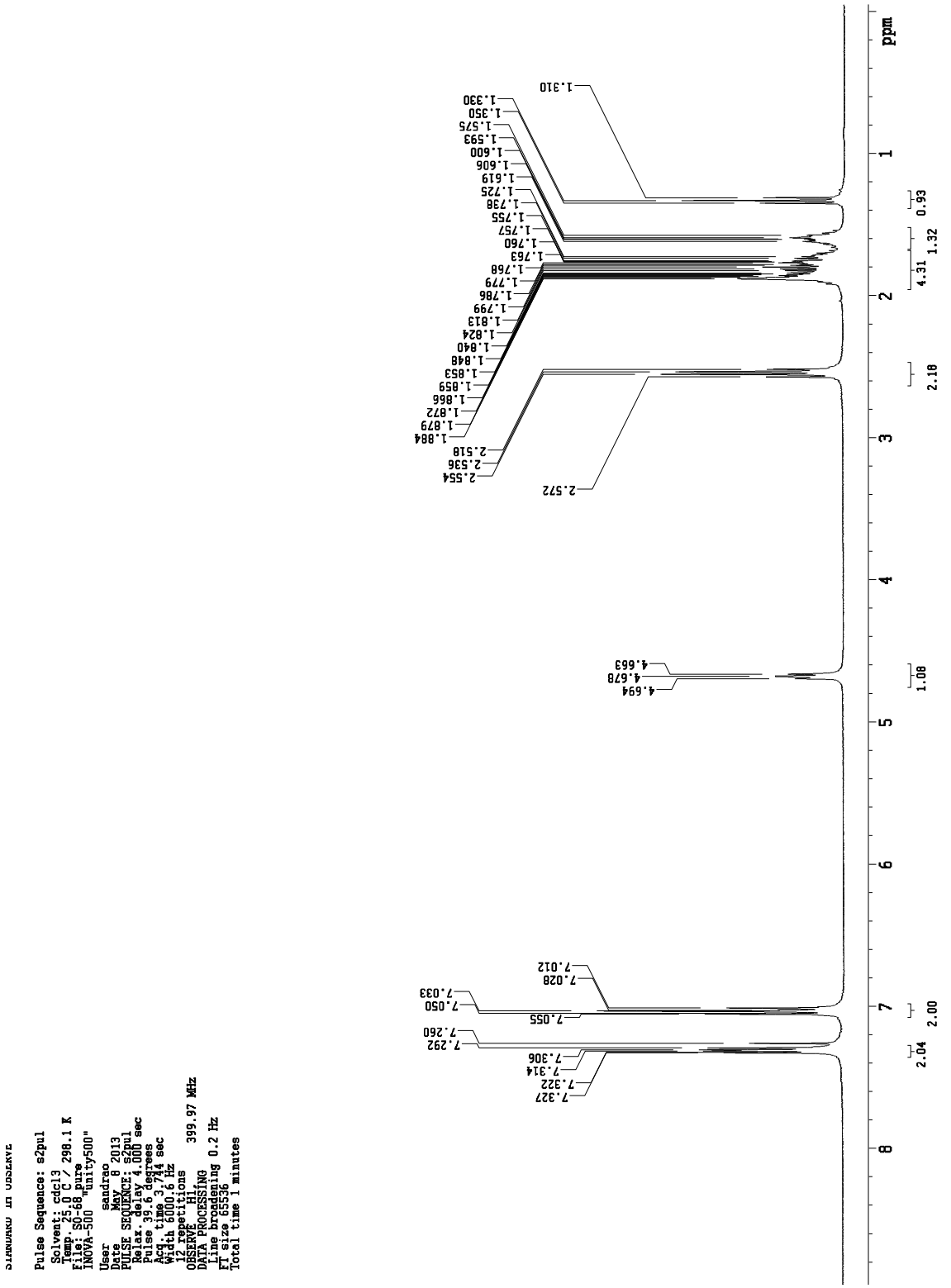


Figure 17. ^{1}H NMR of 6c in $CDCl_3$.

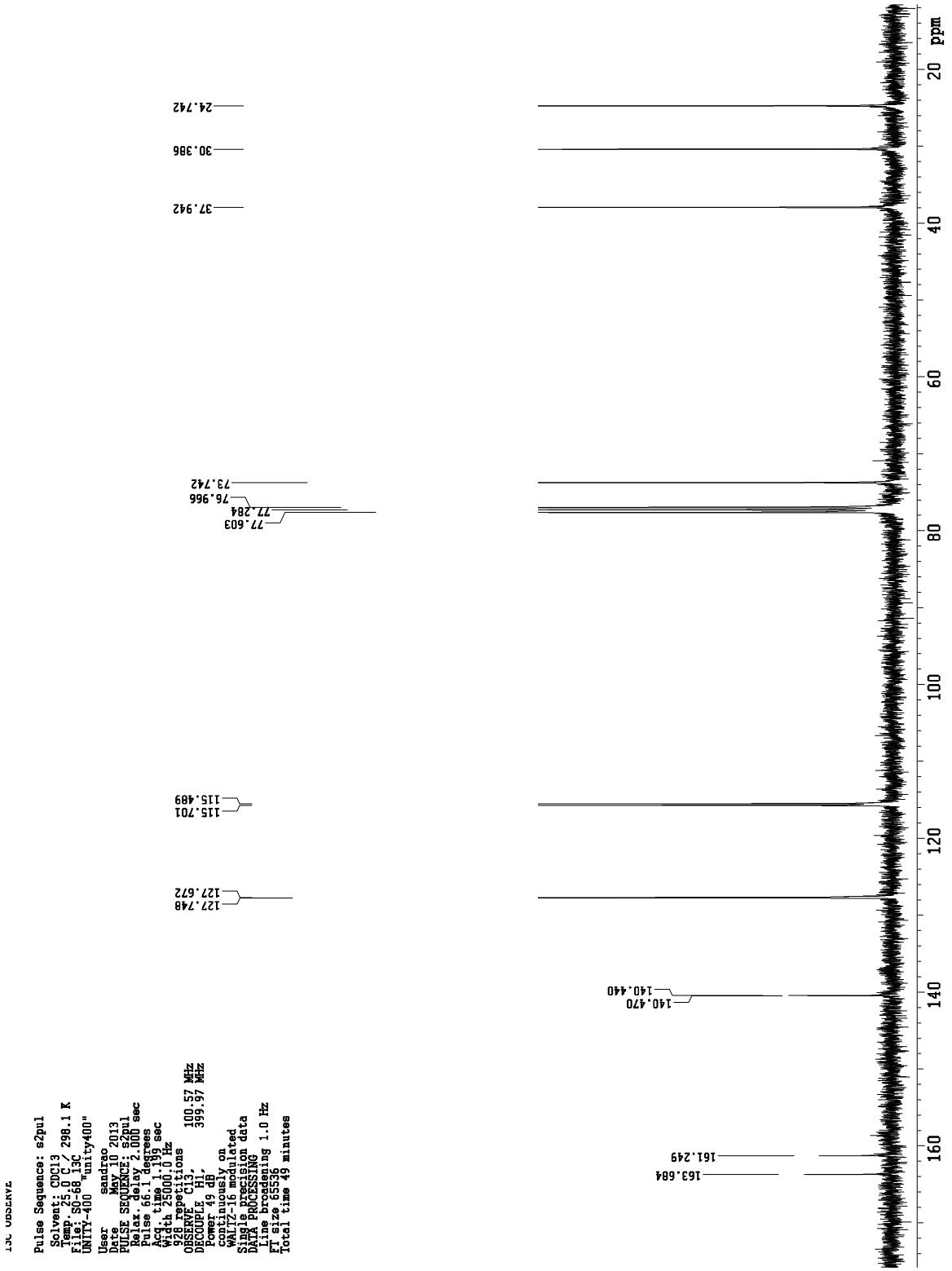


Figure 18. ^{13}C NMR of 6c in $CDCl_3$.

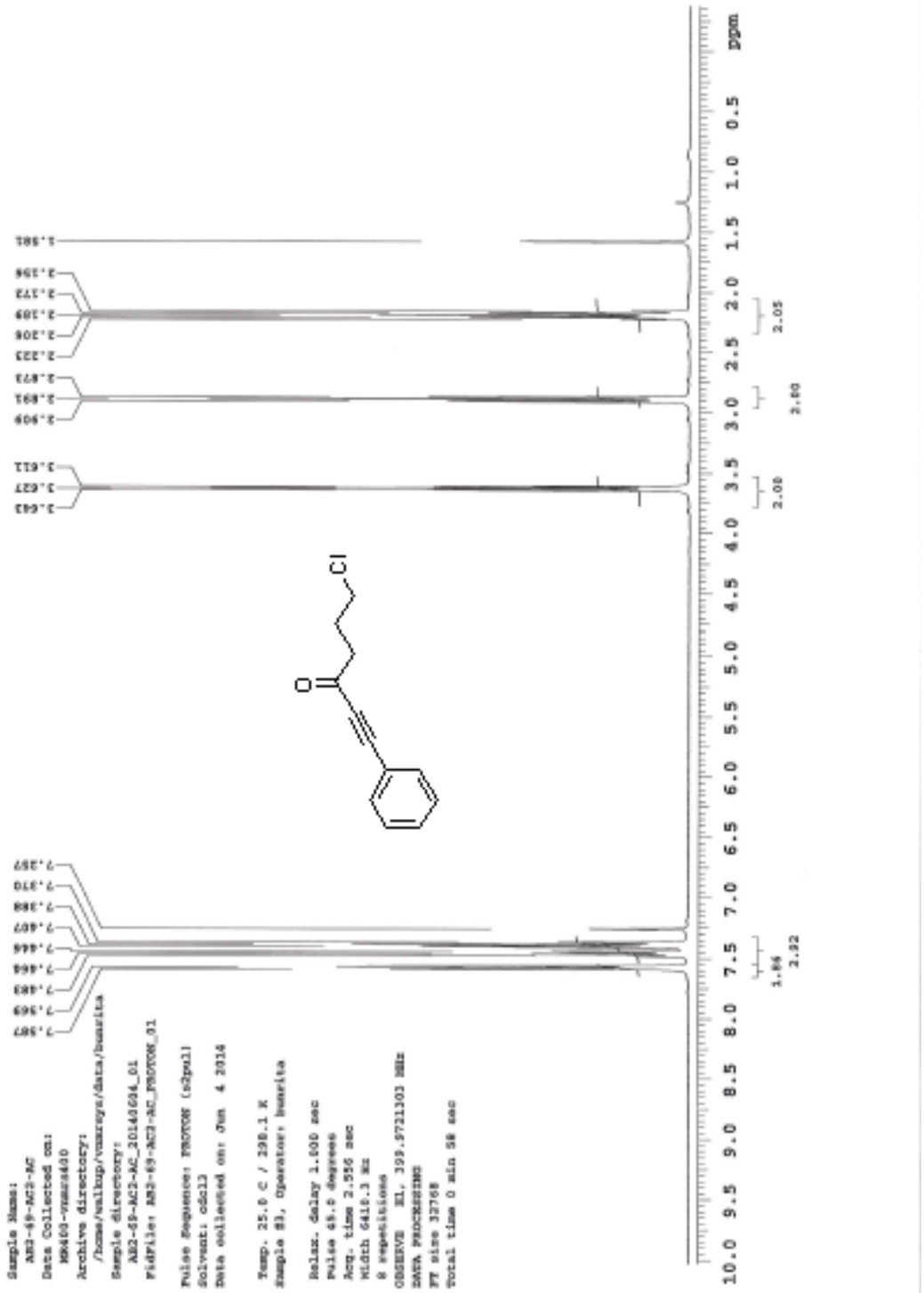


Figure 19. ^{1}H NMR of 3d in $CDCl_3$.

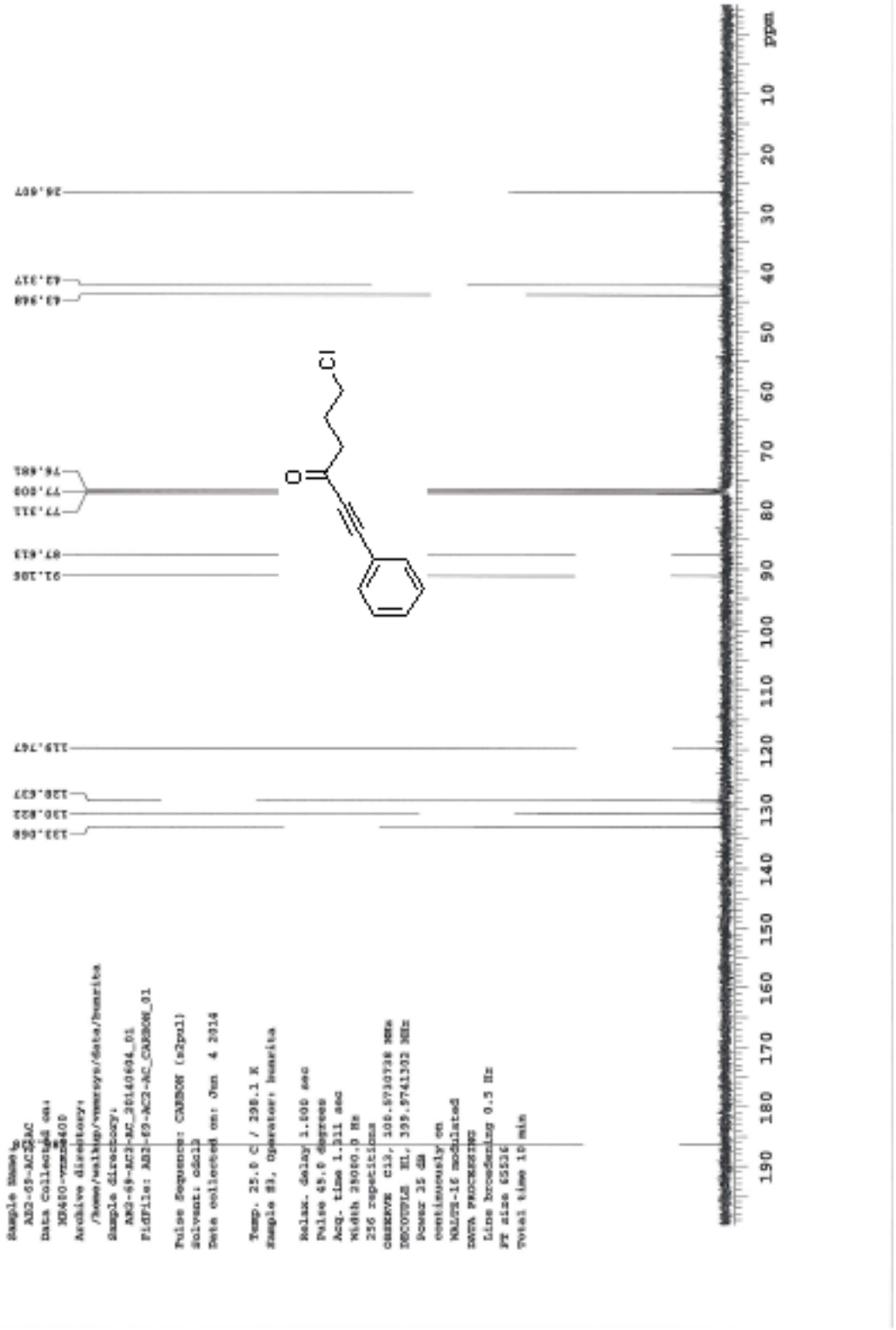


Figure20. ^{13}C NMR of 3d in $CDCl_3$.

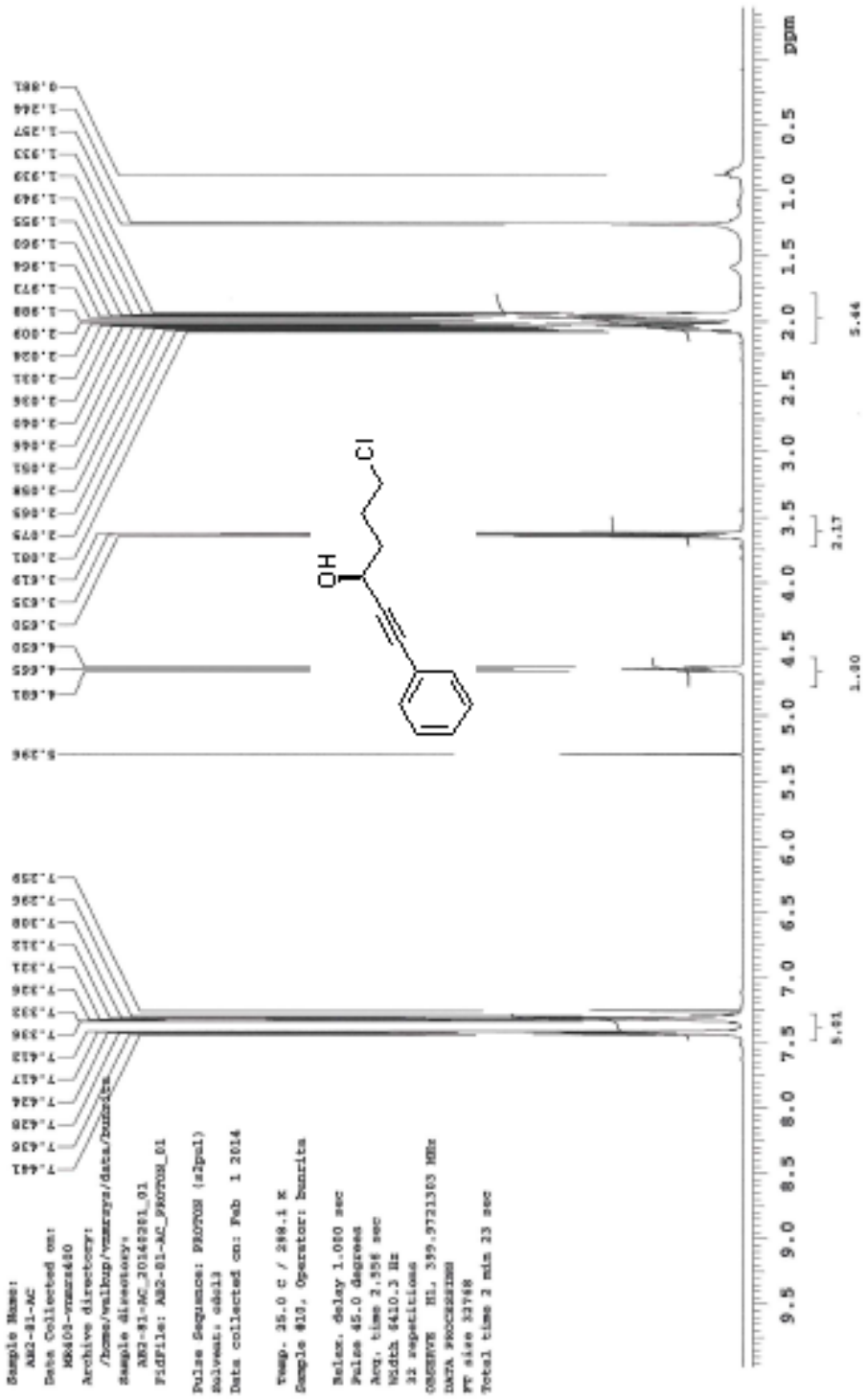


Figure 21. ^{1}H NMR of 4d1 in $CDCl_3$.

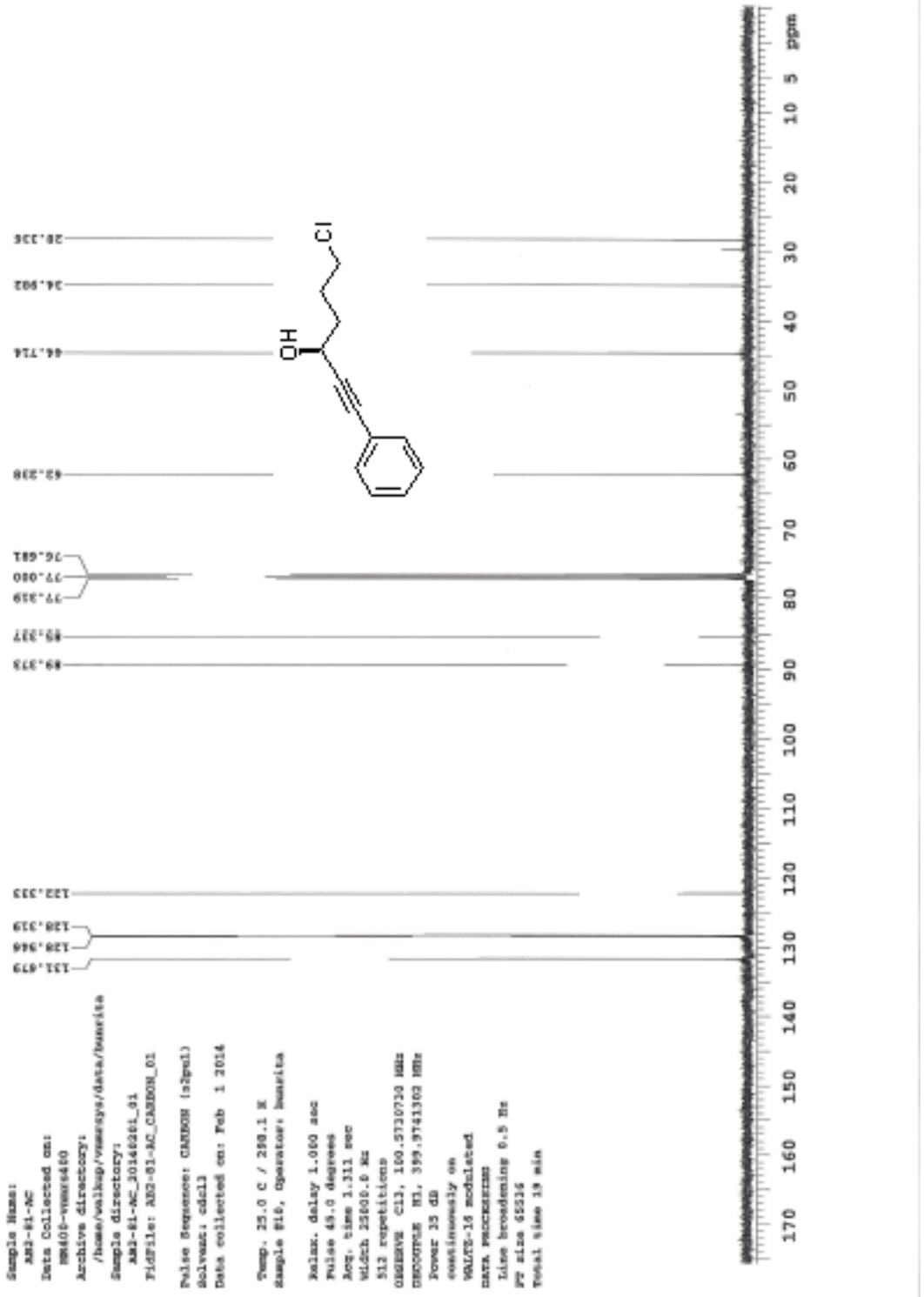


Figure 22. ^{13}C NMR of 4d1 in $CDCl_3$.

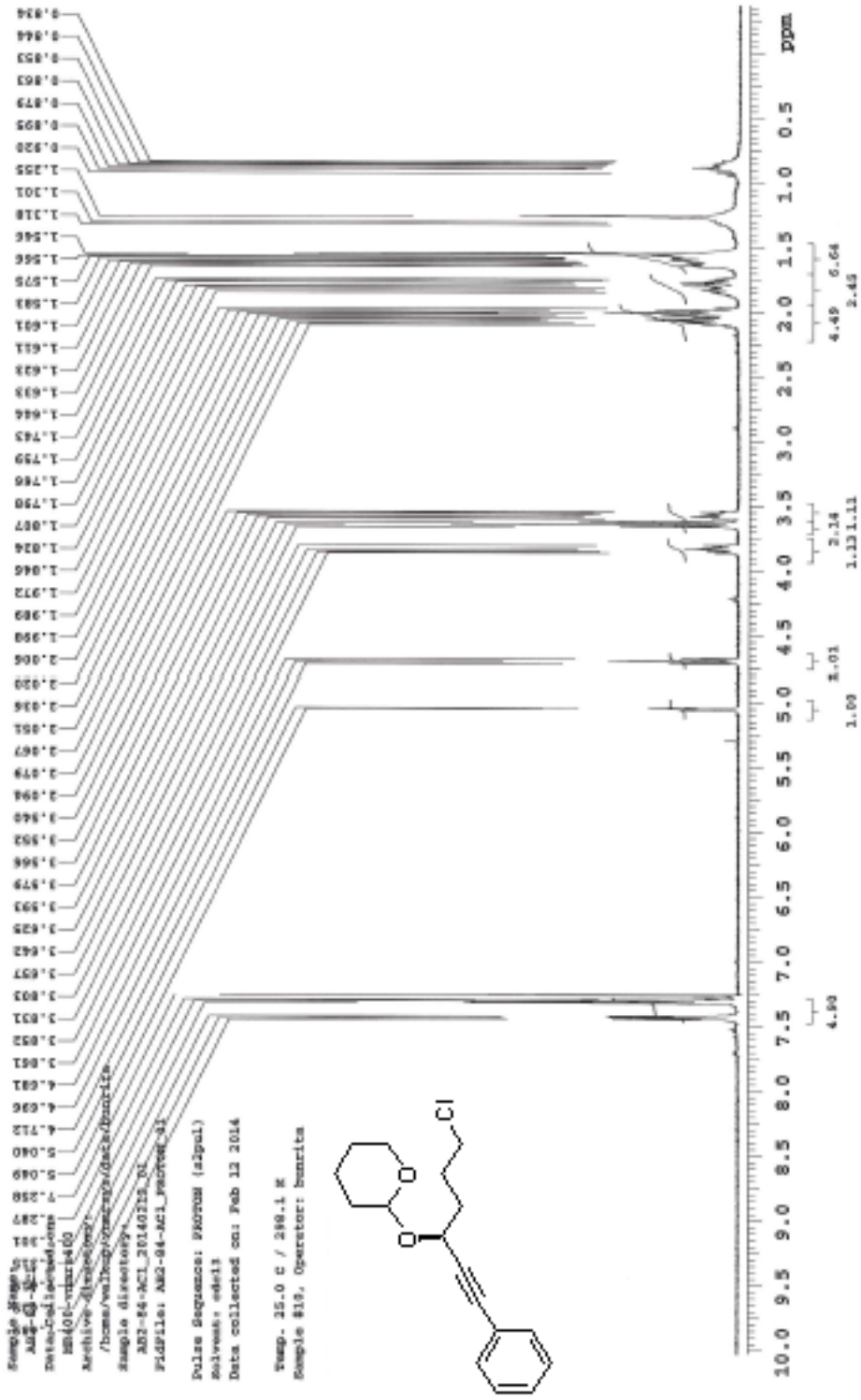


Figure 23. ^{1}H NMR of 4d2 in $CDCl_3$.

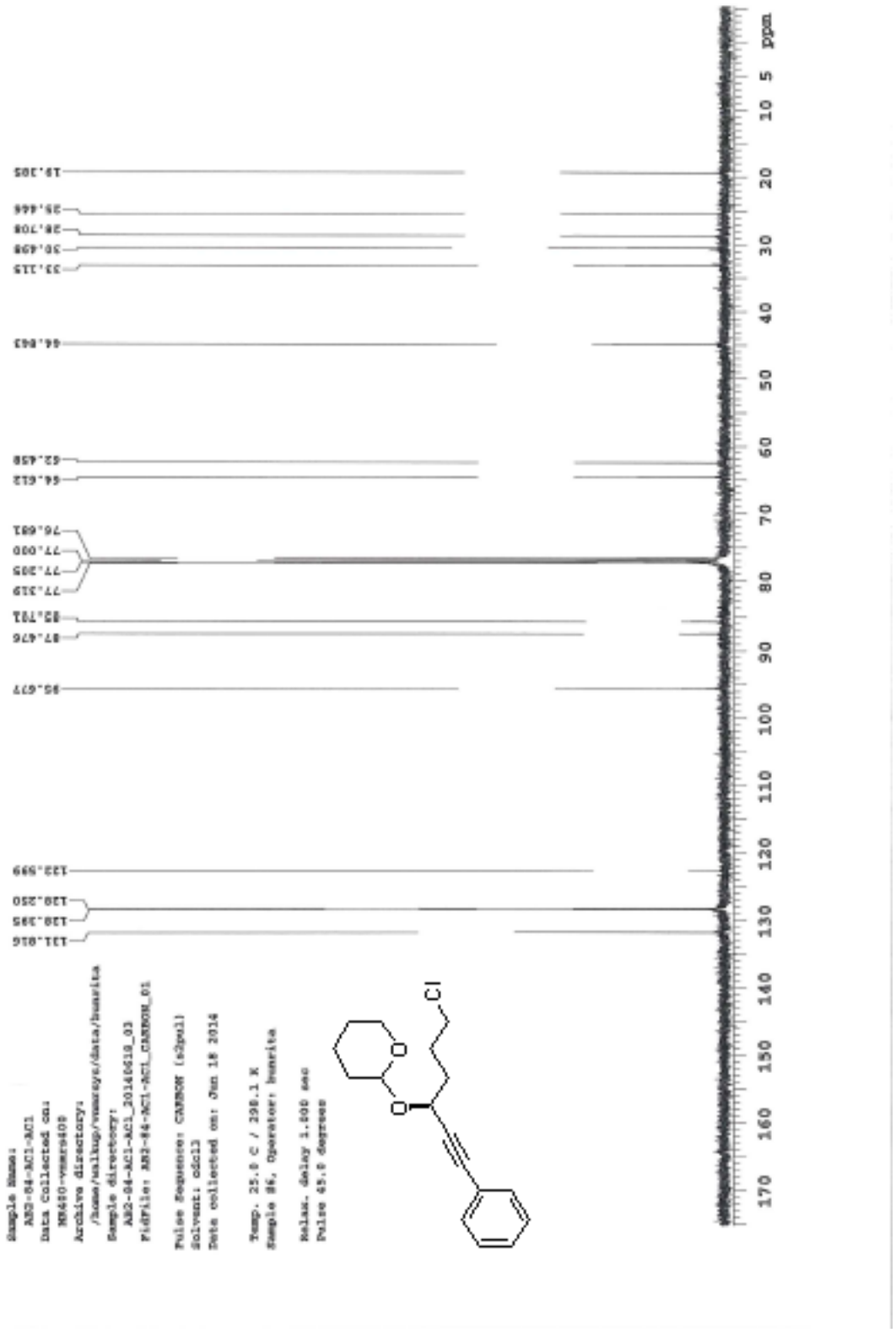


Figure 24. ^{13}C NMR of 4d2 in $CDCl_3$.

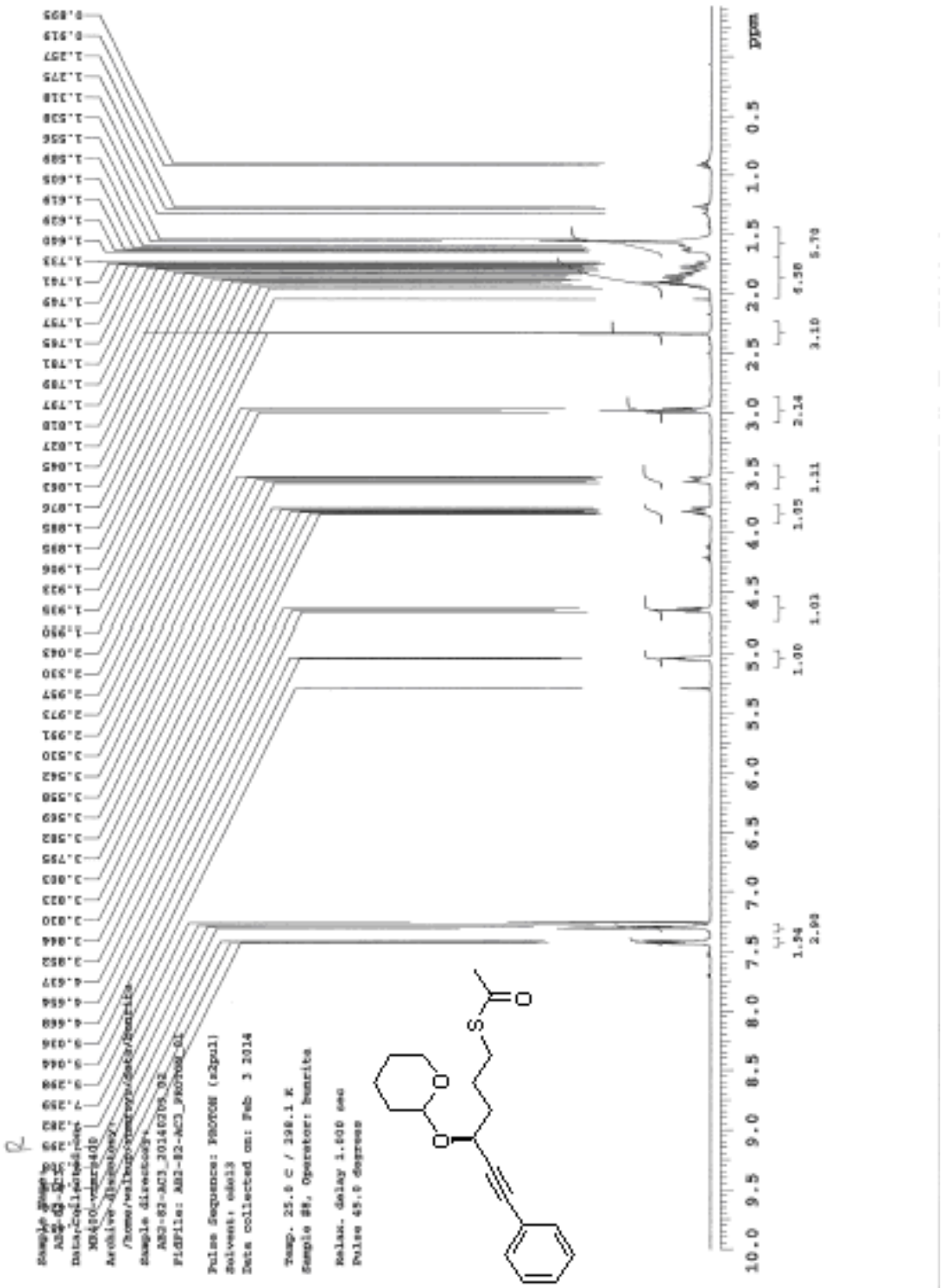


Figure 25. ^{1}H NMR of 4d3 in $CDCl_3$.

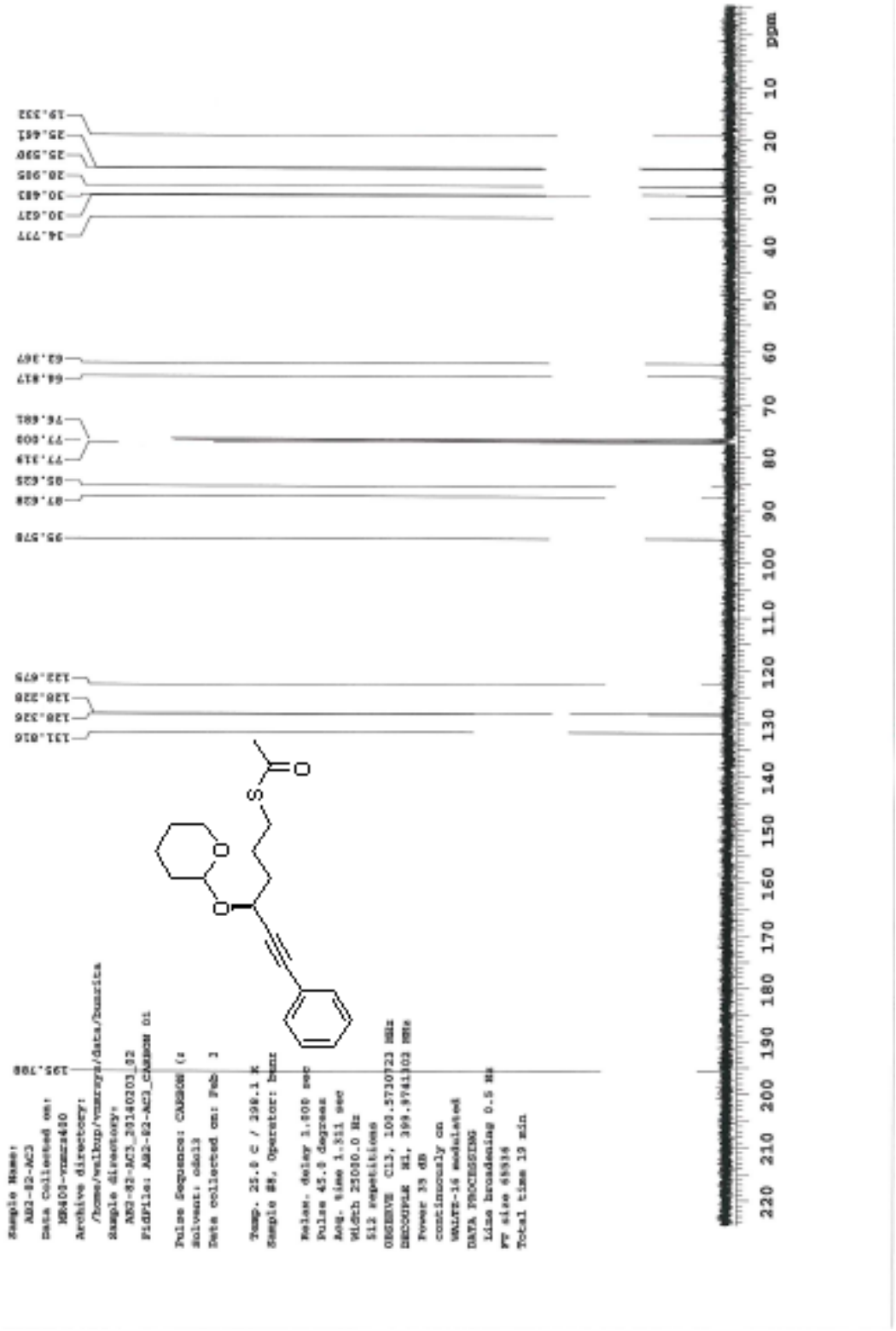


Figure 26. ^{13}C NMR of 4d3 in $CDCl_3$.

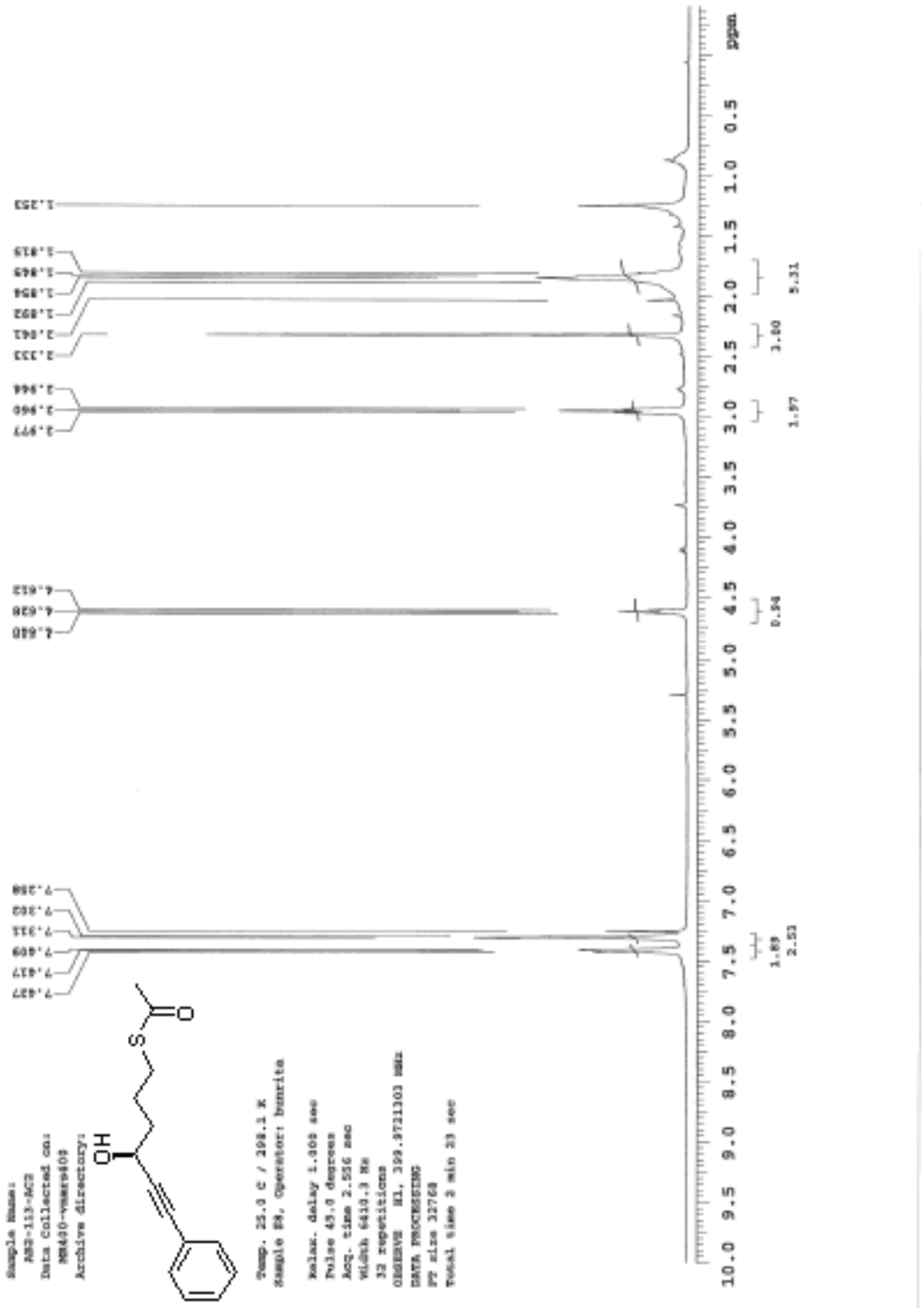


Figure 27. ^{1}H NMR of 5d in $CDCl_3$.

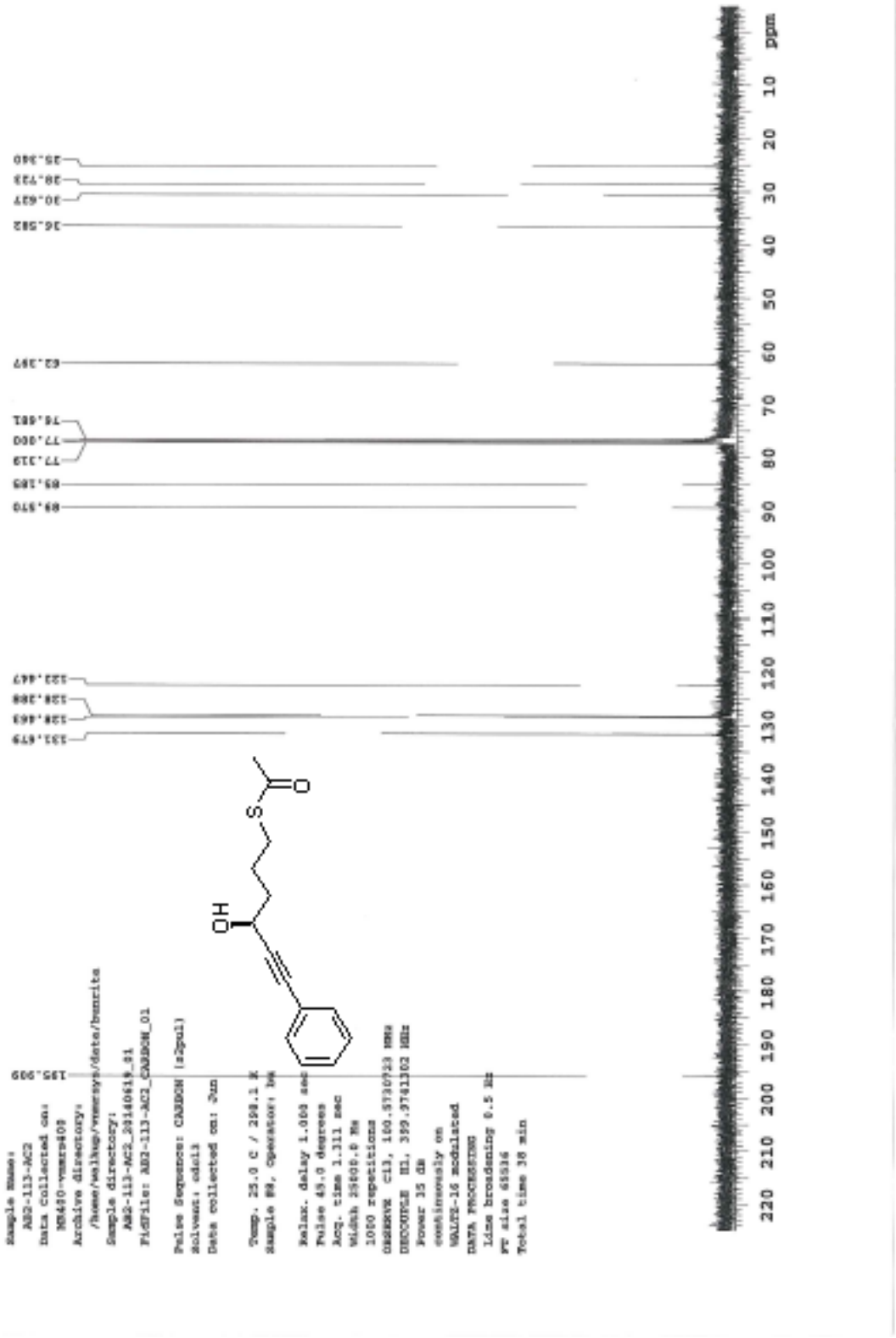


Figure 28. ^{13}C NMR of 5d in $CDCl_3$.

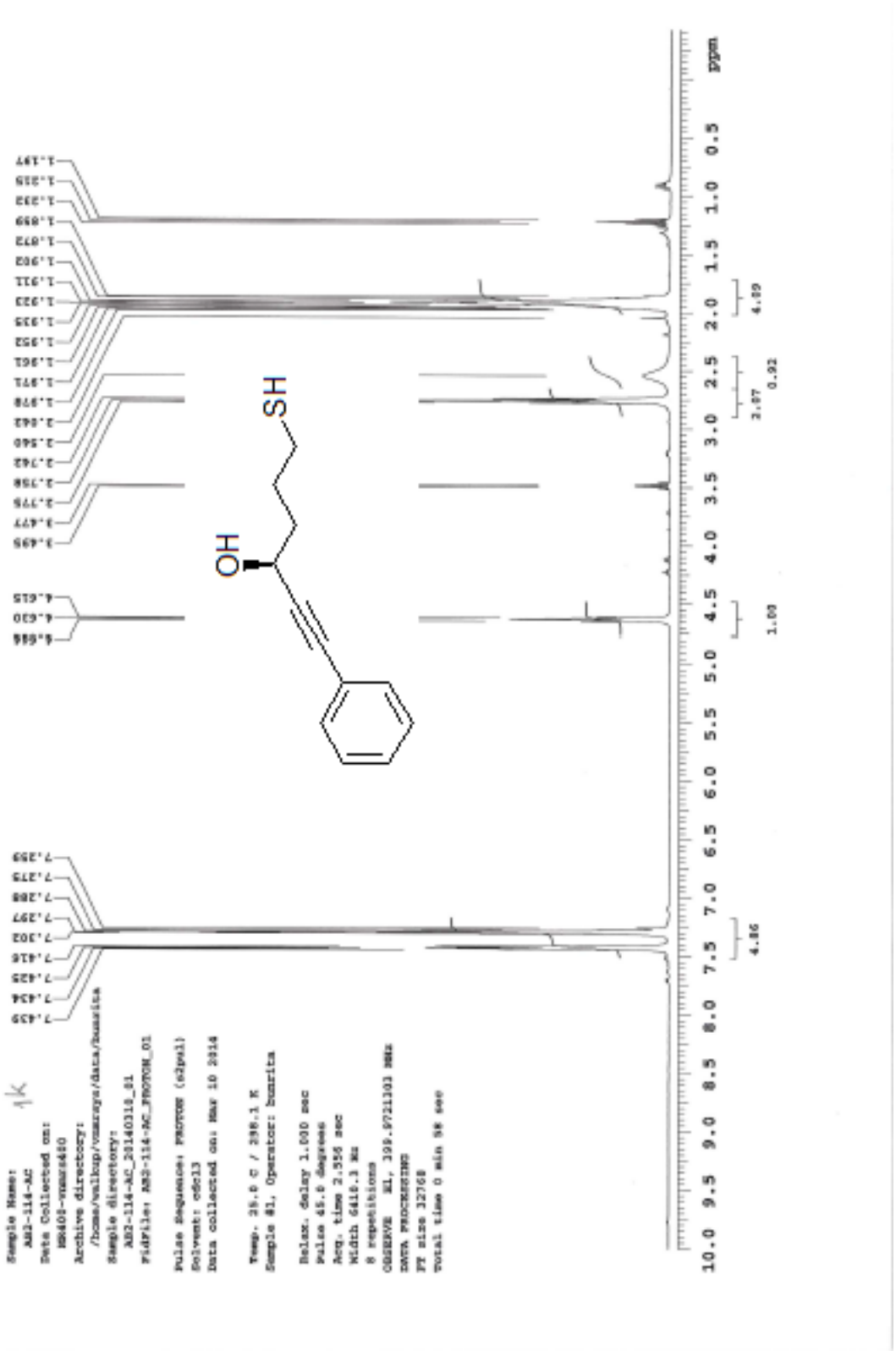


Figure 29. ^{1}H NMR of 5d in $CDCl_3$.

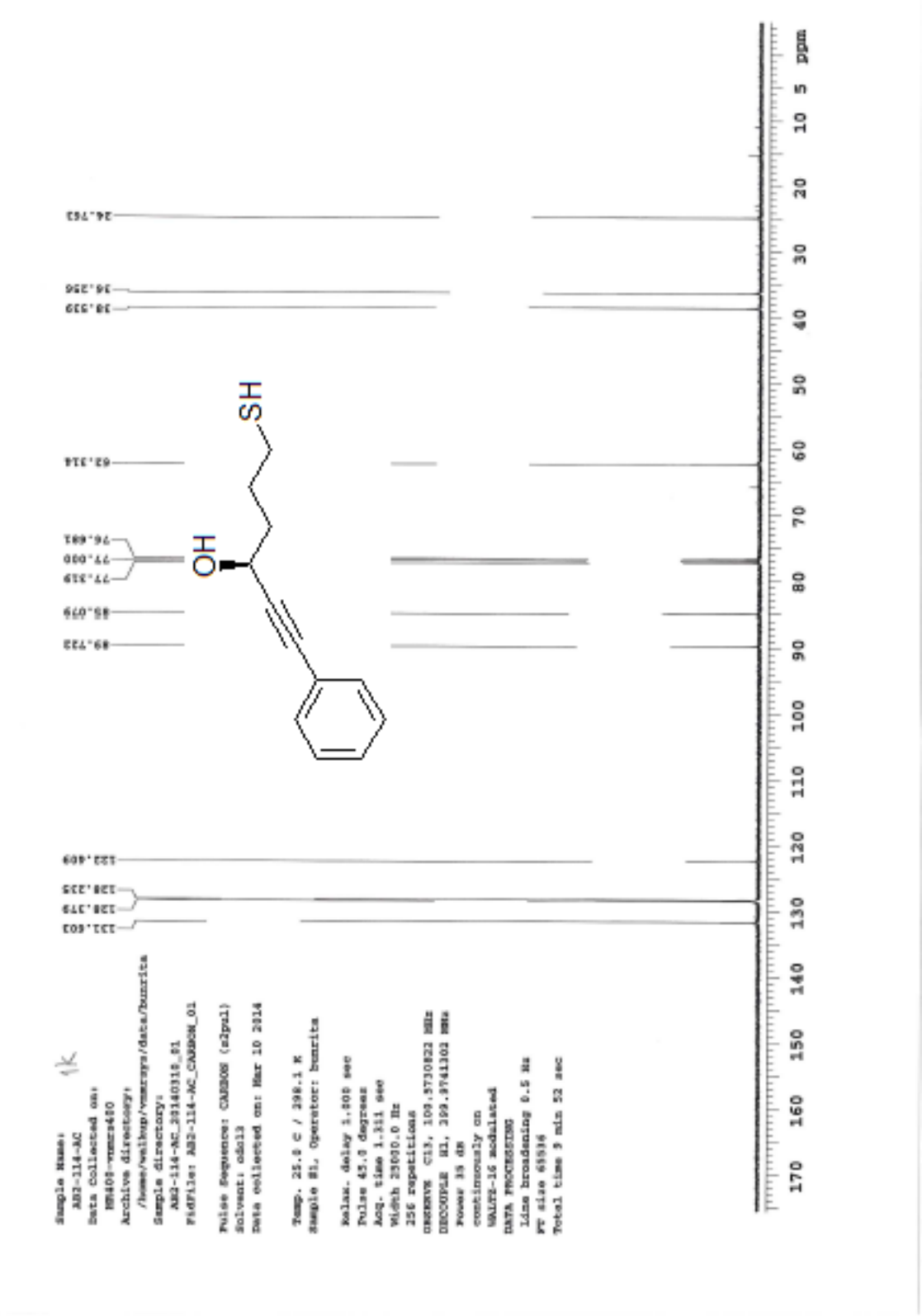


Figure 30. ^{13}C NMR of 5d in $CDCl_3$.

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[2] Y. S. Shim, H. S. Hwang, G. Nam, K. I. Choi, *Bull. Korean Chem. Soc.* **2013**, *34*, 2317.