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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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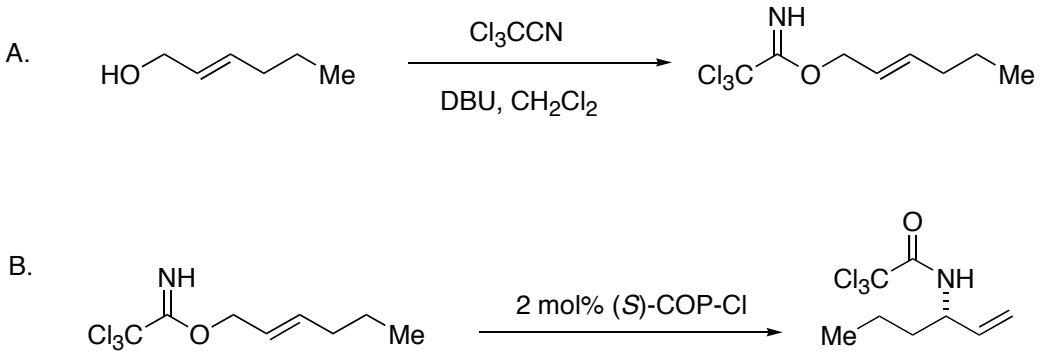
ASYMMETRIC REARRANGEMENT OF ALLYLIC TRICHLOROACETIMIDATES: PREPARATION OF (*S*)-2,2,2-TRICHLORO-*N*-(1-PROPYLALLYL)ACETAMIDE (Acetamide, 2,2,2-trichloro-*N*-[(1*S*)-1-ethenylbutyl]-)



Submitted by Carolyn E. Anderson, Larry E. Overman* and Mary P. Watson.
Checked by Matthew L. Maddess and Mark Lautens.

1. Procedure

Caution! Part A should be carried out in a well-ventilated hood to avoid exposure to trichloroacetonitrile vapors.

A. Preparation of (E)-2,2,2-trichloroacetimidic acid hex-2-enyl ester. A 500 mL round-bottomed flask equipped with a stirring bar is flame dried under a stream of nitrogen and allowed to cool to room temperature. The flask is then charged with *trans*-2-hexen-1-ol (Note 1) (3.3 mL, 27.8 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Note 2) (0.84 mL, 5.6 mmol) and 170 mL of methylene chloride (Note 3). The solution is cooled to 4 °C using an ice/water bath before trichloroacetonitrile (Note 2) (4.2 mL, 42 mmol) is added over five minutes by syringe. With time, the reaction solution is observed to change from clear to orange in color, and within 1 hour the starting materials are consumed (Note 4). The stir bar is removed with a magnetic rod and the solution is then concentrated under reduced pressure using a rotary evaporator to give a brown oil (Note 5). This oil is purified by flash chromatography through a plug of silica gel (Silicycle® 230-400 mesh, 6 cm tall, 5 cm diameter) using 2% ethyl acetate in hexanes

(600 mL, 60 mL fractions) to yield 6.48 g (95%) of nearly pure (*E*)-2,2,2-trichloroacetimidic acid hex-2-enyl ester as a colorless oil (Notes 6, 7).

B. (S)-COP-Cl catalyzed rearrangement of (E)-2,2,2-trichloroacetimidic acid hex-2-enyl ester to (S)-2,2,2-trichloro-N-(1-propylallyl)acetamide. A 150-mL, round-bottomed flask is fitted with a stirring bar and then charged with (*E*)-2,2,2-trichloroacetimidic acid hex-2-enyl ester (6.81 g, 27.8 mmol), Di-μ-chlorobis[η^5-(*S*)-(p*R*)-2-(2'-(4'-isopropyl)oxazolinylcycloentadienyl, 1-*C*, 3'-*N*))-(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium [(*S*)-COP-Cl] (Note 8) (816 mg, 0.56 mmol) and 9.3 mL of methylene chloride (Note 3). The flask is sealed with a polyethylene cap, the cap is secured to the flask with Parafilm, and the flask is placed in an oil bath preheated to 38 °C +/- 2 °C. After 24 h, the solution is cooled to room temperature, the stir bar is removed using a magnetic rod, and the solution is concentrated using a rotary evaporator to yield a brown oil. This oil is purified by flash chromatography through a column of silica gel (Silicycle® 230-400 mesh, 20 cm tall, 5 cm diameter) using 0.5% to 2% ethyl acetate:hexanes as eluent (3 L 0.5% ethyl acetate:hexanes, 1 L 1% ethyl acetate:hexanes, 1 L 2% ethyl acetate: hexanes). Evaporation of solvent provides 6.61 g (97% yield) of (*S*)-2,2,2-trichloro-*N*-(1-propylallyl)acetamide, 94% ee, as a pale yellow oil (Notes 9, 10, 11, 12).

2. Notes

1. The checkers used *trans*-2-hexen-1-ol purchased from Aldrich Chemical Company, Inc. Although of sufficient purity for this series of transformations, the commercial reagent is contaminated with 3% of 1-hexanol.[1] The submitters used (*E*)-2-Hexen-1-ol (>99% *E*) prepared from butanal by Horner-Wadsworth-Emmons reaction with trimethyl phosphonoacetate to form hex-2-enoic acid methyl ester, followed by reduction of this product with diisobutylaluminum hydride (–78 °C to room temperature in THF).

2. 1,8-Diazabicyclo[5.4.0]undec-7-ene and trichloroacetonitrile were purchased from Aldrich Chemical Company, Inc. These chemicals were used as received.

3. Methylene chloride was purified by passage through a solvent purification system. The submitters used a GlassContour alumina solvent

purification columns and the checkers used a MBRAUN® solvent purification system.[2]

4. The reaction progress can be analyzed by thin layer chromatography (Silicycle®, plastic backed, 250 μm thickness). Using 10% ethyl acetate:hexanes as eluent, the product (*E*)-2,2,2-trichloroacetimidic acid hex-2-enyl ester has an R_f of 0.45, whereas the starting alcohol has an R_f of 0.12. Both the imidate and starting alcohol can be visualized by potassium permanganate stain.

5. Upon concentrating the solution, black semi-solids sometimes form. These unwanted byproducts are insoluble in 2% ethyl acetate:hexanes.

6. The product, (*E*)-2,2,2-trichloroacetimidic acid hex-2-enyl ester, exhibits a spectrum that matches that which is reported in the literature.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (broad s, 1H, N*H*), 5.86 (dt, *J* = 15.6, 6.3 Hz, 1H, C*H*), 5.68 (dt, *J* = 15.6 Hz, 6.9 Hz, 1H, C*H*), 4.74 (d, *J* = 6.3 Hz, 2H, CH_2), 2.06 (tq, *J* = 6.9, 6.9 Hz, 2H, CH_2), 1.43 (tq, *J* = 6.9, 7.2 Hz, 2H, CH_2), 0.91 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 136.9, 123.3, 91.7, 70.0, 34.5, 22.1, 13.7.

7. The product is contaminated with 2,2,2-trichloroacetimidic acid hexyl ester (3%) arising from the reaction of hexyl alcohol with trichloroacetonitrile.

8. (*S*)-COP-Cl was purchased from Aldrich Chemical Company, Inc. and was used as received. The specific rotation of this catalyst was measured to be: $[\alpha]_D^{23.8}$ = +1169 (c 0.25, $CHCl_3$). A detailed procedure for the synthesis of (*S*)-COP-Cl has been published: Anderson, C.E.; Kirsch, S.F.; Overman, L.E., Richards, C.J.; Watson, M.P. *Org. Synth.* **2007**, *84*, 148-155.

9. The enantiomeric ratio was determined by HPLC analysis by comparison to a racemic sample:[3a] Hewlett-Packard HP Series 1100, Chiracel OD with guard column, 99:1 hexanes:isopropyl alcohol, 0.4 mL/min, 30 °C, R_t (major) = 15.3 min, R_t (minor) = 16.4 min.

10. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.60 (broad s, 1H, N*H*), 5.81 (ddd, *J* = 16.4, 10.4, 5.6 Hz, 1H, C*H*), 5.17–5.27 (m, 2H, CH_2), 4.39–4.47 (m, 1H, C*H*), 1.55–1.71 (m, 2H, CH_2), 1.35–1.46 (m, 2H, CH_2), 0.96 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) d 161.2, 136.7, 115.9, 92.8, 53.4, 36.5, 18.9, 13.7; IR (neat) cm^{-1}: 3424, 3322, 2961, 2935, 1714, 1520, 1249, 926, 821; HRMS (EI) *m/z* 244.0063 [244.0063 calcd for $C_8H_{13}Cl_3NO$

(M+H)]; R_f = 0.36 (10% ethyl acetate:hexanes).

11. The submitters reported, that when commercially available starting material is used, the product is contaminated with observable quantities of 2,2,2-trichloroacetimidic acid hexyl ester. The checkers, however, report that 2,2,2-trichloroacetimidic acid hexyl ester is not observed to the detection limits of ^{1}H or ^{13}C NMR.

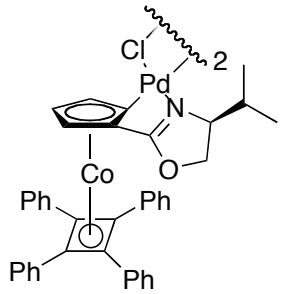
12. On half-scale to that described, with prolonged drying under high vacuum the product was observed to solidify to a white crystalline solid (mp = 28 - 29 °C). On the scale described above, the product remained an oil but could be rapidly induced to crystallize by addition of a seed crystal.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure illustrates a general method for the preparation of enantioenriched chiral allylic trichloroacetamides from readily available prochiral (*E*)-allylic alcohols by catalytic asymmetric rearrangement of trichloroacetimidate intermediates.[4] The rearrangement tolerates a variety of alkyl and Lewis basic substituents at C3 of the starting allylic alcohol; however, substitution at C2 is not permitted (Table 1). [4,5] Although 5 mol % COP-Cl is convenient to use for small scale reactions, the catalyst loading



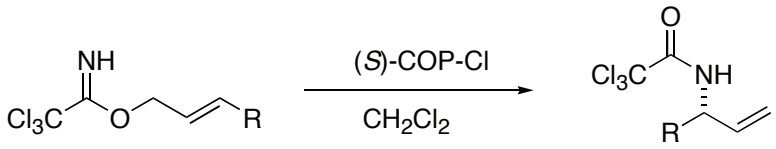
(*S*)-COP-Cl

can be decreased to as low as 1 mol % if the concentration is simultaneously increased (Entry 3). The reaction conditions exemplified in this example (2 mol % COP-Cl, CH_2Cl_2 (3 M), 38 °C, 24 h) were chosen to insure complete

conversion of the allylic imidate intermediate within 24 hours. (*Z*)-Allylic trichloroacetimidates do not undergo COP-Cl catalyzed rearrangement at a practical rate. However, allylic trichloroacetamides of opposite absolute configuration can be prepared using (*R*)-COP-Cl, synthesized from (*R*)-valinol.

The COP-Cl catalyzed transformation of prochiral allylic alcohols to chiral allylic trichloroacetamides is technically simple as allylic trichloroacetimidate intermediates require minimal purification. Additionally, no special precautions are required to protect the rearrangement reaction from light, air or traces of moisture. Moreover, the trichloroacetyl group of the product amide can be readily cleaved or this functional group can be converted to other functional arrays.[6]

Table 1. Enantioselective Synthesis of Allylic Trichloroacetimidates from (*E*)-Allylic Trichloroacetimidates.[a]



		amide	
entry	R	yield (%)[b]	% ee[c]/conf
1	*n*-Pr	99	95/*S*
2	*i*-Bu	95	96/*S*
3[d]	*i*-Bu	92	98/*S*
4	CH_2CH_2Ph	93	93/*S*
5	$(CH_2)_3OAc$	97	92/*S*
6	$(CH_2)_2COMe$	98	95[e]/*S*
7	$CH_2OTBDMS$	98	96/*S*
8	$(CH_2)_3NBn(Boc)$	96	95/*S*

(a) Conditions: 5 mol % (*S*)-COP-Cl, CH_2Cl_2 (0.6 M), 38 °C, 18 h. (b) Duplicate experiments (±3%). (c) Determined by HPLC analysis of duplicate experiments (±2%). (d) 1 mol % (*S*)-COP-Cl, CH_2Cl_2 (1.2 M). (e) Determined by chiral GC analysis of duplicate experiments (±2%).

1. Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Syn., Coll. Vol. 7*, 461.
2. (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520. (b) http://www.glasscontour.com/ or http://www.mbraunusa.com/.
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4. Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412–12413.
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6. For examples, see: (a) Cardillo, G.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1489-1490. (b) Nagashima, H.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1984**, 652-653. (c) Atanassova, I. A.; Petrov, J. S.; Mollov, N. M. *Synthesis* **1987**, 734–736. (d) Yamamoto, N.; Isobe, M. *Chem. Lett.* **1994**, 2299–2302. (e) Urabe, D.; Sugino, K.; Nishikawa, T.; Isobe, M. *Tetrahedron Lett*. **2004**, *45*, 9405-9407.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

trans-2-Hexen-1-ol: 2-Hexen-1-ol, (2E)-; (928-95-0)
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU): Pyrimido[1,2-a]azepine, 2,3,4,6,7,8,9,10-octahydro-; (6674-22-2)
Trichloroacetonitrile; (545-06-2)
(*E*)-2,2,2-trichloroacetimidic acid hex-2-enyl ester: Ethanimidic acid, 2,2,2-trichloro-, (2E)-2-hexenyl ester; (51479-70-0)
(*S*)-COP-Cl: Cobalt, bis[1,1',1",1"'-(η4-1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]](di-μ-chlorodipalladium)bis[μ-[(1-η:1,2,3,4,5-η)-2-[(4*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl-κN3]-2,4-cyclopentadien-1-yl]]di-; (581093-92-7)

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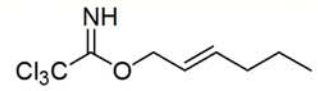

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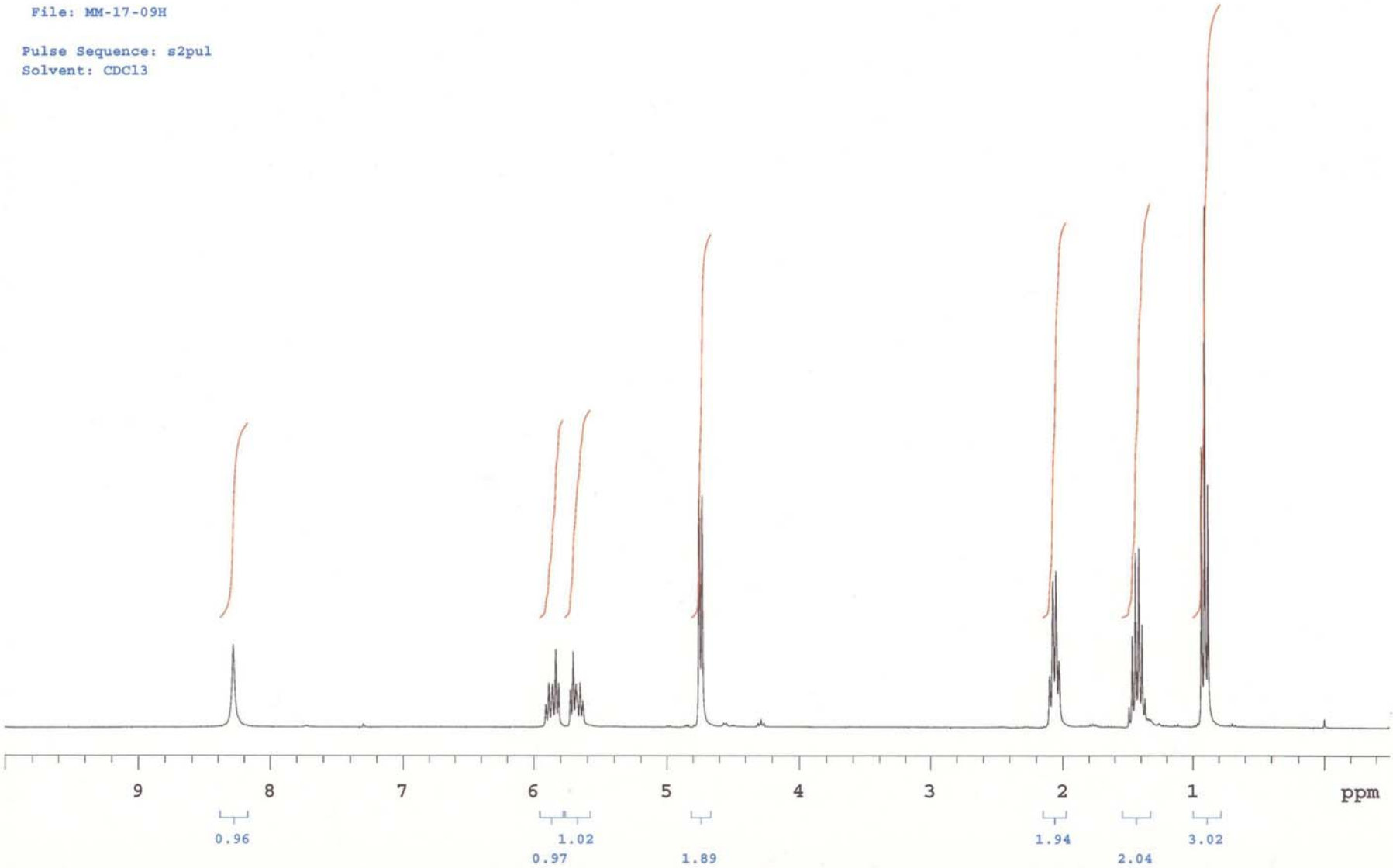

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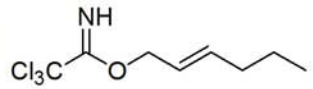

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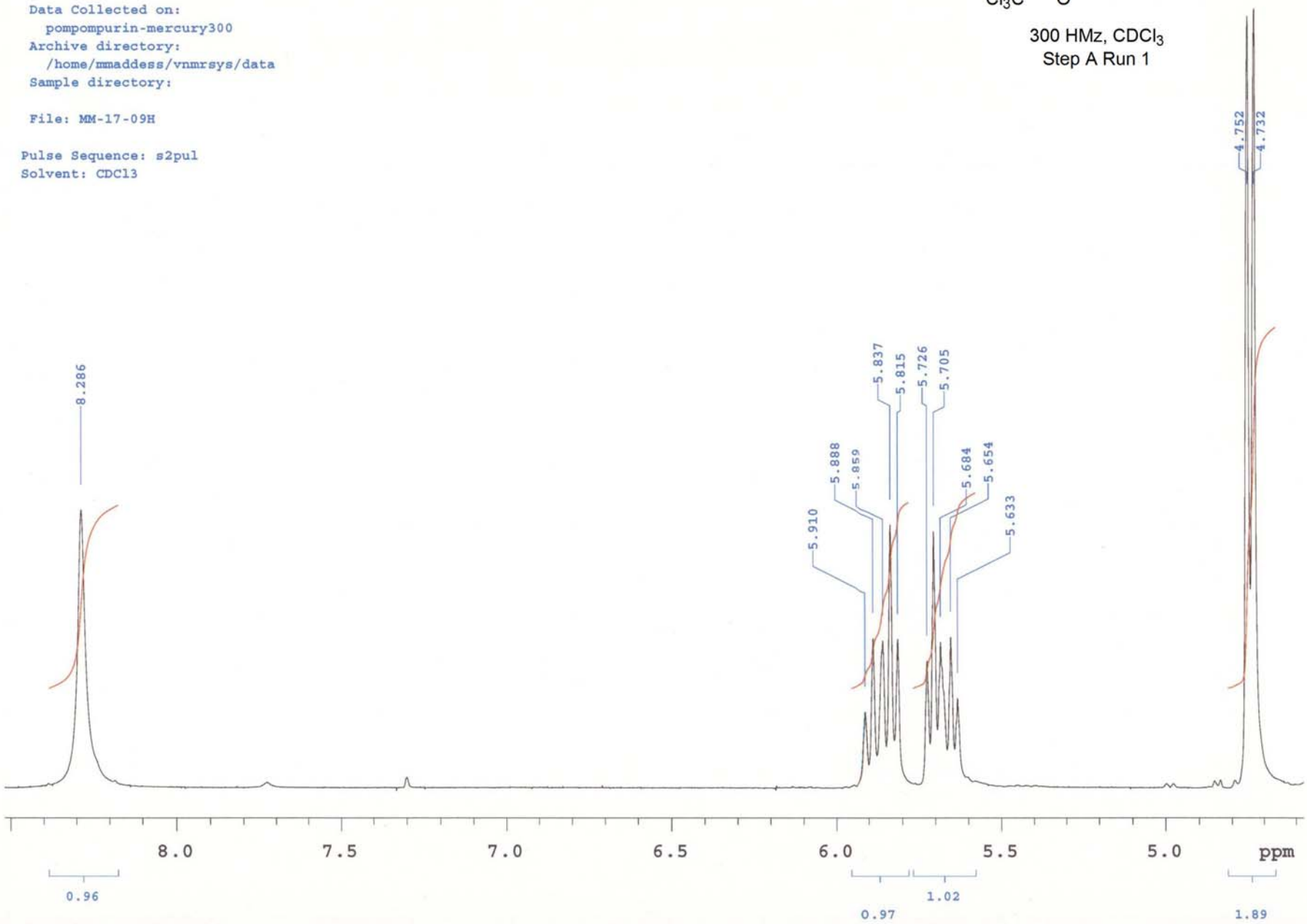

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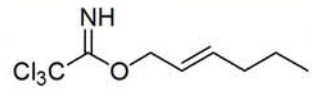

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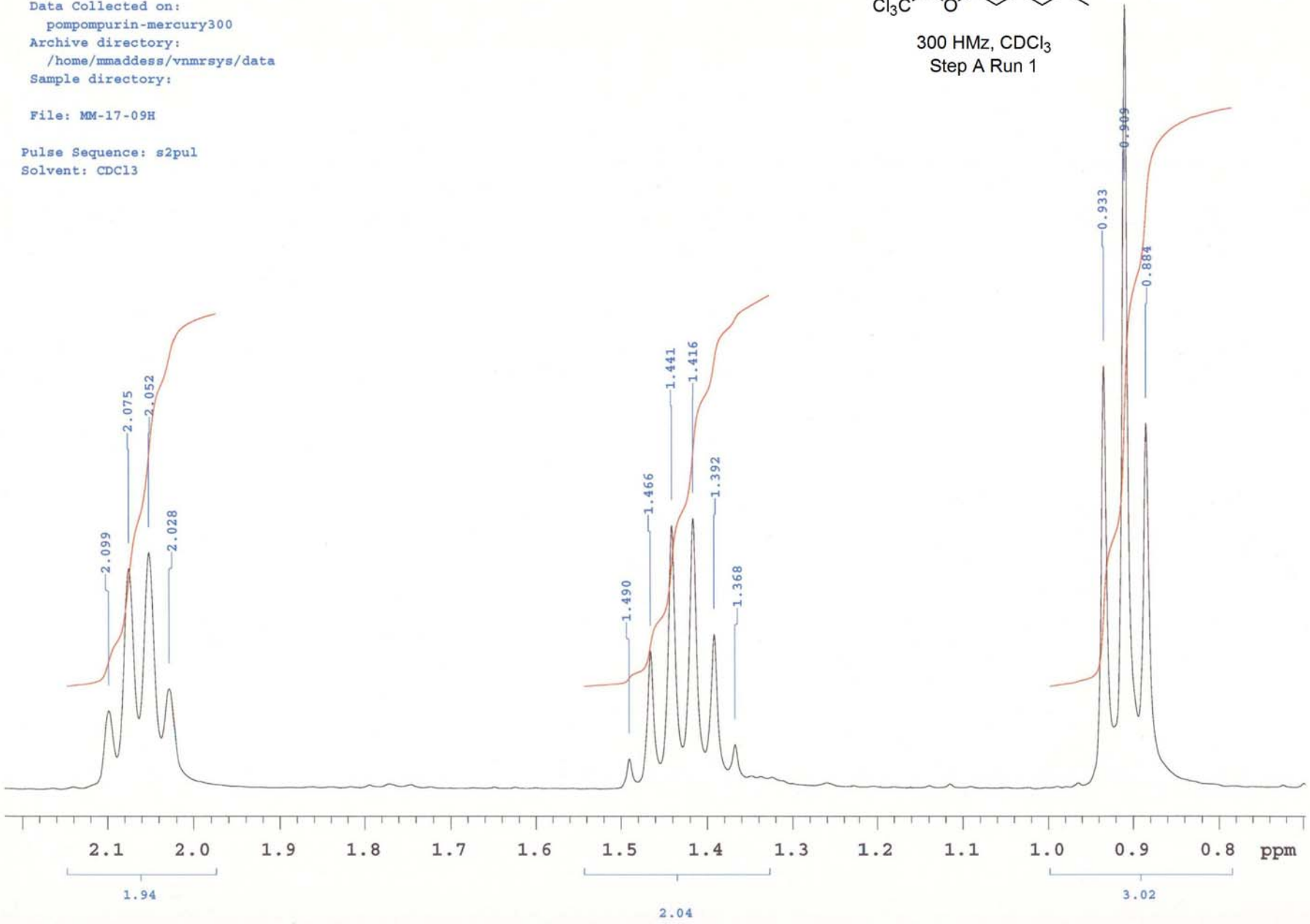

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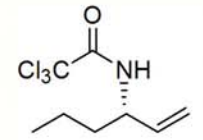

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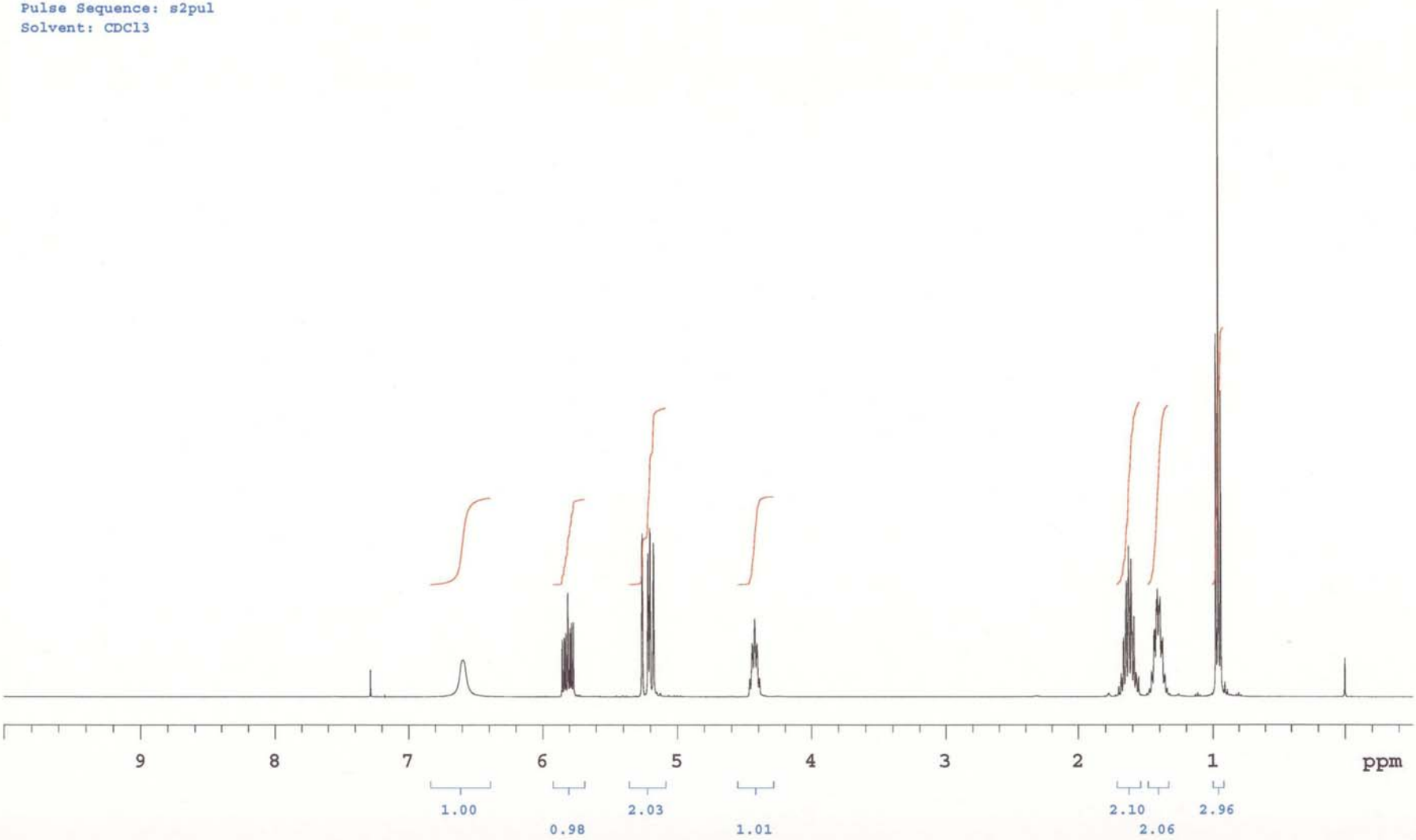

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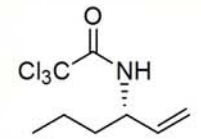

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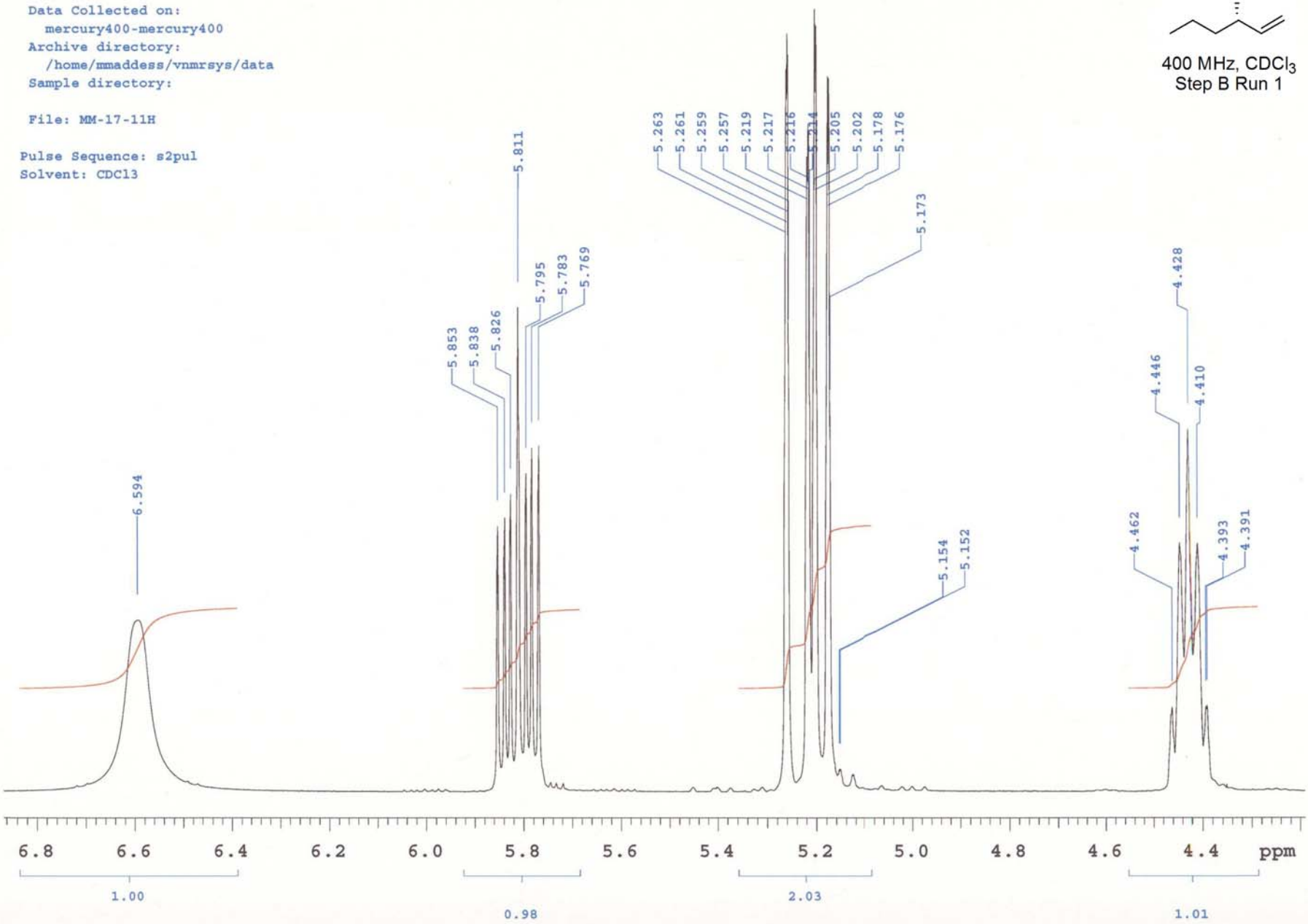

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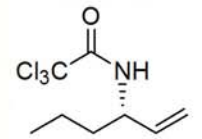

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