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A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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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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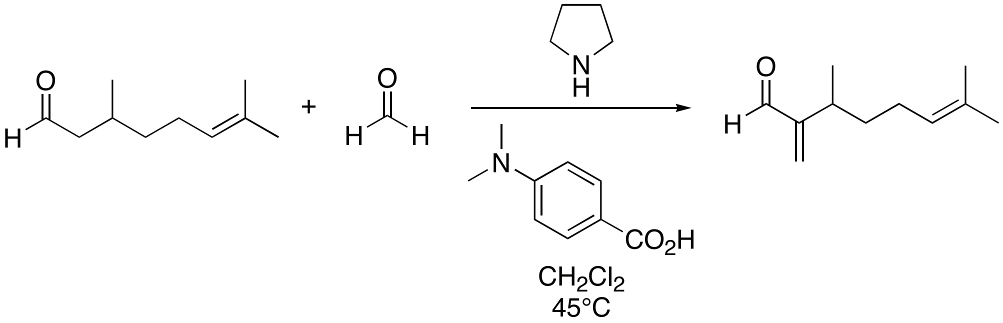
ORGANOCATALYTIC α-METHYLENATION OF ALDEHYDES: PREPARATION OF 3,7-DIMETHYL-2-METHYLENE-6-OCTENAL



Submitted by Meryem Benohoud, Anniina Erkkilä, and Petri M. Pihko.[1]
Checked by Yunus Turkmen and Viresh Rawal.

1. Procedure

A 100-mL, three-necked round-bottomed flask (Note 1), equipped with an 8 x 13 mm octagonal magnetic stir bar, a condenser, a rubber septum, and an internal thermometer, is charged with 4-(dimethylamino)benzoic acid (661 mg, 4.0 mmol) (Note 2). The system is evacuated, filled with nitrogen, and charged with dichloromethane (40 mL) (Notes 3-4) and pyrrolidine (334 μL, 4.0 mmol) (Notes 5-6), added sequentially. The resulting colorless solution is placed in an oil bath and heated to 35 °C (internal temperature). To this stirred solution is added via syringe (±)-citronellal ((±)-3,7-dimethyl-6-octenal) (7.20 mL, 40.0 mmol) (Note 7) and 37% aqueous formaldehyde solution (2.98 mL, 40.0 mmol) (Notes 8-9). The mixture is heated to reflux (bath temperature 50 °C) and maintained at reflux for 30 min (Note 10). The reaction mixture is cooled to room temperature, diluted with dichloromethane (20 mL) and transferred to a 250-mL separatory funnel. The reaction flask was rinsed with additional dichloromethane (3 x 7 mL). The organic phase is washed with water (40 mL) and then a saturated solution of $NaHCO_3$ (40 mL). The combined aqueous layers are extracted with dichloromethane (3 x 20 mL). The combined organic phases are dried over anhydrous Na_2SO_4 (35 g), filtered and concentrated by rotary evaporation (30 °C, 20 mmHg). The flask is then placed under a vacuum (1.5 mmHg) (Note 11) for ca. 30 min to afford 3,7-dimethyl-2-methylene-6-octenal as a light yellow liquid in quantitative yield

(6.65 g). The resulting material is sufficiently pure for further reactions. Distillation of the product from a 25-mL flask, under reduced pressure, using a one-piece distillation apparatus equipped with a 6-cm Vigreux column, affords 3,7-dimethyl-2-methylene-6-octenal (5.44–5.93 g, 82–89%) as a colorless liquid (bp 68 °C/0.3 mmHg) (Notes 12-16).

2. Notes

1. The checkers carried out the reaction under an inert atmosphere. The apparatus was oven-dried overnight and assembled while hot. It was then evacuated and filled with nitrogen three times and maintained under a positive pressure of nitrogen during the course of the reaction.
2. 4-(Dimethylamino)benzoic acid (98%) was purchased from Aldrich Chemical Co.
3. A white suspension is observed at this point. 4-(Dimethylamino)benzoic acid is only sparingly soluble in dichloromethane.
4. Dry dichloromethane was obtained from an MBraun Solvent Purification System. Checkers used dichloromethane (Optima®) purchased from Fisher Scientific, Inc. and purified through an Innovative Technology solvent purification system (activated alumina). The solvent was dried to ensure reproducible water content in the reaction mixture. However, the conditions are not strictly anhydrous as water is present in the formaldehyde solution.
5. The submitters obtained pyrrolidine from Aldrich Chemical Co. and purified it before use by distillation under argon. Checkers purchased pyrrolidine (≥99.5%, redistilled, Sure/Seal™) from Aldrich Chemical Co. and used it as received.
6. Most of the white suspension disappeared when pyrrolidine was added to the reaction mixture. The remaining few solid particles dissolved when the internal temperature reached 30 °C
7. (±)-Citronellal (purum, >95.0% (GC)) was obtained from Aldrich Chemical Co. and used as received. This compound should be handled carefully as it is irritating to the eyes, skin and respiratory system.
8. Formaldehyde (37 wt. % solution in water, A.C.S. reagent) was purchased from Aldrich Chemical Co. and used as received.
9. The checkers used 1.05 equiv (42.0 mmol, 3.13 mL) of formaldehyde for the second run. However, the ^{1}H-NMR of the crude

product didn't show any improvement when compared with that of the first run.

10. The progress of the reaction can be followed by TLC (hexanes/ethyl acetate 9/1, anisaldehyde stain). (±)-Citronellal $R_f = 0.51$, product $R_f = 0.60$).

11. The submitters used 0.1 mmHg vacuum.

12. The submitters reported the boiling point as 94–97 °C at 0.1 mmHg.

13. The submitters reported obtaining 5.60 g (84%) of the product.

14. The checkers carried out the reaction twice at full scale. First run: 5.44 g, 82% (68 °C, 0.3 mmHg). Second run: Fraction 1 (0.72 g), fraction 2 (5.04 g), fraction 3 (obtained by heating the Vigreux column with a heat gun, 0.17 g); total yield 5.93 g, 89%; bp 73 °C at 0.4 mmHg. All three fractions were pure by NMR. ^{1}H and ^{13}C NMR, GC-MS, and elemental analysis data were obtained by using the 2nd fraction.

15. Spectroscopic data of (±)-3,7-dimethyl-2-methyl-6-octenal closely matched published data[2,3]: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 (d, J = 7.0 Hz, 3 H), 1.32–1.40 (m, 1 H), 1.47–1.53 (m, 1 H), 1.54 (s, 3 H), 1.65 (s, 3 H), 1.85–1.96 (m, J = 8.0 Hz, 2 H), 2.68 (sext, J = 7.0 Hz, 1 H), 5.05 (m, J = 7.0, 1.5 Hz, 1 H), 5.97 (s, 1 H), 6.21 (s, 1 H), 9.51 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.8, 19.7, 25.8, 25.9, 31.1, 35.8, 124.3, 131.8, 133.2, 155.7, 194.8; IR (film) 2966, 2926, 2857, 1696, 1454, 1377, 945 cm^{-1}; Anal. calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91; O, 9.63; found: C, 79.66; H, 10.88; O, 9.46; GC-MS (column ZB-5MS 0.25 μm x 250 μm x 30 m, initial T = 50 °C for 1.0 min, ramp = 15.0 °C/min to 260 °C, hold for 10 min., MS: Source T = 150 °C, EI^+): R_t = 7.15 min., m/z 165.9, 151.0, 149.0, 123.0, 109.0, 81.0.

16. The product may polymerize during storage and it should be stored in the freezer (–20 °C).

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

Several methods for the preparation of α-substituted acroleins are available; however, typically, these require relatively drastic conditions, including high temperature and high pressure.[4,5] Moreover, only the preparation of simple α-substituted acroleins has been reported using these methods. More complex aldehydes have required milder, but non-catalytic, procedures[6,7] such as Horner-Wadsworth-Emmons reactions[8,9] or Mannich reactions[10] with Eschenmoser's salt. The present method allows the rapid synthesis of α-substituted-α,β-unsaturated aldehydes in good yields with simple reagents and tolerates a variety of functionalities (Table 1). The procedure described herein represents an improved and faster protocol when compared to our originally published method.[11] The products are potentially highly useful intermediates in organic synthesis,[12] given the range of possible transformations, such as 1,2-[13,14] and 1,4-additions,[15-18] Baylis-Hillman reactions,[19-20] Diels-Alder reactions,[21-24] and a number of organocatalyzed transformations.[25-27]

Table 1 Formation of α-substituted acroleins

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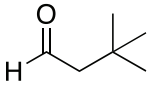
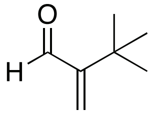
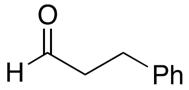
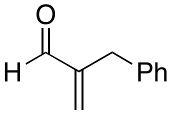
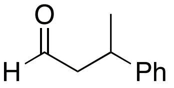
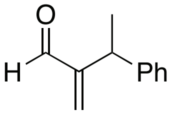
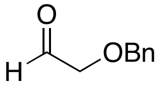
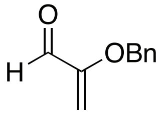
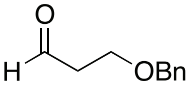
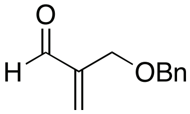
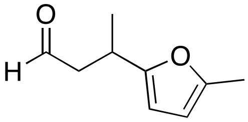
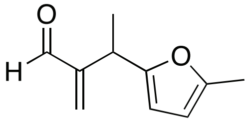
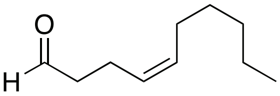
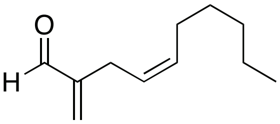
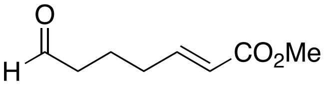
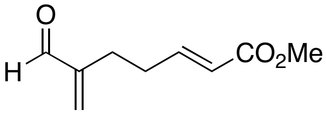
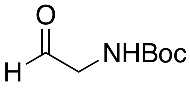
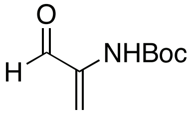
		180	85
		5	99
		25	> 99
		60	> 99
		10	85
		25	> 99
		20	> 99
		40	> 99
		15	98

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

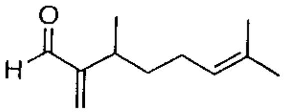
4-(Dimethylamino)benzoic acid: (619-84-1)
Pyrrolidine (123-75-1)
(±)-Citronellal: ((±)-3,7-dimethyl-6-octenal); (106-23-0)
3,7-Dimethyl-2-methylene-6-octenal; (22418-66-2)
37% Aqueous formaldehyde; (50-00-0)

Petri Pihko was born in 1971 in Oulu, Finland. He became interested in chemistry several years before entering the University, assisted by inspiring teachers, Maija Aksela (currently a Professor of Chemical Education at the University of Helsinki) and Prof. Hans Krieger, who also taught him organic chemistry at the University of Oulu before his retirement. Petri Pihko then joined the research group of Professor Ari Koskinen, graduating with a Ph.D. in 1999. Between 1999 and 2001, he enjoyed nearly two years of a wonderful time as a postdoctoral associate with Professor K. C. Nicolaou at the Scripps Research Institute in La Jolla, California, USA. In 2001, he joined the faculty of Helsinki University of Technology (TKK), and in 2008, his research group moved to the University of Jyväskylä, Finland. His research interests include organocatalysis, catalyst design, and total synthesis of natural products.

Meryem Benohoud was born in 1981 in Antwerp, Belgium. She graduated from the Université Paris XI Orsay with a Ph.D. in 2008 realized under the supervision of Robert H. Dodd at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette, France. She is now a postdoctoral associate with Petri M. Pihko at the University of Jyväskylä, Finland, and she works on the development of oxidation reactions using organocatalysis and tertiary and quaternary centers formation.

Anniina Erkkilä was born in 1980 in Helsinki, Finland. She received her M.Sc. (Tech.) degree in Organic Chemistry from the Helsinki University of Technology in 2003. Subsequently, she joined the research group of Professor Petri Pihko working on developing new methodologies for organocatalytic reactions, earning her D.Sc. (Tech.) degree in 2007. In 2005, she worked as a visiting researcher in the laboratory of Professor Benjamin List at Max-Planck-Institut für Kohlenforschung in Germany for 3 months. In May 2007, she was awarded the Publication Prize of the Division of Synthetic Chemistry, Association of the Finnish Chemical Societies.

Yunus E. Turkmen was born in Bursa, Turkey in 1983. He received his B.S. and M.S. in chemistry from Middle East Technical University, Turkey and in 2006, he started his PhD study at the University of Chicago. He's currently a graduate student in Prof. Viresh Rawal group, working on hydrogen-bond catalysis.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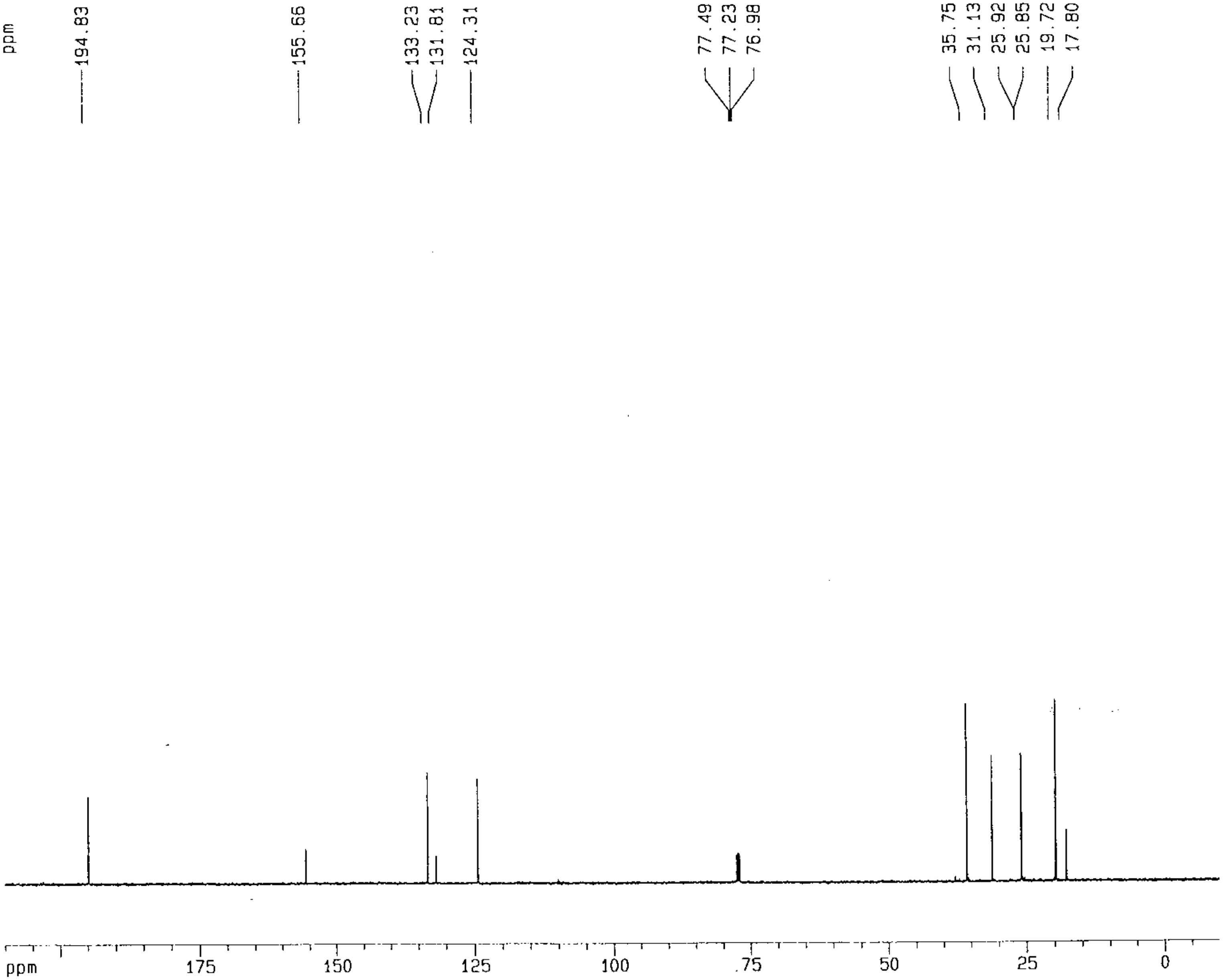
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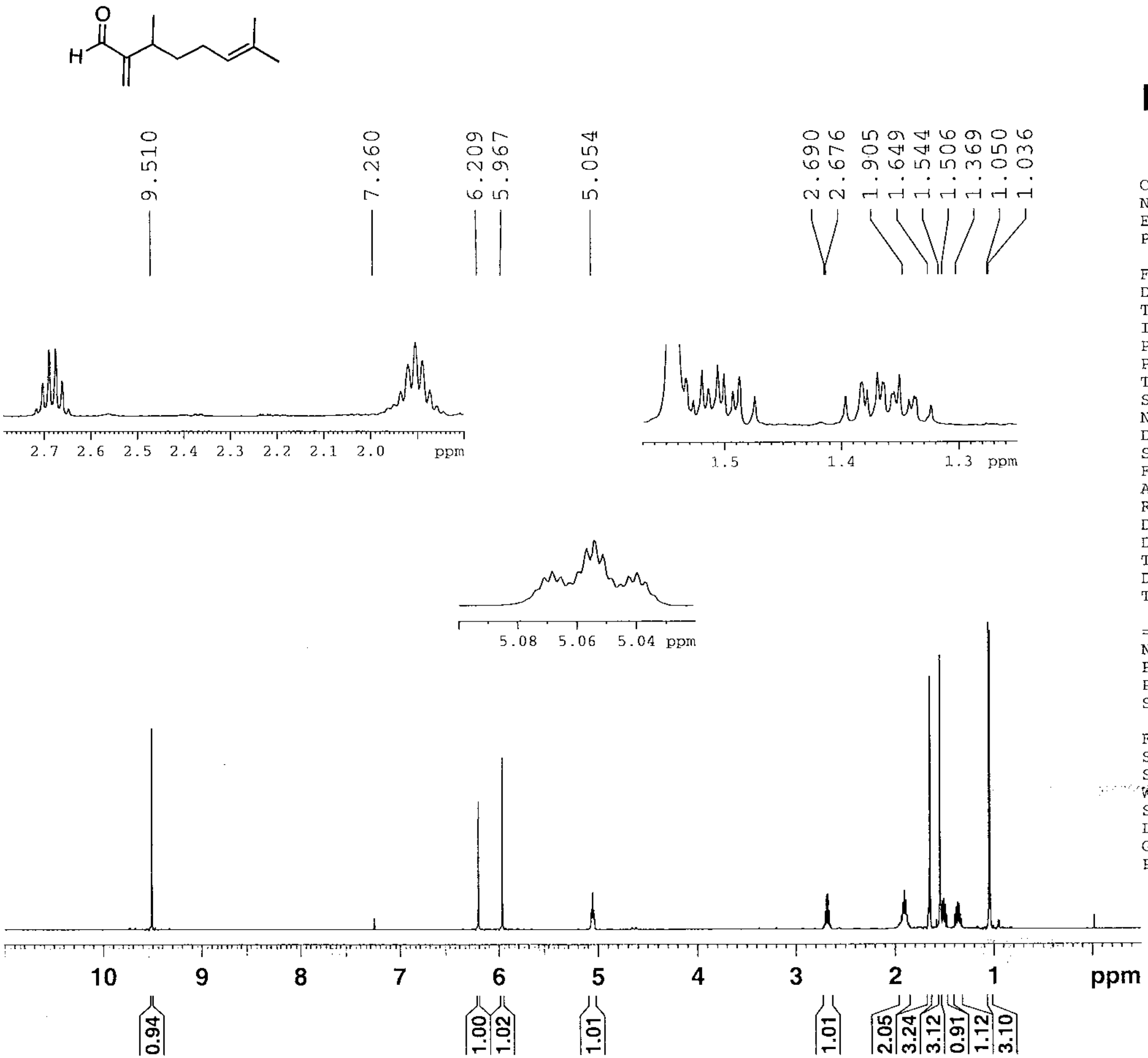

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