

SUPPORTING INFORMATION

Rapid Catalyst Screening by a Continuous-Flow Microreactor Interfaced with Ultra High Pressure Liquid Chromatography

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Side reaction analysis

Reactions were carried out in vials. Analysis by GC- and LC-MS proceeded without purification. GC column: XTI-5, 30 m, thickness 0.25 μm , diameter 0.25 mm. GC separation conditions: 100 $^{\circ}\text{C}$ \rightarrow 250 $^{\circ}\text{C}$ at 25 $^{\circ}\text{C}/\text{min}$, held 10 min, inlet temperature 250 $^{\circ}\text{C}$, carrier flow 3 mL/min He, split ratio 50. LC column: C18, 3 μm , 120 \AA pore, 2.1mm \times 150 mm. LC separation conditions: 0.2 mL/min, gradient 5-95% $\text{CH}_3\text{CN}/\text{water}$ (0.1% CH_3COOH) in 20 min, oven 40 $^{\circ}\text{C}$, UV detector 220 nm.

Strong acid catalysts

In Figure S1A, Unknown 1 (See Figure 3) and the product are well separated by GC. In Figure S1B, the mass spectrum (EI) of Unknown 1 peak shows a possible molecular ion of 263 m/z . Comparison to the product mass spectrum, S1C, shows that, except for their molecular ions (product, 291 m/z), most of their fragment ions are identical.

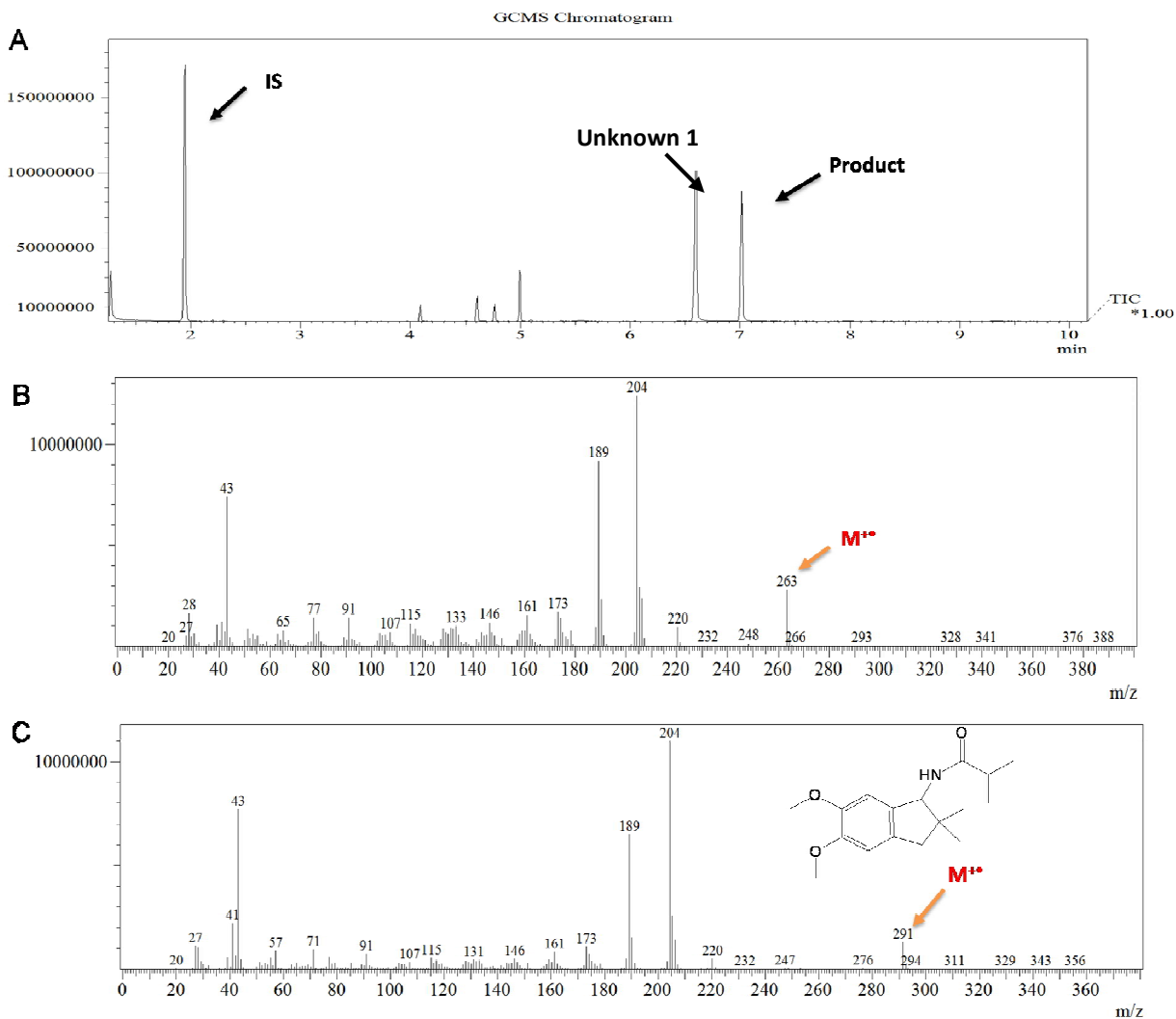


Figure S1. GC-MS studies of batch reaction catalyzed by perchloric acid.

GC chromatogram of reaction solution (A), mass spectrum of Unknown 1 (B) and mass spectrum of product (C).

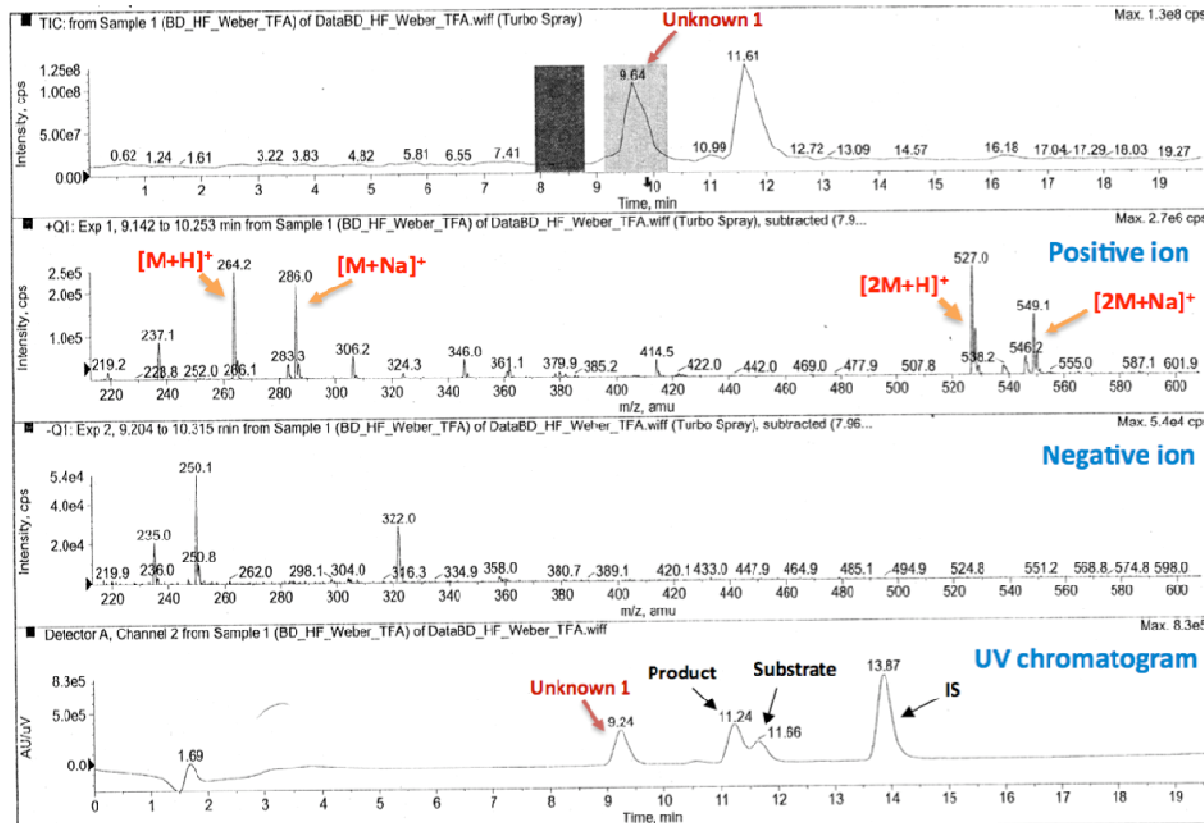


Figure S2. LC-MS studies of reaction sample catalyzed by trifluoroacetic acid.

The results of LC-MS analysis of reaction outcomes are shown in Figure S2. The positive ion spectrum shows the protonated molecular ion of Unknown 1 at 264 m/z and sodium plus ion at 286 m/z . The nominal molecular weight of Unknown 1 is thus 263, as in the GC-MS study.

2.2 Weak acid catalysts

In these reactions, Unknown 2 (Figure 3) is the predominant byproduct. We noted that weak acids led to low product yield and only moderate substrate conversion. The only identifiable peak from GCMS is the isolated aldehyde byproduct whose mass spectrum and structure are shown in Figure S3. This known aldehyde byproduct largely comes from the thermal decomposition of the substrate.

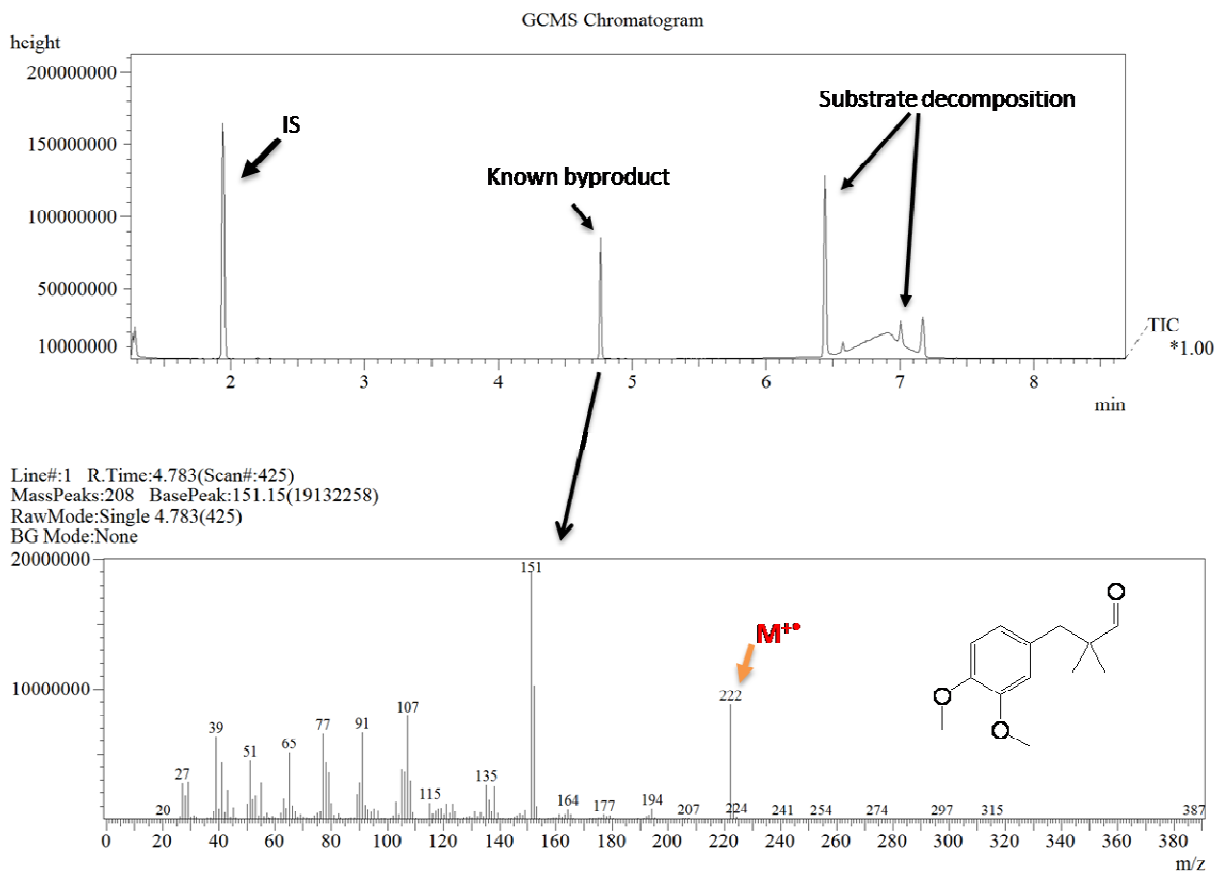


Figure S3. GC-MS studies of reaction sample catalyzed by trichloroacetic acid.

Figure S4 shows positive ion spectra (LC-MS) with two fragment ion peaks corresponding to the molecular ion of Unknown 2 at 309 m/z . This byproduct is prone to losing a hydroxyl group during ionization, resulting in a major fragment ion of 292 m/z . From the negative ion spectrum, we can deduce the same molecular weight. A possible mechanism to form Unknown 2 is shown in Scheme S2, in which water reacts with the acyliminium ion intermediate and leads to the formation of Unknown 2. This byproduct can also decompose into the known aldehyde byproduct. This side reaction is likely to compromise the cyclization process severely. When low concentrations of weak acids are used, the cyclization process becomes so slow that this side reaction becomes prominent and leads to very low yield. Therefore, reaction solutions have to be dried very well to minimize this side reaction, especially under the catalysis of weak acids.

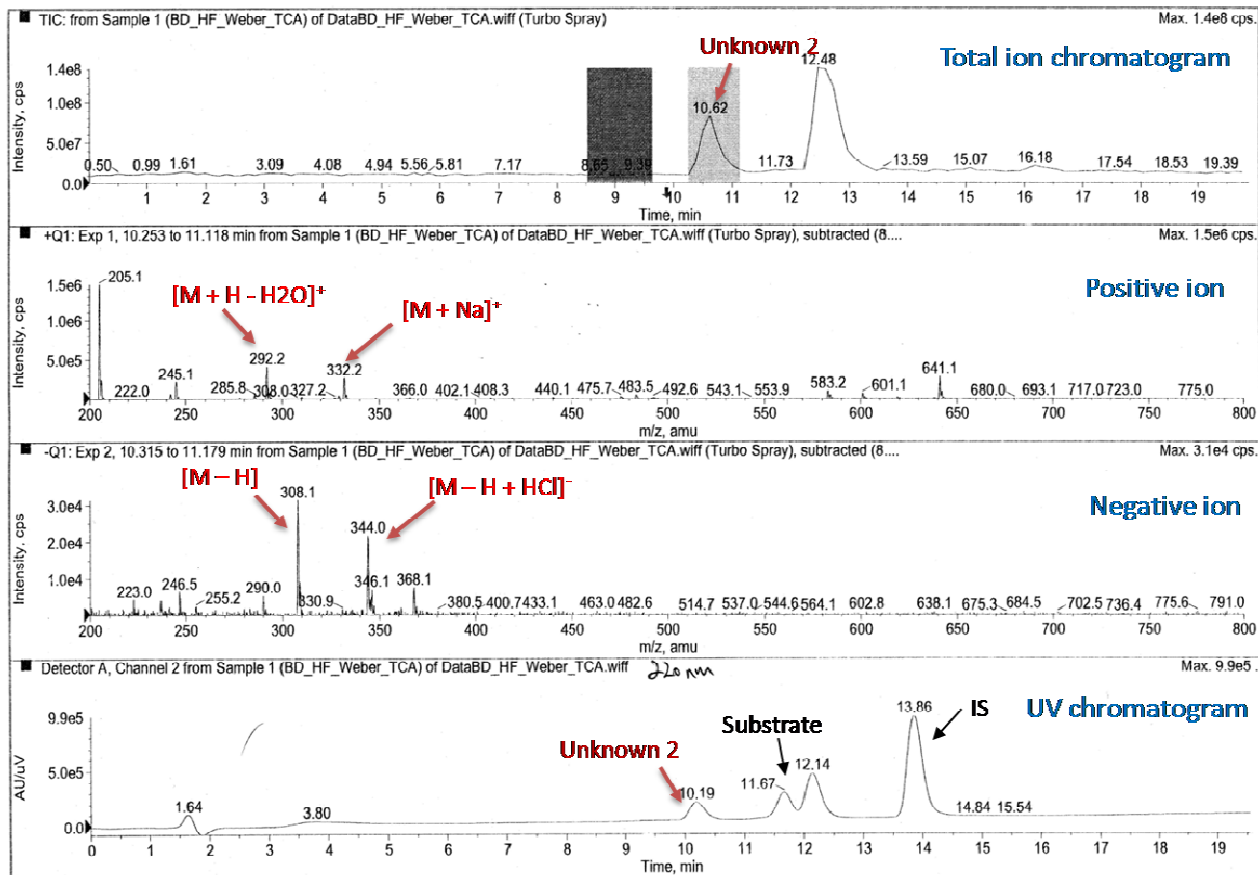
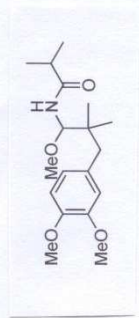
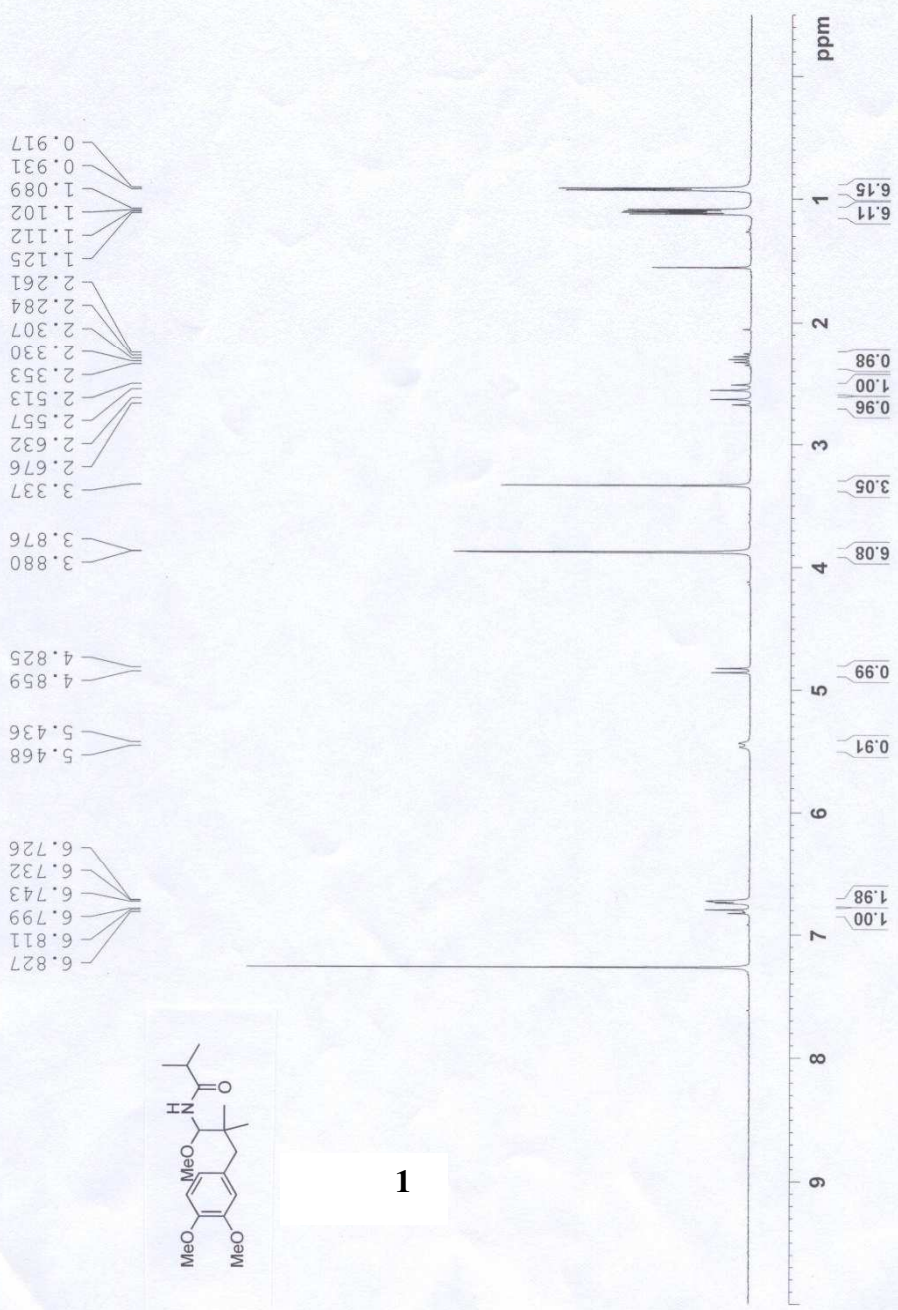


Figure S4 LC-MS studies of reaction sample catalyzed by trichloroacetic acid.

wfh1-147-1 301



1



wfh1-147-1C 301

177.17

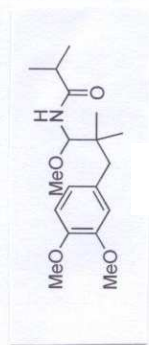
148.11
147.25

130.65
122.53
113.85
110.64

85.67
77.40
76.98
76.55

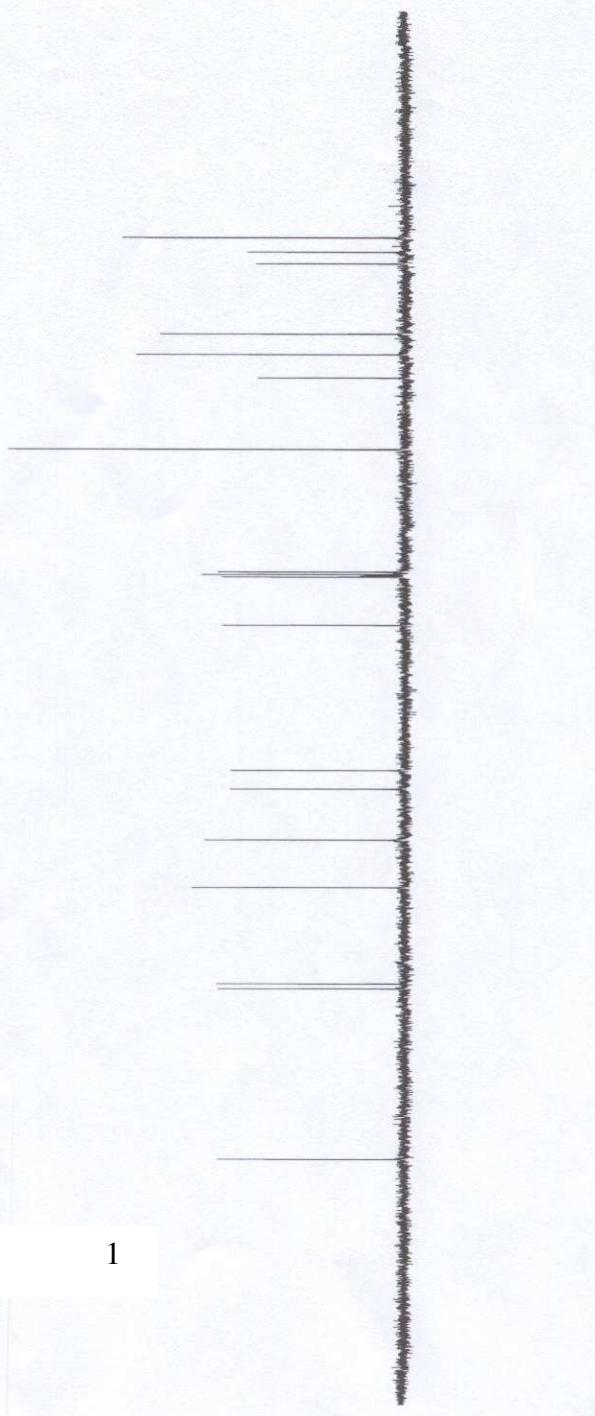
55.60
55.54

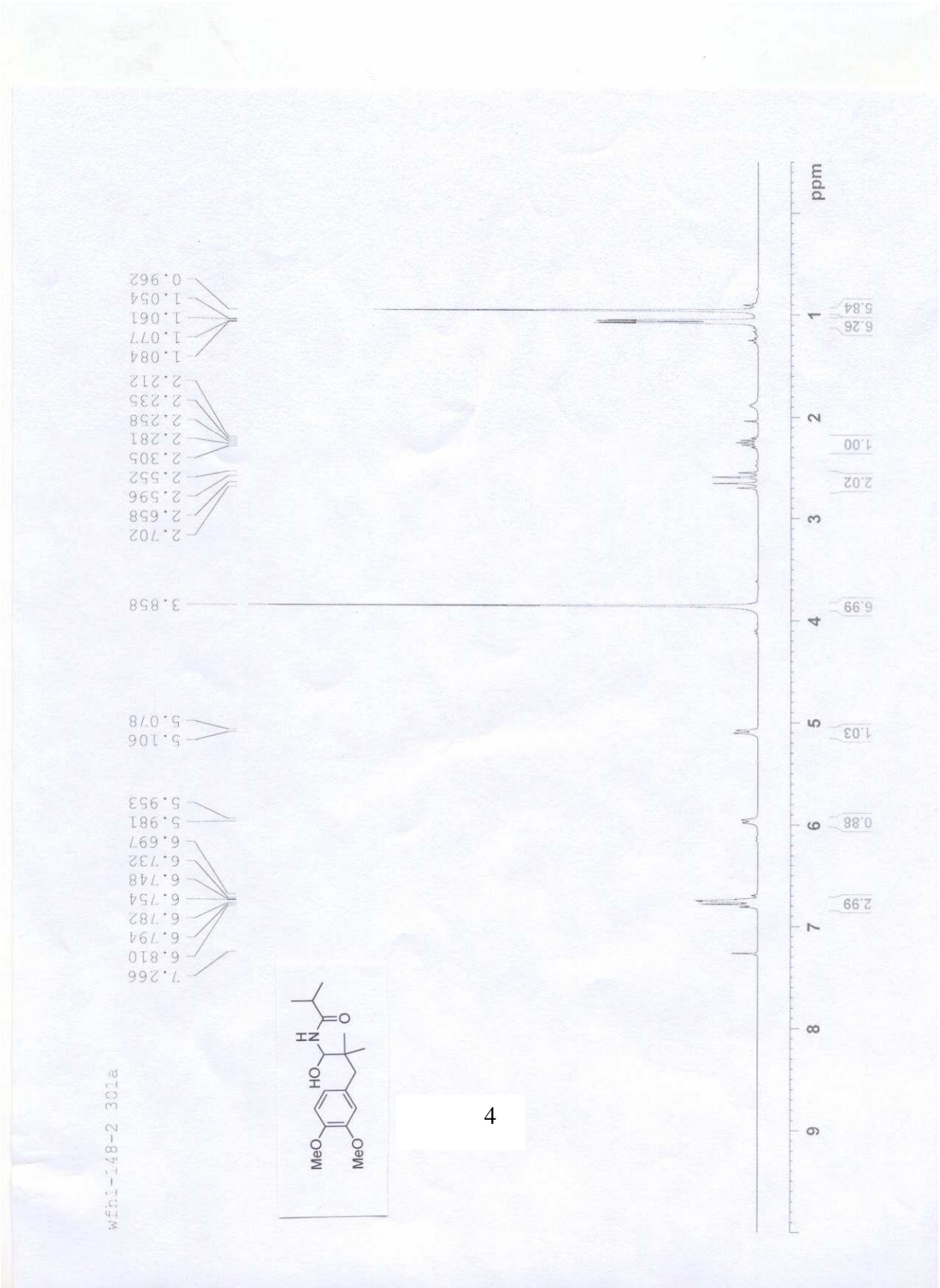
43.30
39.14
35.65
23.75
21.77
19.36
19.32



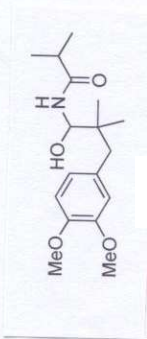
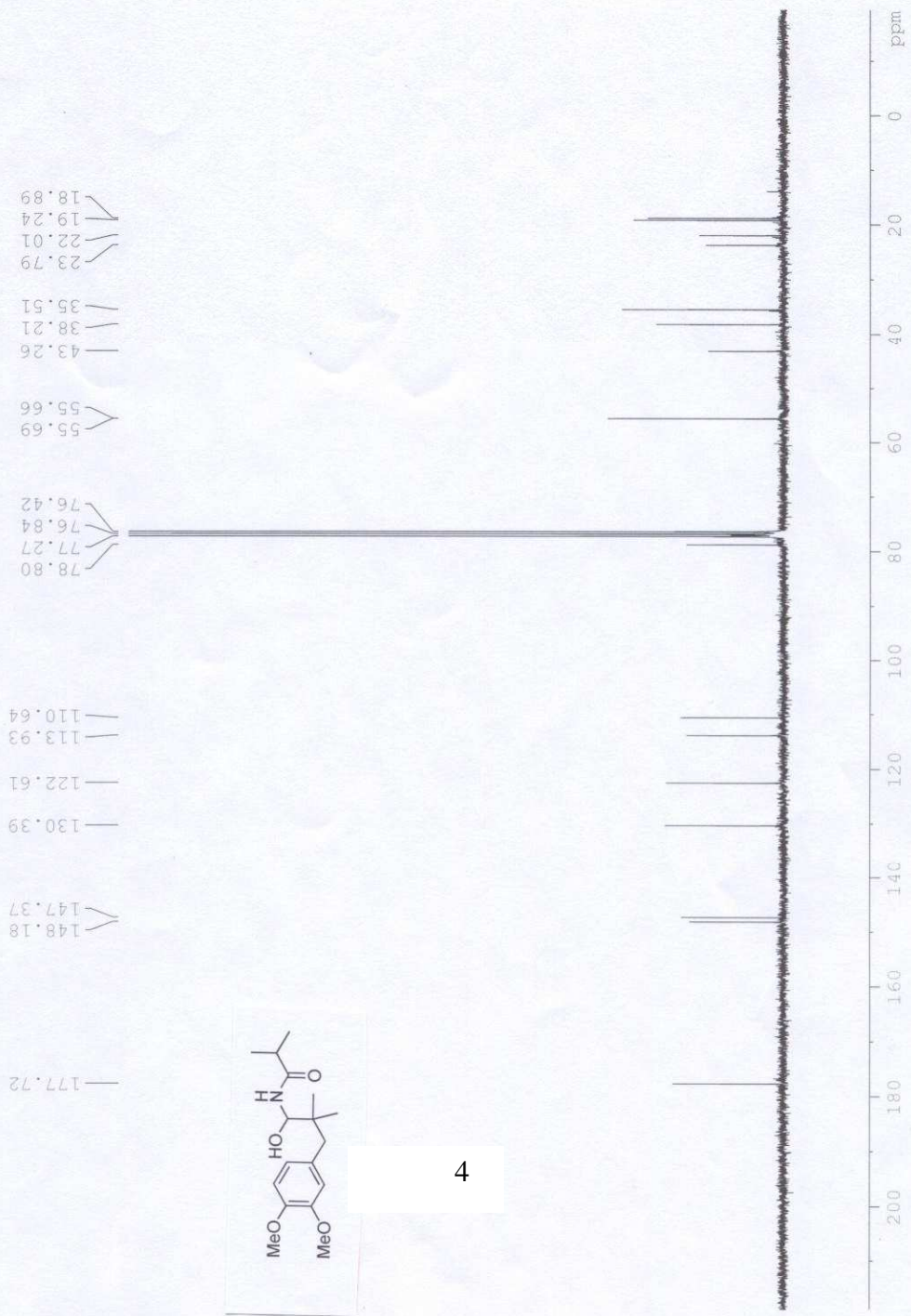
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200 180 160 140 120 100 80 60 40 20 0 ppm

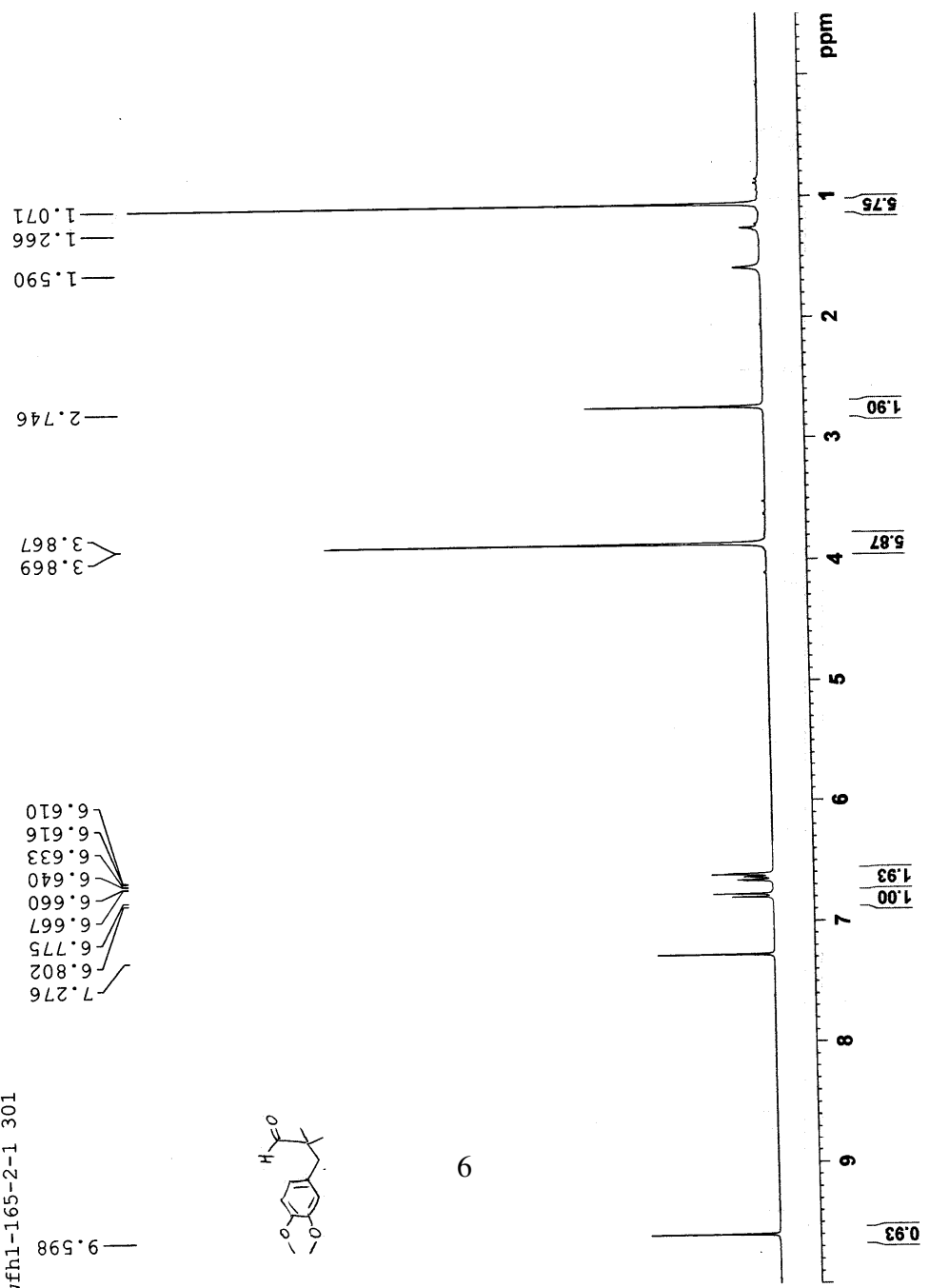




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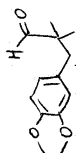


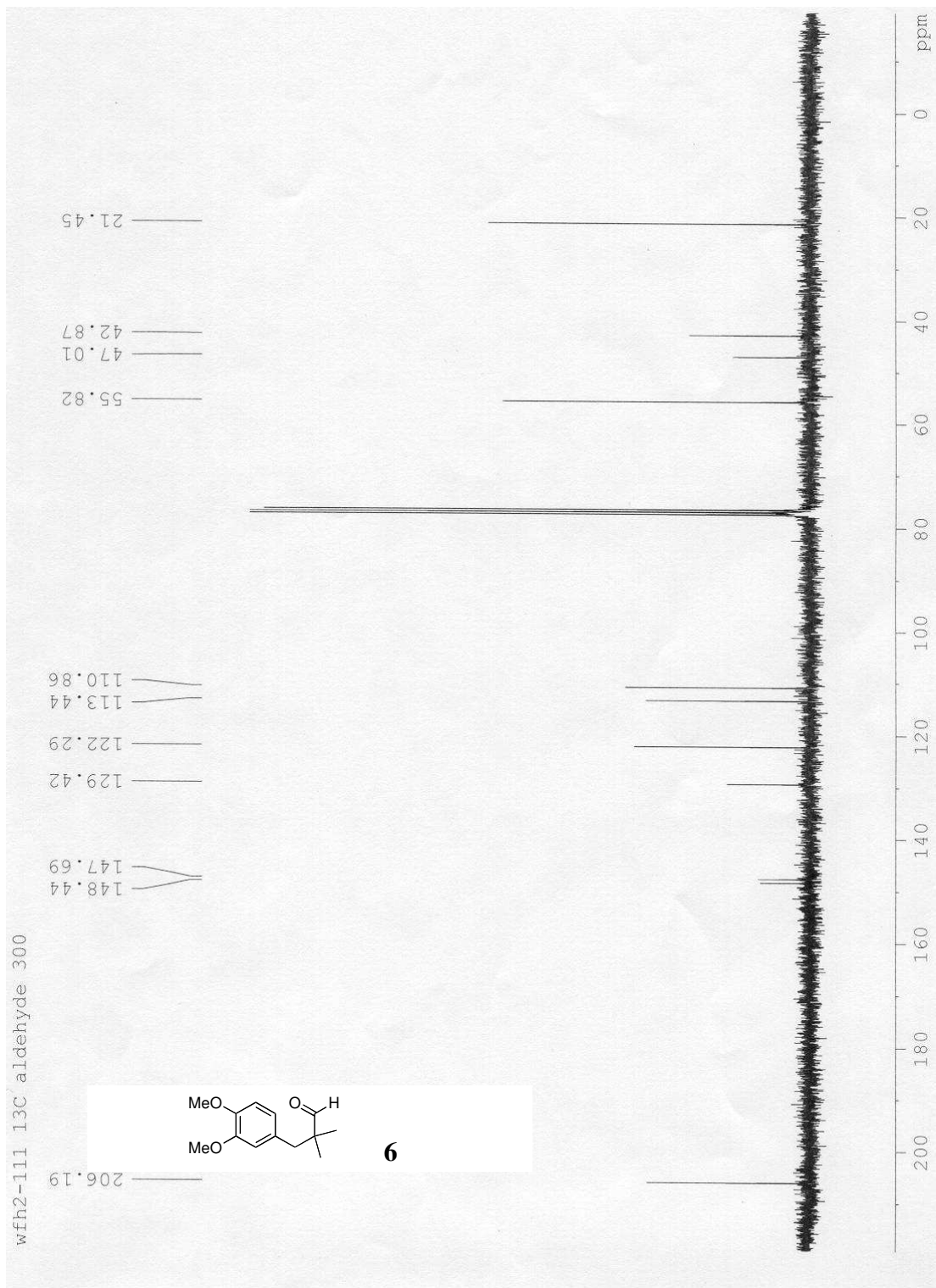
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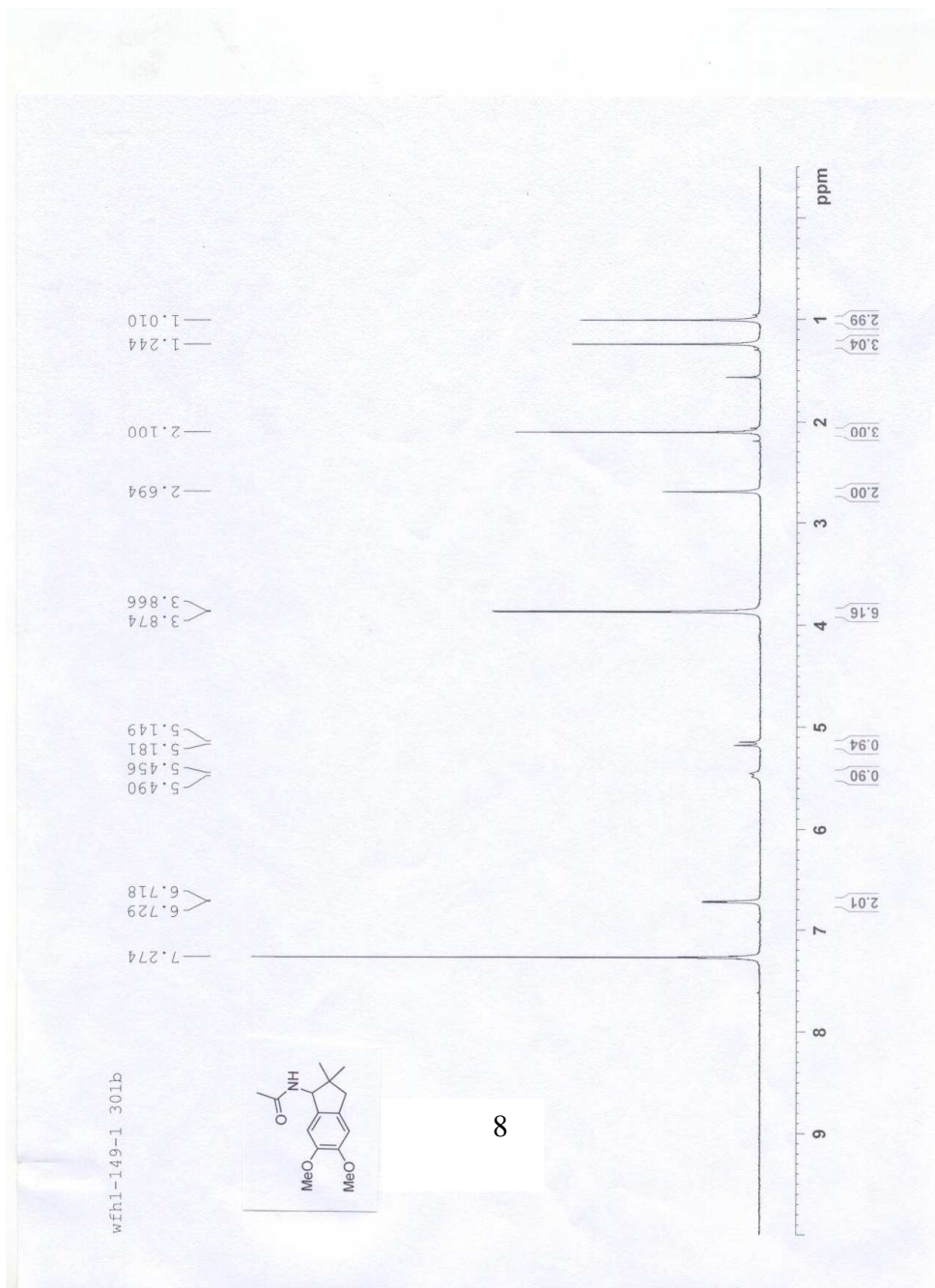


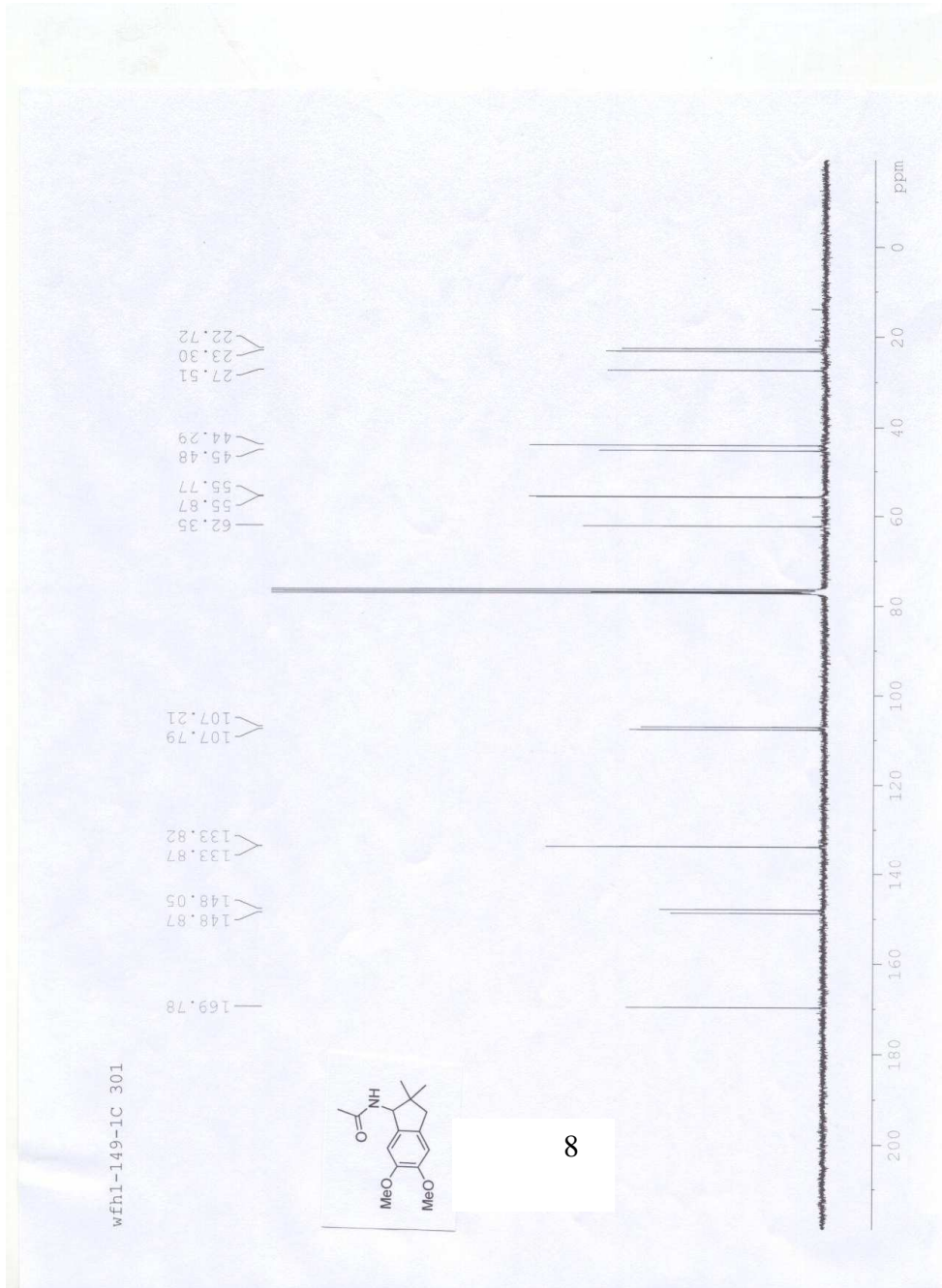
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9







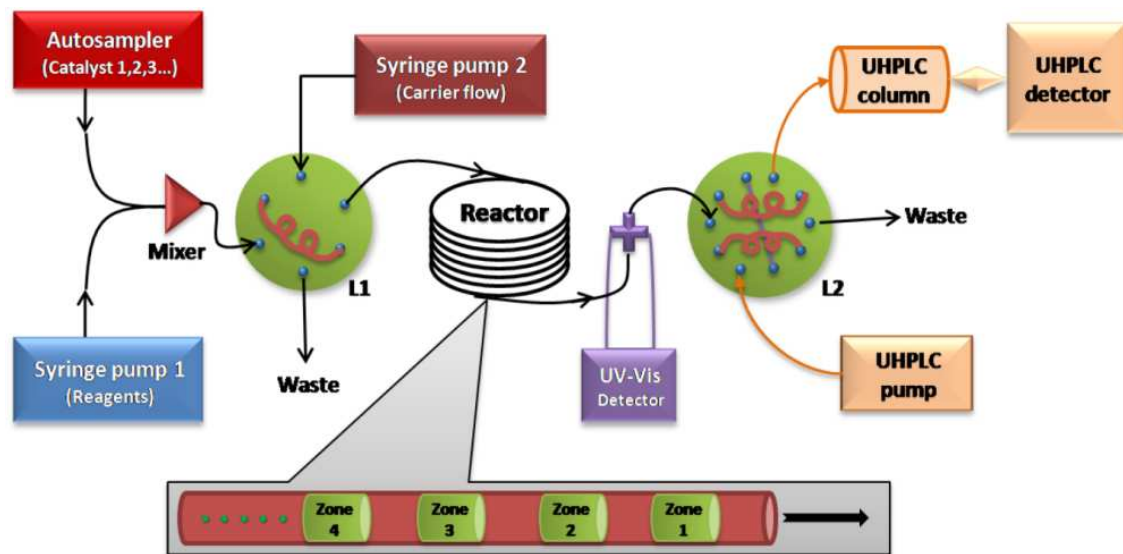


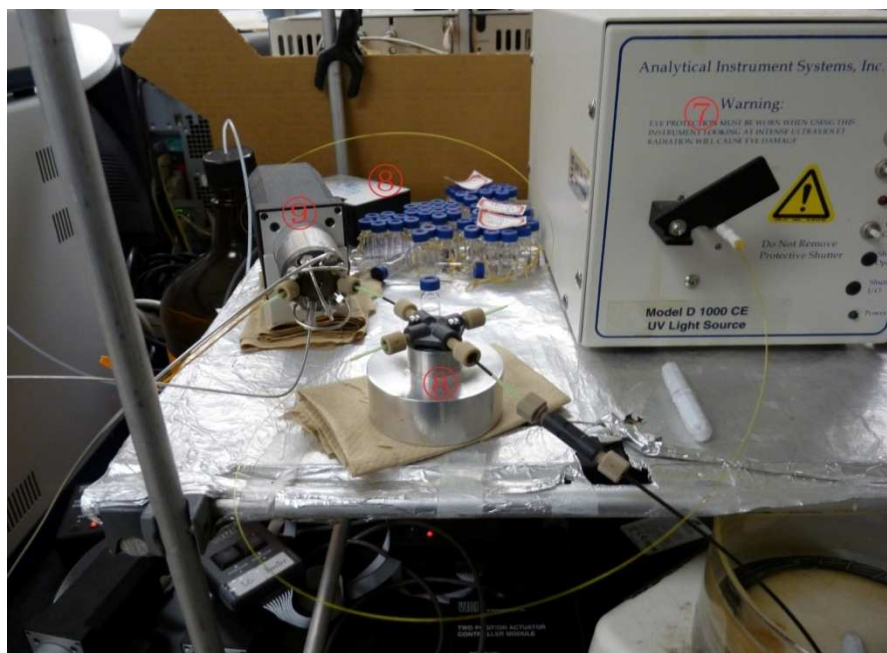
SAMPLING PROGRAM OF HPLC AUTOSAMPLER (HP1050) FOR CATALYST

LOADING AND 6-PORT INJECTOR TRIGGERING

- 10 Utility Contact 1 off
- 20 Utility Contact 2 on // 6-port injector: switch to load position
- 30 Wait 0.01 min
- 40 Utility Contact 2 off
- 50 Utility Valve bypass
- 60 Eject max sample into seat at max speed // prepare sample loading
- 70 Draw 25 μ L sample from vial at max speed // Sample withdrawal
- 80 Eject max sample into seat at speed 15 μ L/min // Sample loading into 6-port injector,
speed equal to the syringe pump for equal mixing with reagent.
- 90 Utility Contact 1 on // 6-port injector: switch to inject position
- 100 Wait 0.01 min
- 110 Utility Contact 1 off
- 120 Wait 3.0 min // 6-port injector: injection time into the microreactor
- 130 Utility Contact 2 on // 6-port injector: switch to load position
- 140 Wait 0.01 min
- 150 Utility Control 2 off
- 160 Utility Valve mainpass // washing pump to clean the autosampler

MICROREACTOR PARTS AND SPECIFICATIONS





(1) Washing pump: clean the autosampler tubes and injection needle.

HPLC Pump (115-230 V), Isocratic pump, Pulse free solvent delivery, Flow rate range 0.001 to 10.000 mL/min.

(2) Autosampler: load catalysts from vials.

Autosampler, 21-position sample tray, programmable, injection volumes 0.1 — 100 μ l.

(3) 6-port microinjector: load and inject reaction samples into reaction capillary.

6 port valve, nanovolume - 5,000 psi - 1/32" Cheminert fittings, 0.10 mm ports (.004"). With standard electric actuator: Standard two position electric actuators- 110 VAC. 60 degree, closeout.

(4) Syringe pump 2: deliver carrier flow (solvent) into the reactor capillary.

Standard infusion only, single syringe pump, flow rate 0.0014 μ l/hr to 26.56 ml/min, syringe size 0.5 μ L to 60 mL.

(5) Syringe pump 1: deliver carrier flow (solvent) into the reactor capillary.

Standard infusion only, single syringe pump, flow rate 0.0014 $\mu\text{l/hr}$ to 26.56 ml/min, syringe size 0.5 μL to 60 mL.

(6) Reactor capillary: immersed into a water bath on a heating plate.

Teflon FEP tubing, 100 μm i.d., 1/16" o.d.

(7) UV-Vis light source: emit UV light to the flow cell (cross) via a fiber optic, dual fiber optic UV/Vis Source, wavelength range 190 to 850 nm

(8) Fiber optic UV-Vis detector: detect UV response of reaction zones; Computer interface: USB-to-PC; Detector: 2048-element linear silicon CCD array; Wavelength range: 200-1100 nm.

(9) 10-port microinjector: load and inject reaction zones into UHPLC.

UHPLC 10-port 15,000 psi nanobore valve, 1/16" fittings, 0.15 mm ports (.006"). With microelectric actuator, two position, high speed.

(10) UHPLC: analyze reaction products.

(15,000 psi), dual wavelength UV-Vis detector (190 nm— 650 nm).