Complete functionalisation of small and large diameter bromopolystyrene beads; applications for solid-supported reagents, scavengers and diversity-oriented synthesis

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Supplementary Material

Experimental Techniques and Apparatus

Except as otherwise indicated, reactions were carried out under argon with dry, freshly distilled solvents. Dry tetrahydrofuran was dispensed from a delivery system which passes the solvent through packed columns of dry neutral alumina and Q5 reactant. Dichloromethane was distilled from calcium hydride. *n*-BuLi in hexane (Aldrich) and *i*-PrMgCl in diethyl ether (Aldrich) were titrated with 1,10-phenanthroline and anhydrous 2-butanol before use.[1] All other reagents were purified in accordance with the instructions in *"Purification of Laboratory Chemicals"*[2] or used as obtained from commercial sources.

Yields refer to chromatographically and spectroscopically pure compounds. All reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with Merck silica gel 60 F_{254} or aluminum oxide 60 F_{254}. Visualization was by the quenching of UV fluorescence (λ_{max} = 254 nm) or by staining with ceric ammonium molybdate or potassium permanganate or Dragendorff ' s reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3M aq. AcOH). Retention factors (R_f) are quoted to 0.01. Melting points were obtained using a Mel-Temp II melting point apparatus and are uncorrected. Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad. Proton magnetic resonance spectra were recorded on Bruker Ultrashield 400 or 500.[3] Proton assignments are supported by ^1H-^1H spectra where necessary. Chemical shifts (δ_H) are quoted in ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants (*J*) are reported in Hertz to the nearest 0.5Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (*e.g.* dd, dt, *etc.*)], coupling constant(s) and assignment. Diastereotopic protons are assigned as X and X', where the ' indicates the higher field proton. Carbon magnetic resonance spectra were recorded on Bruker Ultrashield 500 spectrometers. Carbon spectra assignments are supported by DEPT editing and where necessary ^{13}C-^1H (HMQC) correlations. Chemical shifts (δ_C) are quoted in ppm to the nearest 0.01 ppm, and are referenced to the deuterated solvent. Phosphorous magnetic resonance spectra (^{31}P) were recorded on a DPX 400MHz spectrometer. Chemical shifts (δ_P) are quoted in ppm to the nearest 0.01 ppm and are referenced to H_3PO_4 (external). Only molecular ions, fractions from molecular ions and other major peaks are reported. LCMS spectra were recorded on an HP/Agilent MSD LC-MS APCI 120-1000 full gradient ACq T= 1 min 1µl. High resolution mass measurements were made by the EPSRC mass spectrometry service (Swansea) and reported mass values are within the error limits of ±5 ppm mass units. Microanalyses were performed by the University of Cambridge Microanalytical Laboratory in the Department of Chemistry, and are quoted to the nearest 0.1% for all elements except for hydrogen, which is quoted to the nearest 0.05%. Reported atomic percentages are within the error limits of ±0.4%.

Experimental Procedures

General Procedure For Alcohol Attachment: Dry silane polystyrene **3** (ca. 2 mequiv. per gram) was added to a dry, fritted polypropylene column (Bruker) fitted with a Teflon stopcock and capped with a suba seal. The vessel was evacuated and purged with Ar. The beads were swollen with CH_2Cl_2 (10 ml per gram of beads) and TMSCl (6 equiv.) and occasionally agitated over 30 min, at room temperature, under Ar. The solution was then drained under positive Ar pressure, and washed/drained three times with anhydrous CH_2Cl_2. The beads were then suspended in a CH_2Cl_2 solution of 1,3-dichloro-5,5-dimethylhydantoin (3 equiv.) and agitated occasionally over 2 h, at room temperature, under Ar. The solution was then drained under positive Ar pressure, and washed/drained two times with anhydrous CH_2Cl_2 to give **4**. The silyl chloride beads were suspended in a CH_2Cl_2 solution of 2,6-lutidine (4 equiv.), DMAP (0.1 equiv.) and anhydrous alcohol (3 equiv.; 1.5 equiv. can be used if the alcohol is valuable), the mixture was agitated then left to stand overnight, at room temperature, under Ar. The solution was then drained under positive Ar pressure (excess alcohol can be recovered), and washed/drained as in ref. 10. The beads were air-dried under suction for 2 h with occasional agitation, and then placed under high vacuum.

General Procedure For Alcohol Cleavage: The beads (100 mg) were swollen in THF (0.5 ml) and HF•Pyr (50 μl, 1.77 mmol) was added. The vials were sealed and agitated for 2.5 h, then quenched using trimethylethoxysilane. The vials were agitated for a further 30 min to ensure complete quenching. Then the solvent was filtered through a plug of silica gel and the resin washed with CH_2Cl_2. The solvent was removed *in vacuo* and the product purified by column chromatography.

General Mitsunobu Reaction Procedure: To a mixture of carboxylic acid (1 equiv.), alcohol (1.5 equiv.) and polymer bound triphenylphosphine (0.9 mmol/g, 1.5 equiv.) in THF (*ca.* 0.1M) under nitrogen at 0 °C was added di-tert-butyl azodicarboxylate (1.5 equiv.) in THF (1 ml). The reaction was warmed to room temperature and stirred overnight. The reaction was filtered and the resins washed with CH_2Cl_2. The organic filtrate was washed with 3N HCl (x 2), brine (x 2) dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using CH_2Cl_2 as the eluent to yield a colourless oil.

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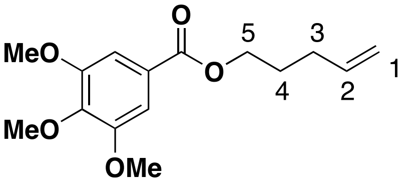
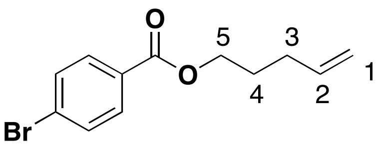
1 Watson, S. C.; Eastham, *J.* F. *J. Organometal. Chem.* **1967**, *9*, 165-168.
2 Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals, Fourth Edition*; Butterworth-Heinemann: Oxford, 1997.
3 See: http://www-methods.ch.cam.ac.uk/meth/nmr.html

3,4,5-Trimethoxy-benzoic acid pent-4-enyl ester



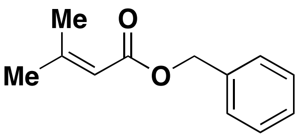
R_f 0.29 (SiO_2; CH_2Cl_2); ν_{max} (neat)/cm^{-1} 1712s (C=O), 1124s (C-O); δ_H (500 MHz; $CDCl_3$) 7.32 (2H, s, aryl C<u>H</u>), 5.91-5.80 (1H, ddt, *J* 16.0, 15.0, 10.0 Hz, H2), 5.11-5.07 (1H, d, *J* 16.0 Hz, H1), 5.04-5.02 (1H, d, *J* 10.0 Hz, H1'), 4.36-4.33 (2H, t, *J* 6.5 Hz, H5), 3.92 (9H s, OC<u>H</u>$_3$), 2.23-2.20 (2H, dt, *J* 15.0, 6.5 Hz, H3), 1.92-1.84 (2H, tt, *J* 6.5, 6.0 Hz, H4); δ_C (125 MHz; $CDCl_3$) 166.21 (C), 152.95 (C), 142.24 (C), 137.47 (CH), 125.45 (C), 115.35 (CH_2), 106.85 (CH), 64.56 (CH_2), 60.91 (CH_3), 56.25 (CH_3), 30.18 (CH_2), 27.96 (CH_2); LCMS (MeCN) 3.74 min; 281 (MH^+); HRMS found 281.1385 $C_{15}H_{21}O_5$ (MH^+) required 281.1384.

4-Bromo-benzoic acid pent-4-enyl ester



R_f 0.81 (SiO_2; CH_2Cl_2); ν_{max} (neat)/cm^{-1} 1717s (C=O); δ_H (500 MHz; $CDCl_3$) 7.90-7.87 (2H, d, *J* 8.5 Hz, aryl C<u>H</u>), 7.60-7.55 (2H, d, *J* 8.5 Hz, aryl C<u>H</u>), 5.88-5.78 (1H, m, H2), 5.10-5.03 (1H, br dt, *J* 17.0 Hz, H1), 5.02-5.00 (1H, br dt, *J* 10.0 Hz, H1'), 4.33-4.30 (2H, t, *J* 6.5 Hz, H5), 2.23-2.18 (2H, dt, *J* 14.0, 6.5 Hz, H3), 1.90-1.84 (2H, tt, *J* 7.0, 6.5 Hz, H4); δ_C (125 MHz; $CDCl_3$) 165.86 (C), 137.35 (CH), 131.70 (CH), 131.09 (CH), 129.35 (C), 127.96 (C), 110.00 (CH_2), 64.65 (CH_2), 30.13 (CH_2), 27.88 (CH_2); LCMS (MeCN) 4.60 min, 271 (MH^+);

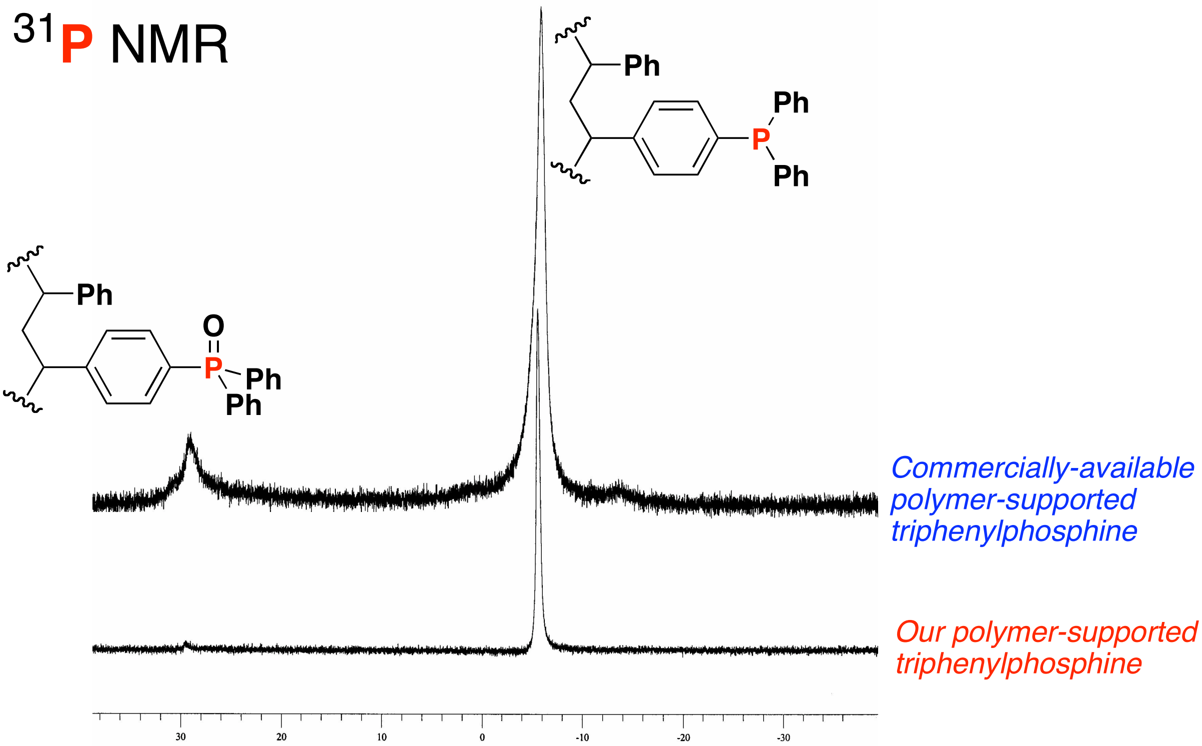
3-Methyl-but-2-enoic acid benzyl ester



R_f 0.88 (SiO_2; CH_2Cl_2); ν_{max} (neat)/cm^{-1} 1715s (C=O), 1648m (C=C); δ_H (500 MHz; $CDCl_3$) 7.53-7.22 (5H, m, aryl C<u>H</u>), 5.75 (1H, s, C<u>H</u>CO_2Bn), 5.12 (2H, s, C<u>H</u>$_2$), 2.18 (3H, s, C<u>H</u>$_3$), 1.88 (3H, s, C<u>H</u>$_3$); δ_C (125 MHz; $CDCl_3$) 166.41 (C), 157.23 (C), 136.51 (C), 128.51 (CH), 128.11 (C), 128.01 (CH), 115.82 (CH), 65.36 (CH_2) 27.42 (CH_3), 20.28 (CH_3); LCMS (MeCN) 4.15 min; 191 (MH^+);

IR analysis of resins

Electrophile	***IR absorbance***
CO_2	3372 O-H 1687 C=O
Benzophenone	3414 O-H 1491-1450 C=C
DMF	1700 C=O (aldehyde)
4-Iodophenyl isocyanate	1654 C=O (amide)
Allyl bromide	3026, 1638, 993, 911 RCH=CH_2
Trimethyl borate	3358 O-H 1340 B-O
S_8	~3300 S-H
PhSSPh	2857 C-S



Gel-phase ^{31}P NMR spectra comparing our polymer-supported triphenylphosphine (**2a**) with a version available commercially (**2b**).

ppm

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PROCNO 1

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FIDRES 0.157632 Hz
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RG 228.1
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

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SSB 0
LB 0.30 Hz
GB 0
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F2 0.00 Hz
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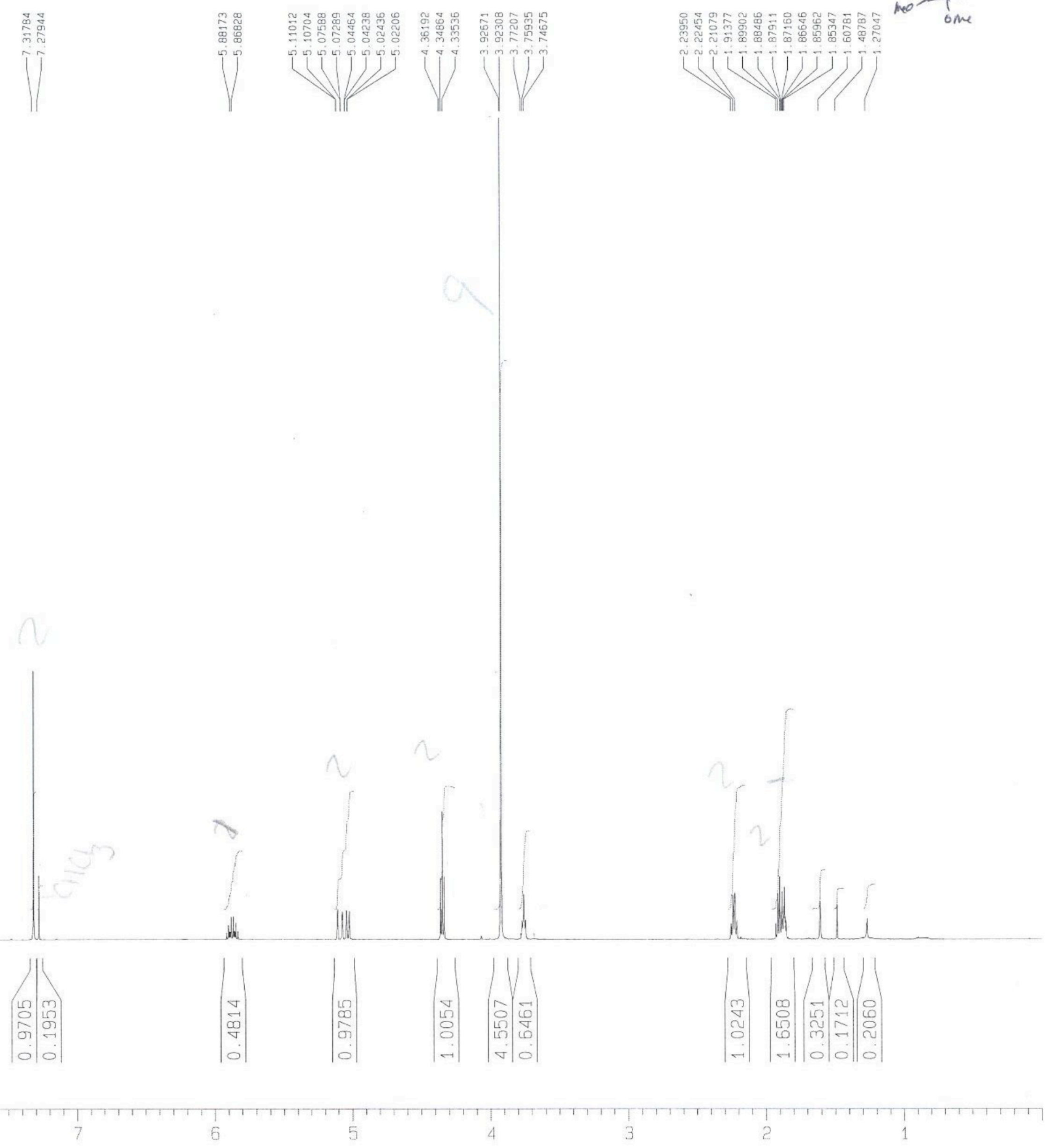

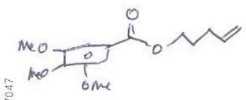

ppm

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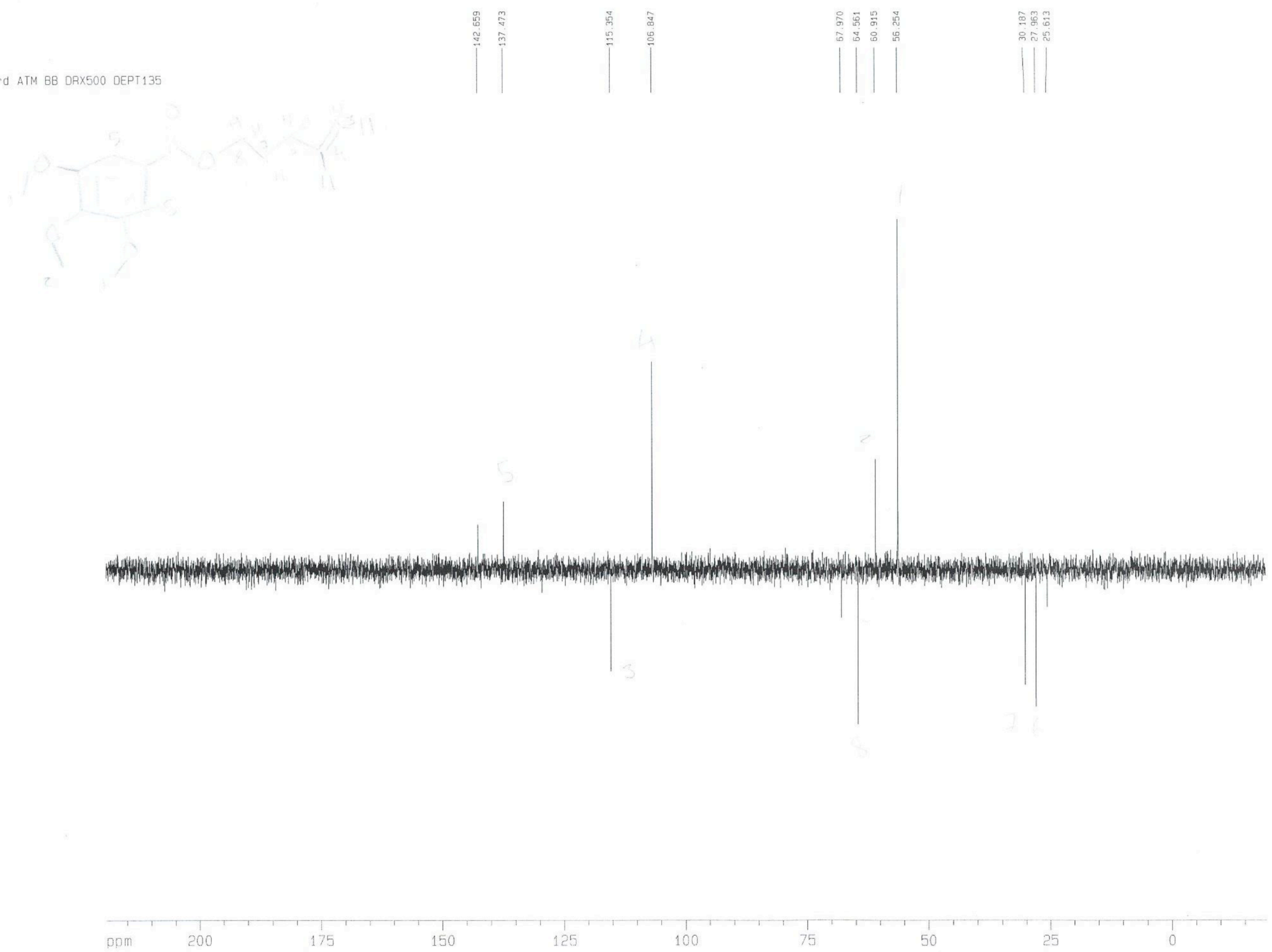

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GB 0
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1D NMR plot parameters
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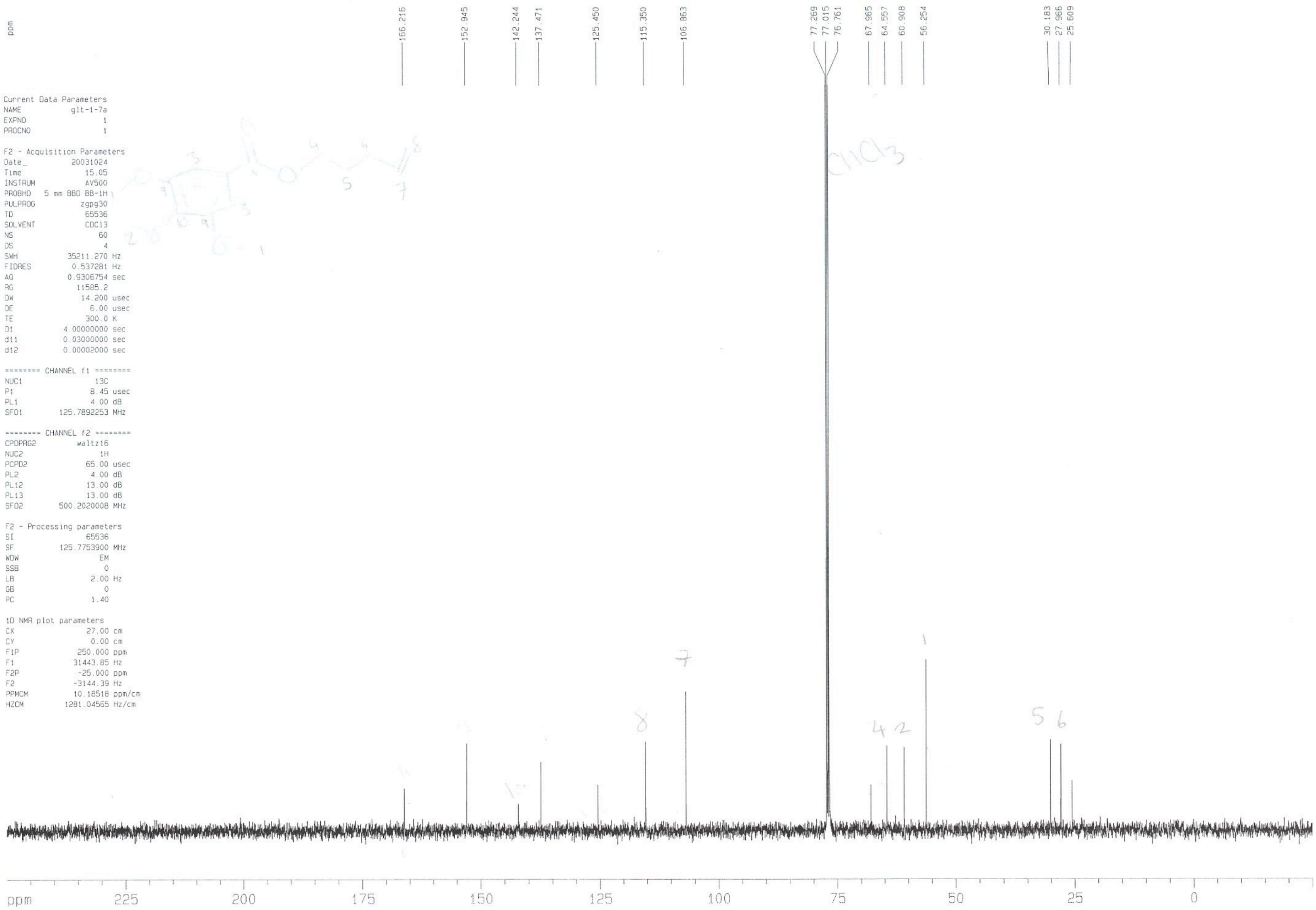

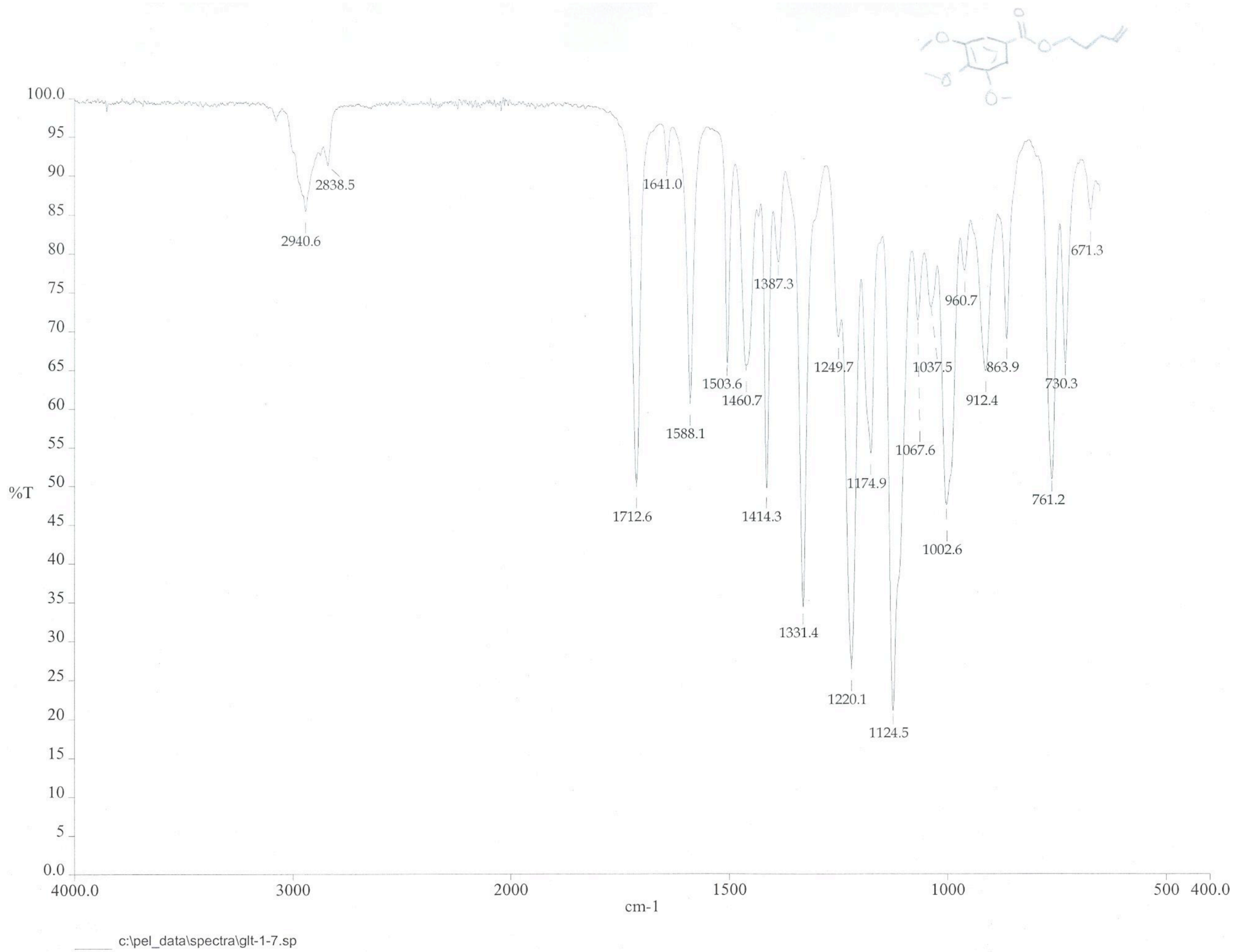

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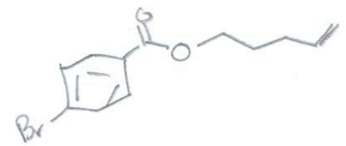

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TE                300.0 K
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1D NMR plot parameters
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F2P               0.000 ppm
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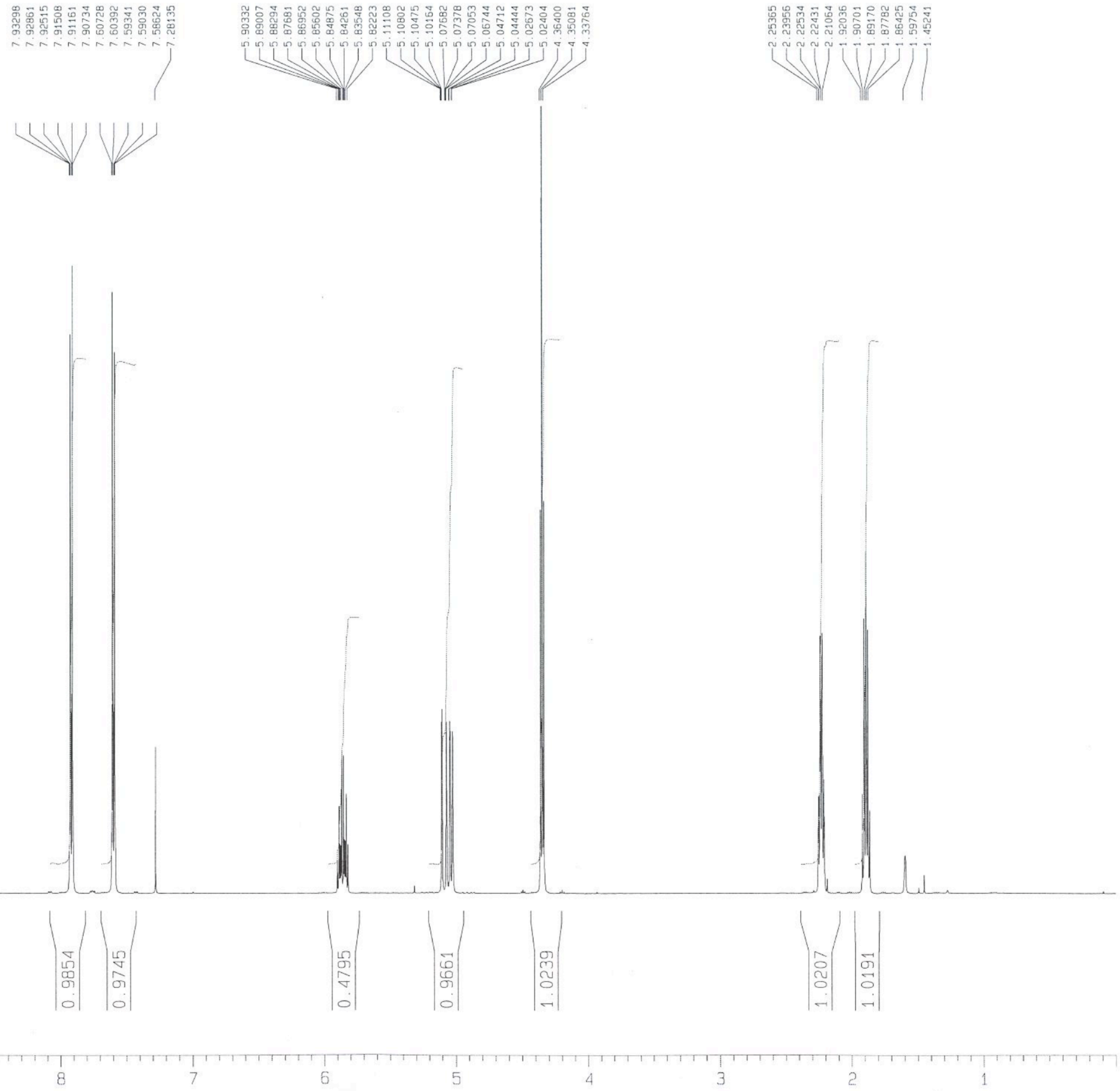

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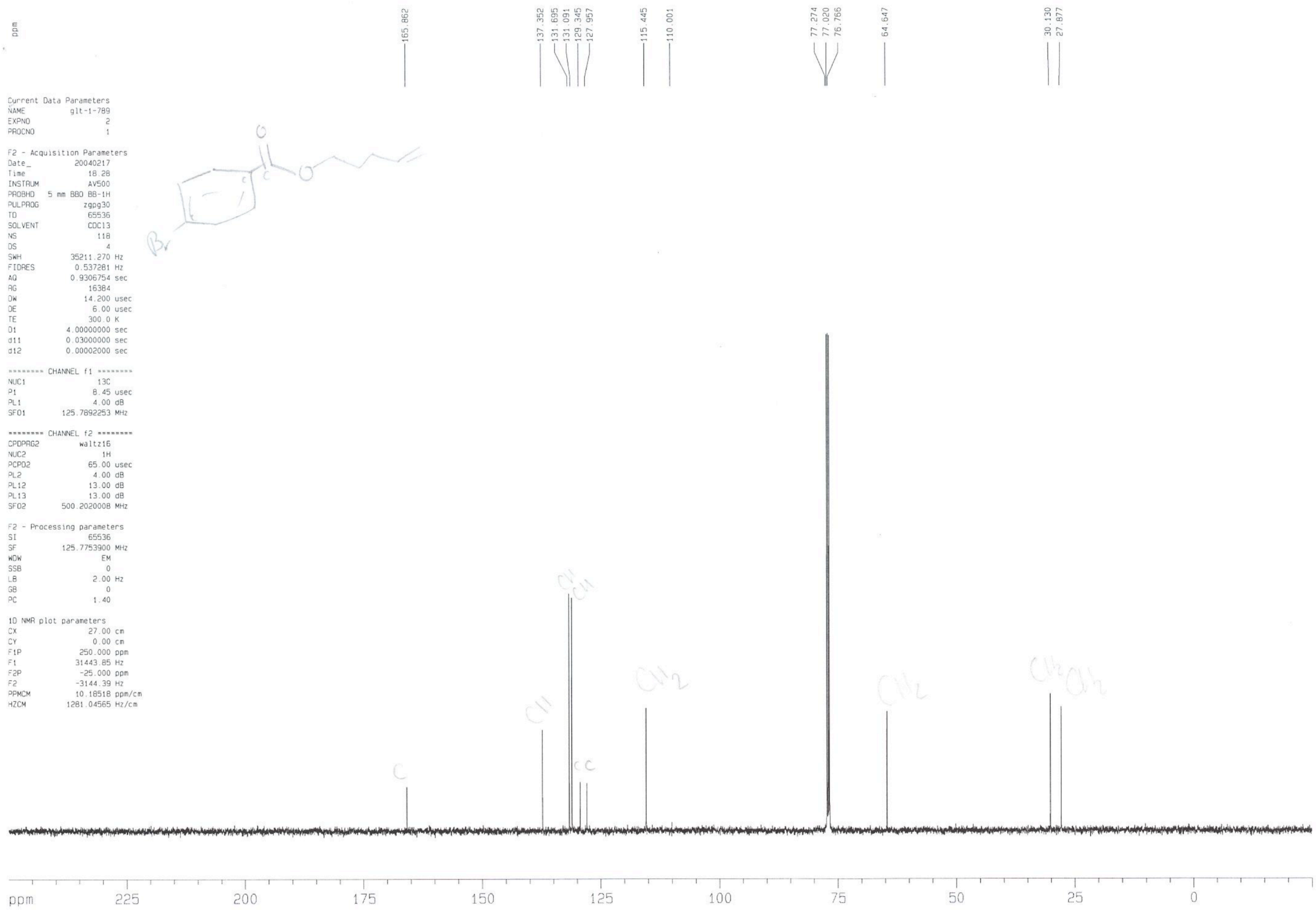


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RG                16384
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PL1                4.00 dB
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NUC2                 1H
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PL2                4.00 dB
PL12              13.00 dB
PL13              13.00 dB
SFO2        500.2020008 MHz

F2 - Processing parameters
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LB                 2.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                27.00 cm
CY                 0.00 cm
F1P             250.000 ppm
F1             31443.85 Hz
F2P             -25.000 ppm
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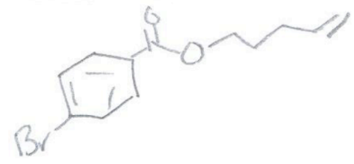
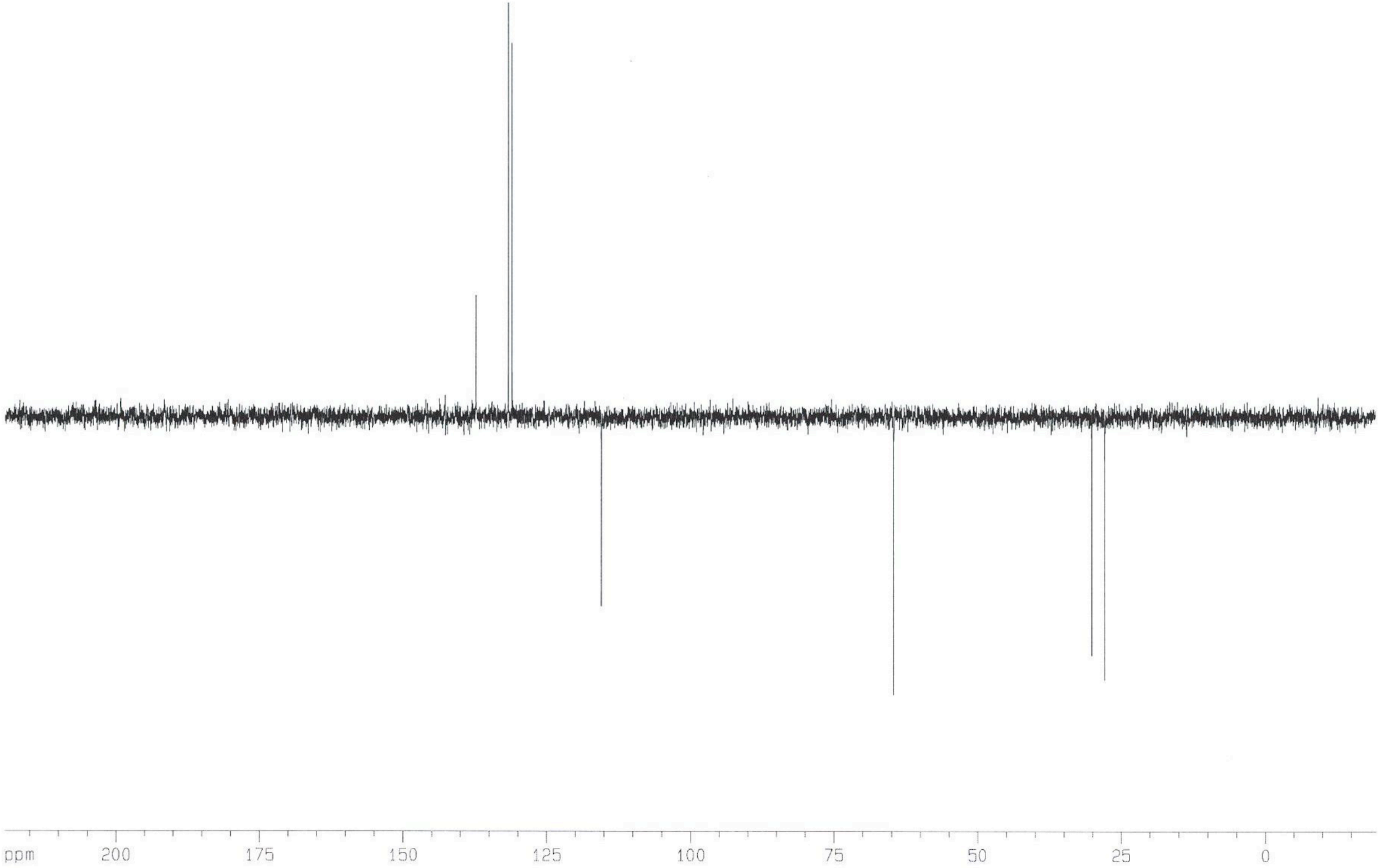
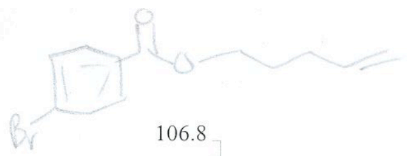




78A



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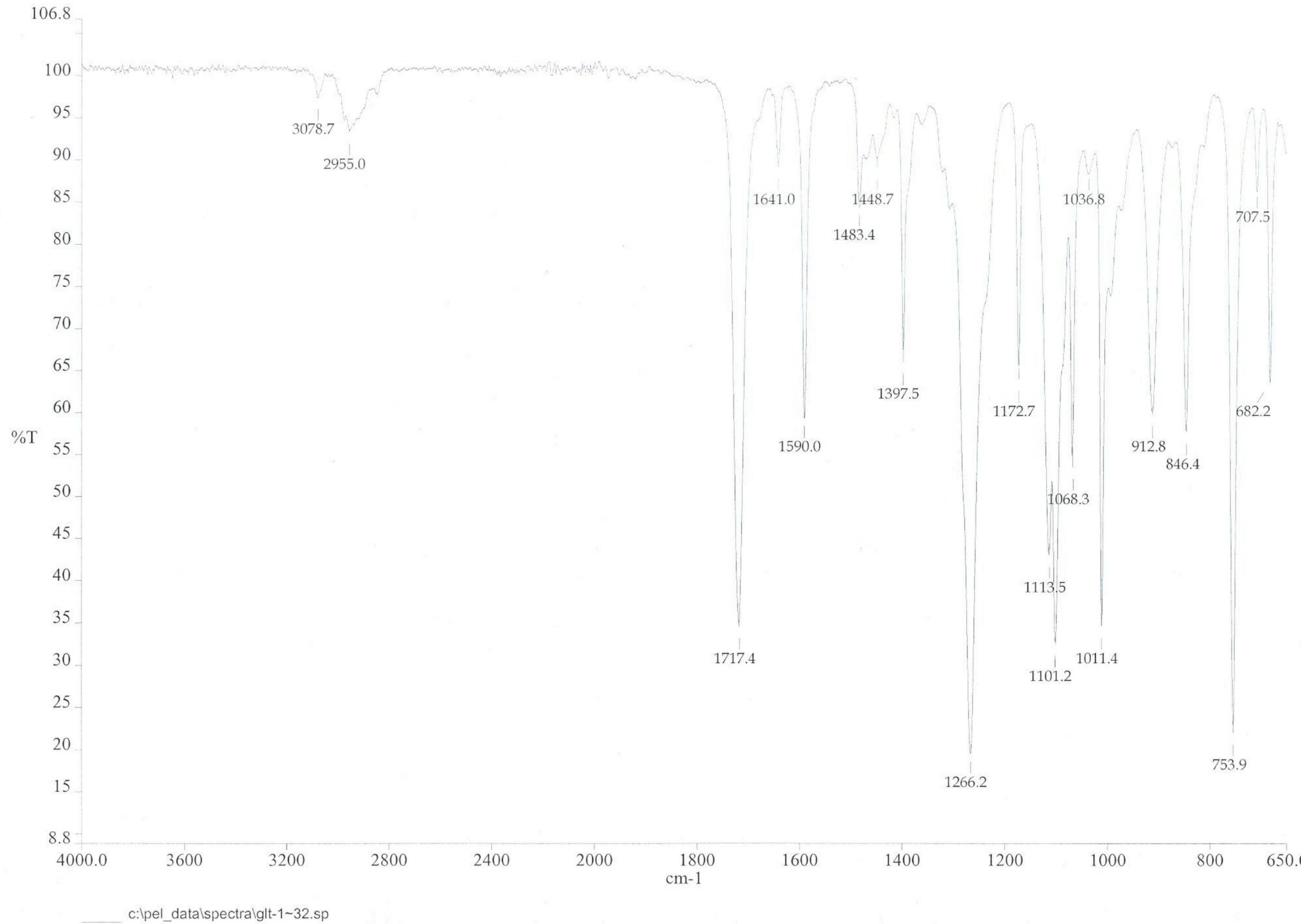

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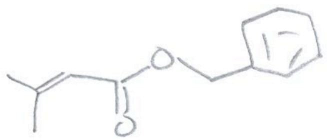
Standard ATM BB DRX500 1H



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SFO1 500.2030889 MHz

F2 - Processing parameters
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1D NMR plot parameters
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CY 13.50 cm
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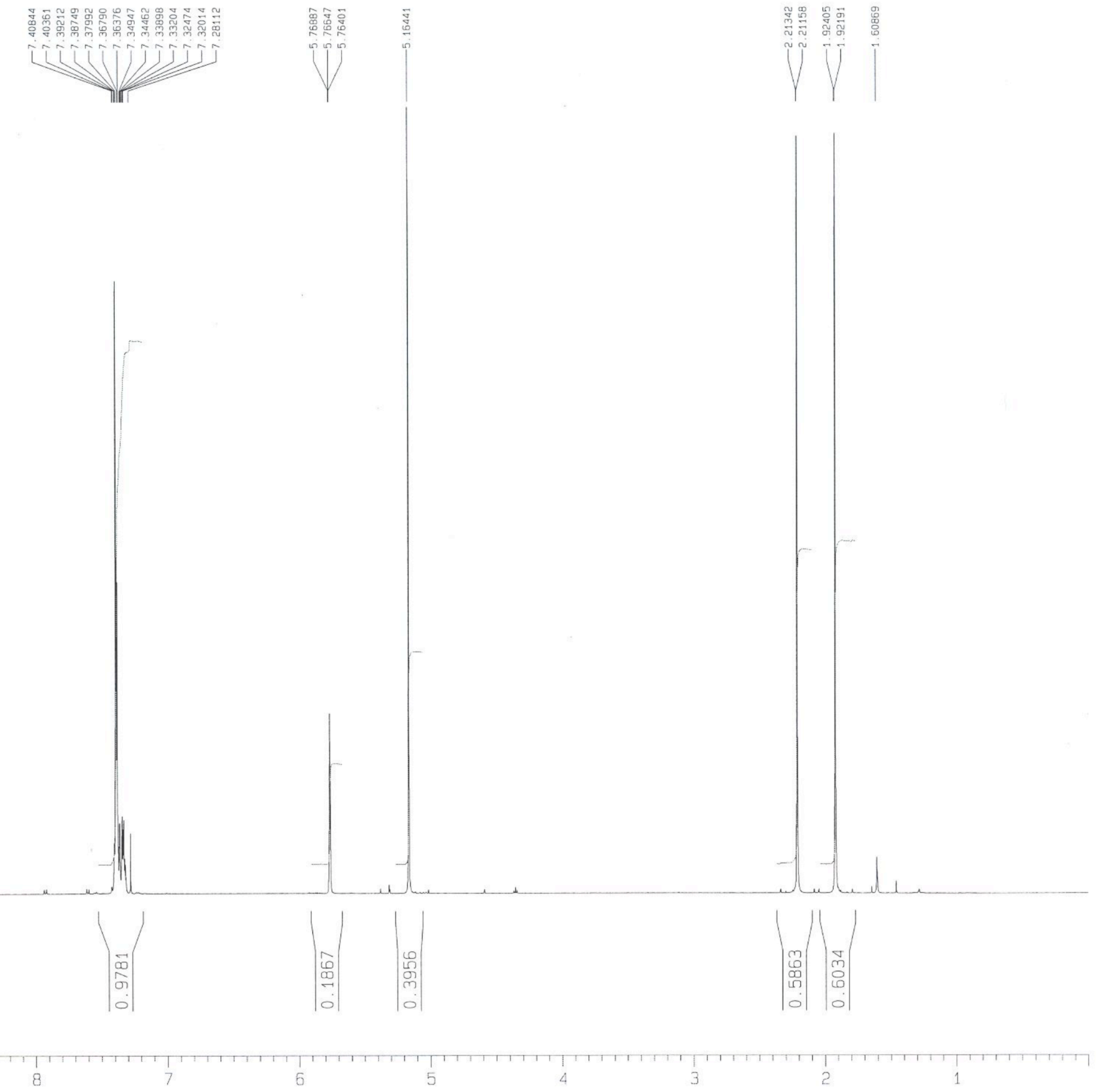
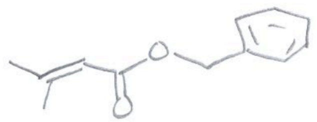
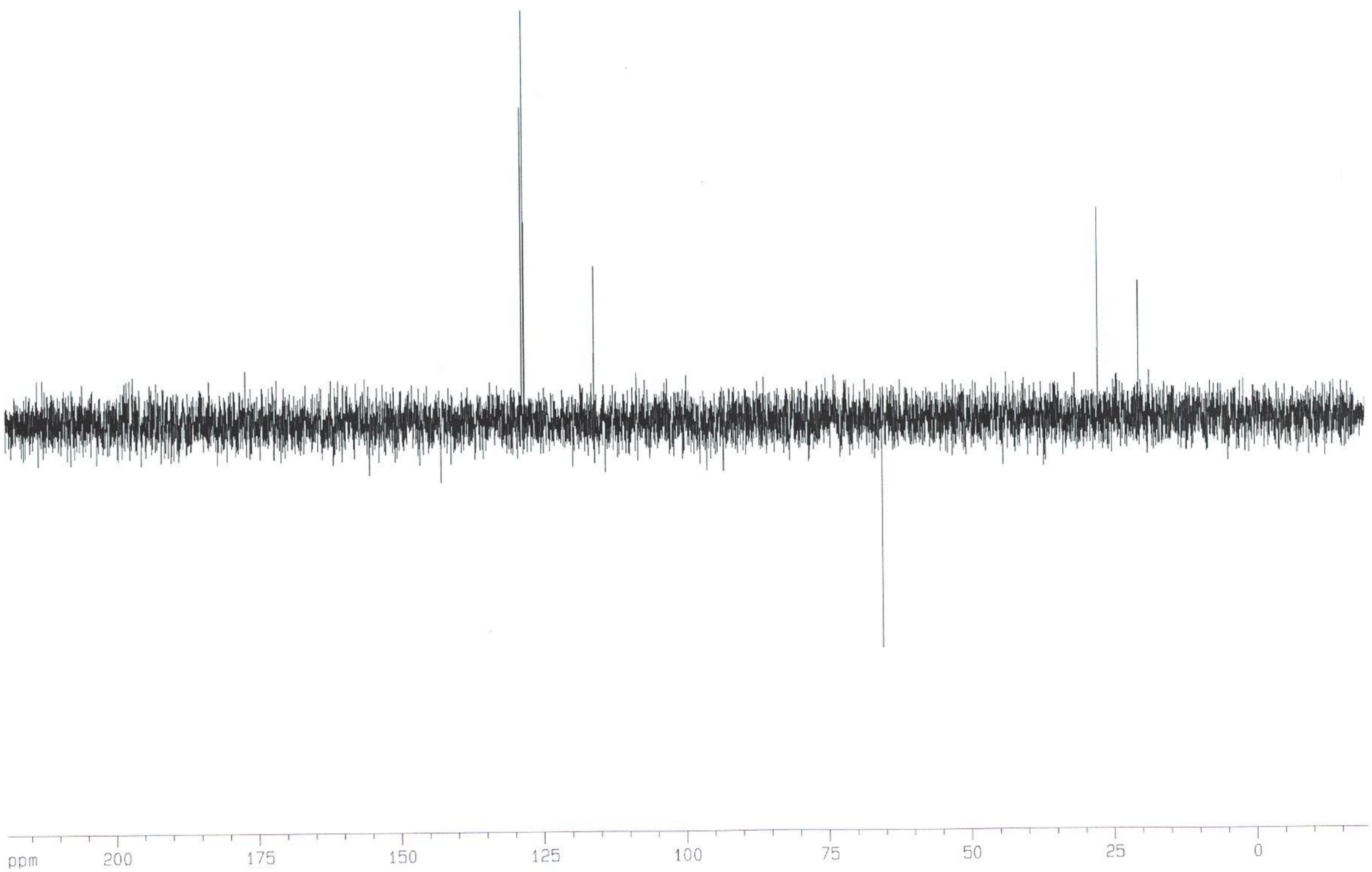
F1 6002.40 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.44444 ppm/cm
HZCM 222.31111 Hz/cm



Standard ATM BB DRX500 DEPT135





Standard ATM BB DRX500 13C

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PROCNO 1

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PL1 4.00 dB
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======== CHANNEL f2 ========
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PL13 13.00 dB
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F2 - Processing parameters
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1D NMR plot parameters
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CY 0.00 cm
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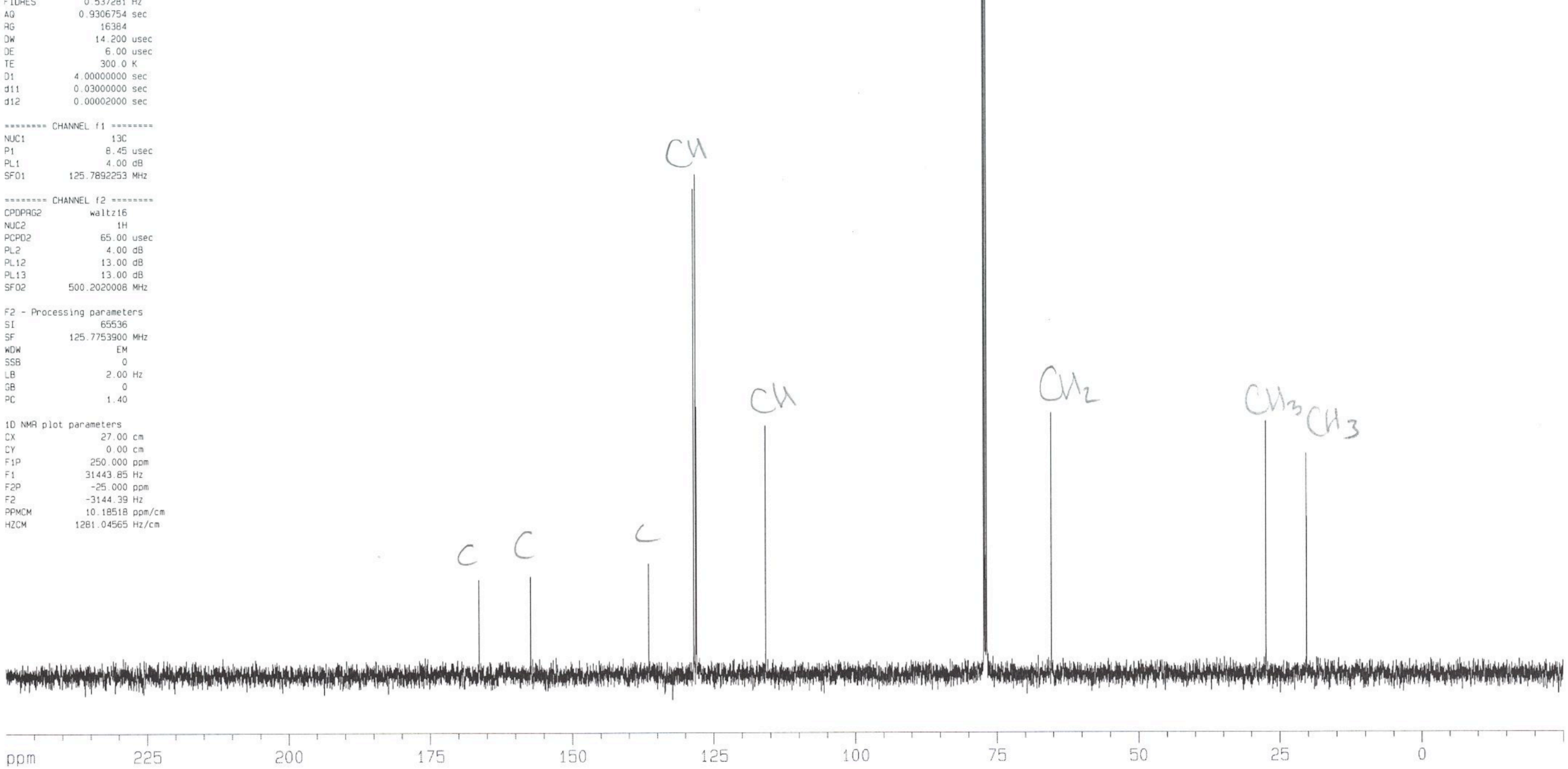
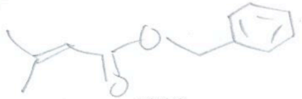
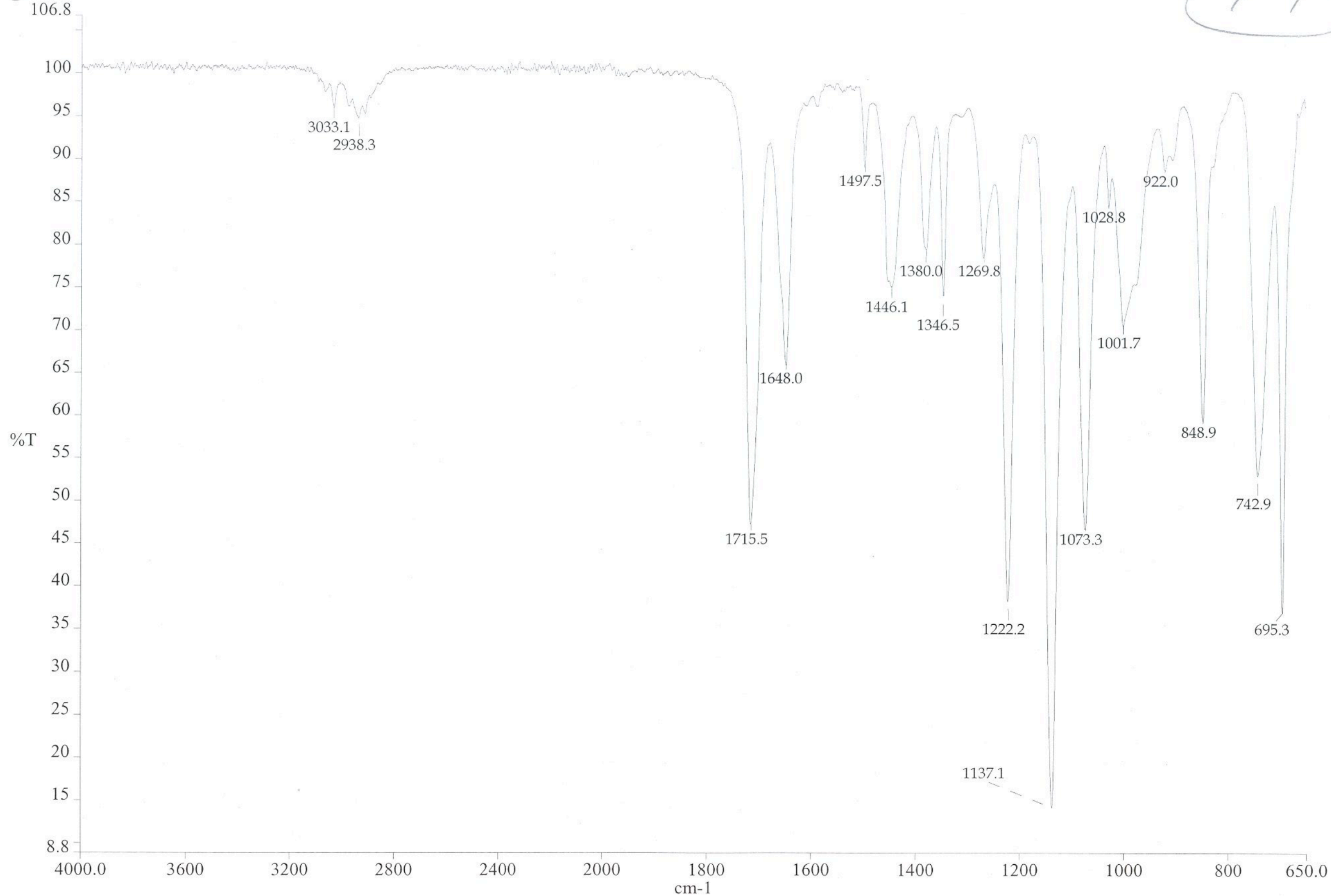




77A



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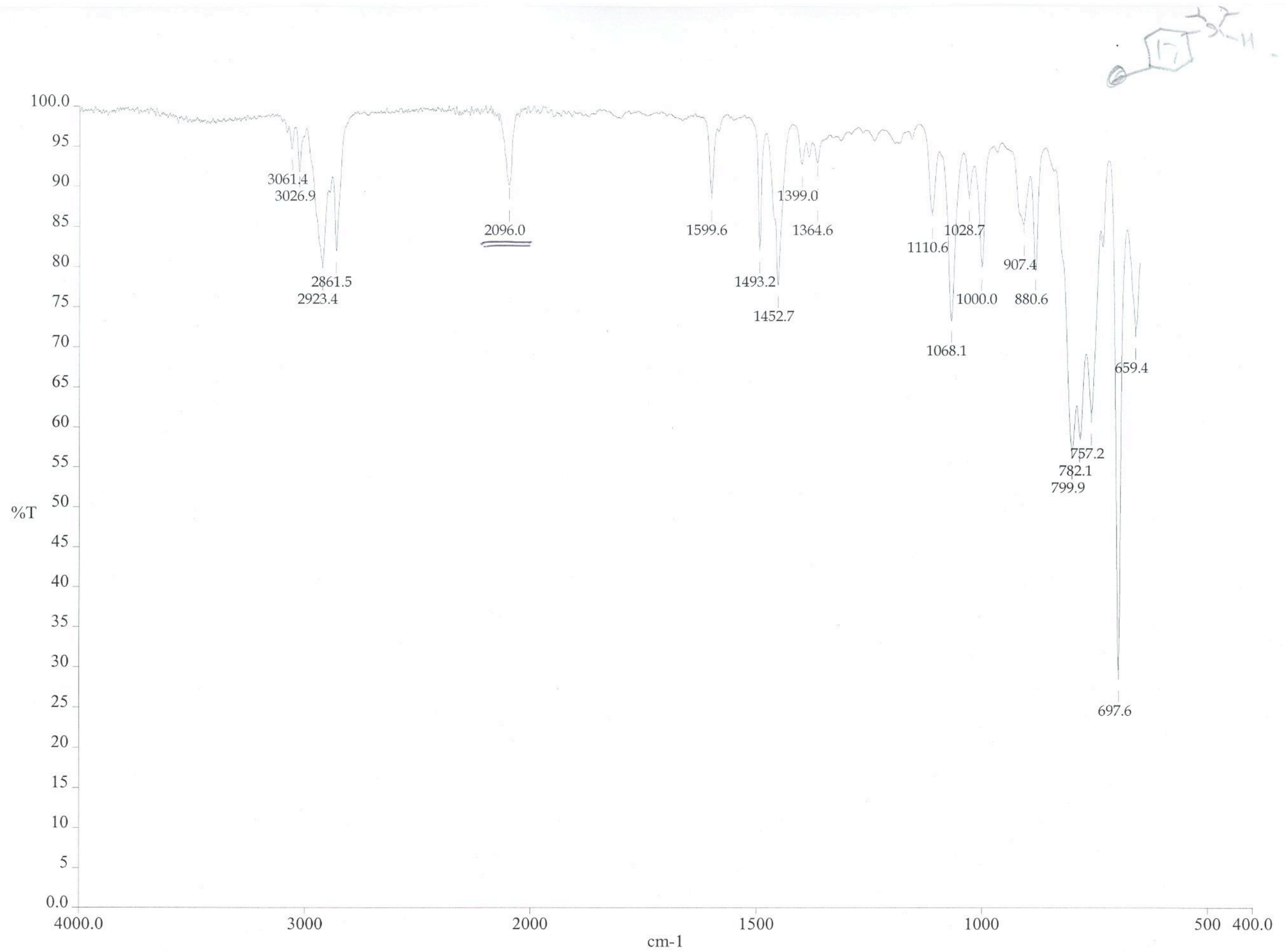

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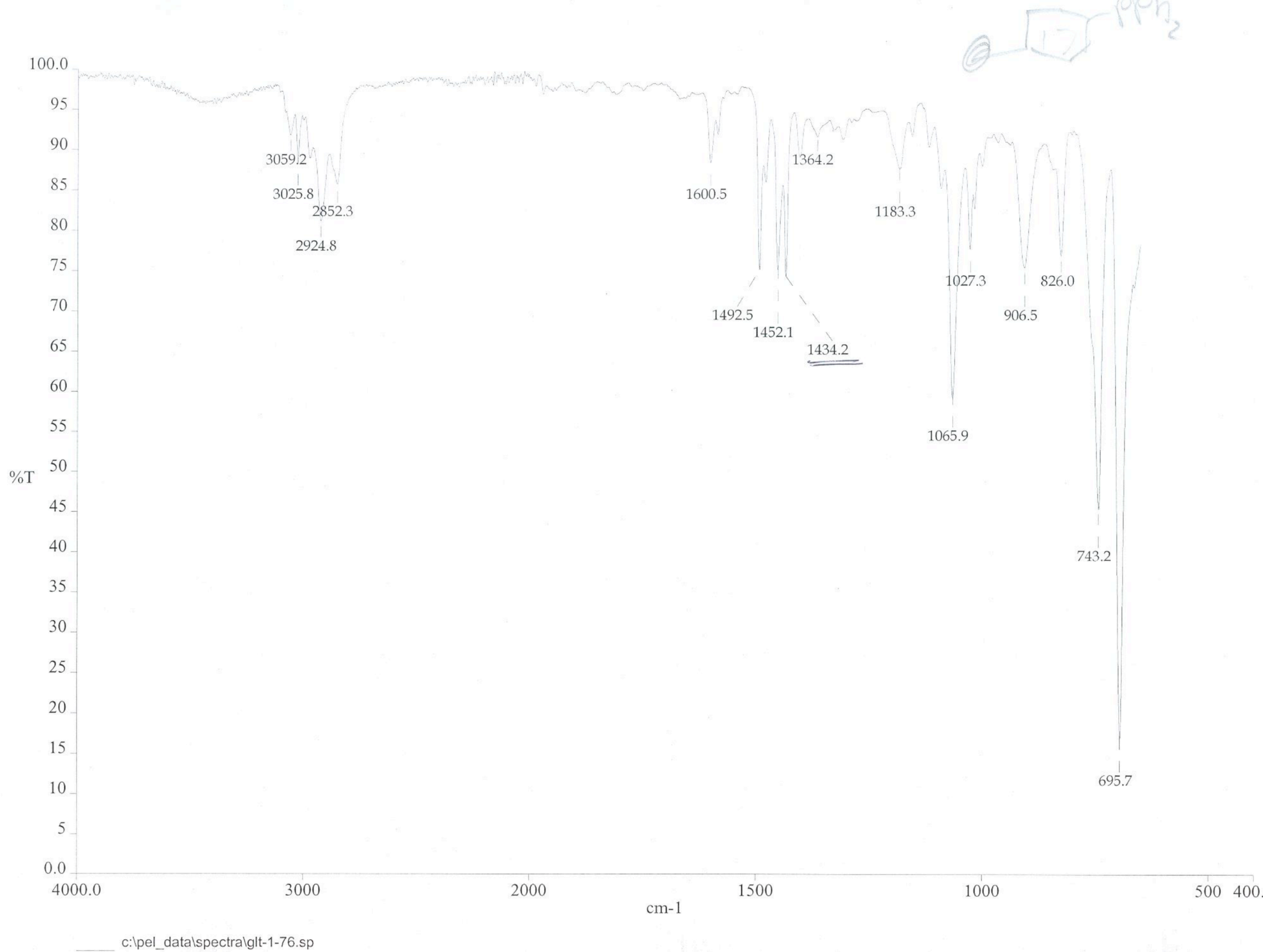
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90
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30
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15
10
5
0.0
%T
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3025.8
2852.3
2924.8
1600.5
1364.2
1492.5
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1183.3
1027.3
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906.5
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743.2
695.7
4000.0
3000
2000
1500
1000
500
400.0
cm-1
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