Supporting Information

Pyridine is an organocatalyst for the reductive ozonolysis of alkenes

Rachel A. Willand-Charnley, Thomas J. Fisher, Bradley Johnson and Patrick H. Dussault*
Department of Chemistry, University of Nebraska-Lincoln
Lincoln NE 68588-0304, USA; e-mail: pdussault1@unl.edu.

Table of Contents

Abbreviations: EA = ethyl acetate; Hex = hexane; RBF = round bottom flask.

Substrates: Decene, methyl oleate, dihydrocarvone, methylcyclopentene, methylcyclohexene, ethyl vinyl ether, and beta pinene were used as obtained from commercial sources. 9-Acetoxy-1-decene,[1] 4-*t*-butyl-1-methylenecyclohexane,[2] 4-*t*- butyl-1-methoxymethylenecyclohexane (**3a**),[3] 3-phenyl-1-methoxy-1-butene (**4a**),[4] 1-methoxy-1-nonene (**1a**),[5] 9-acetoxy-1-methoxy-1-decene (**2a**),[6] and 2-(3-butenyl)pyridine were prepared through reported procedures.[7]

General Experimental Conditions: All reagents and solvents were used as supplied commercially, except CH_2Cl_2, which was distilled from CaH_2. Thin layer chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates containing a fluorescent indicator. Developed TLC plates were visualized with a hand-held UV lamp or by staining: 1% ceric sulfate / 10% ammonium molybdate in 10% H_2SO_4 (general stain, after charring); 1% *N,N'*-dimethyl-p-phenylenediamine in 1:20:100 acetic acid/water/methanol (specific for peroxides: hydroperoxides and some ozonides give a pinkish color upon dipping; nearly all peroxides will give a reddish-pink coloration upon mild heating).[8] Unless noted, NMR spectra were acquired in $CDCl_3$. IR spectra were recorded as neat films on a ZrSe crystal with selected absorbances reported in cm^{-1}.

Ozonolysis in the presence of pyridine: The alkene substrate (1-3 mmol) and dry pyridine (3-9 mmol) were dissolved in dry CH_2Cl_2 (15-20 ml) in a flame-dried flask under N_2. The solution was cooled to-78 °C, at which point a stream of O_3/O_2 (~ 1 mmol/min of O_3) was introduced through a disposable pipet for a period that varied with the amount of alkene (~ 1 min/mmol). Once complete, the reaction was sparged with O_2 and then N_2. The crude reaction mixture was diluted with CH_2Cl_2 (10 ml) and sat. aq. $NaHCO_3$ (15 ml). The aqueous layer was extracted (3 x 5 mL) with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and filtered through a cotton plug. The residue obtained upon concentration was purified via flash chromatography with ethyl acetate/hexanes to furnish the aldehyde or ketone.

Preparative scale: Application on a 10 mmol scale resulted in similar yields (e.g., ozonolysis of dihydrocarvone to 5-acetyl-2-methylcyclohexanone was achieved in 80% isolated yield).

Nonaqueous work-up: In lieu of an aqueous work-up, the sparged reaction solution resulting from ozonolysis could be partially concentrated and then directly loaded onto a silica column and eluted with ethyl acetate/hexane. Yields were comparable to the extractive workup. For example ozonolysis of 9-decenyl acetate followed by concentration and chromatography furnished 9-acetoxynonanal in 87% yield vs. the 80% yield (Table 1) obtained with an aqueous workup.

Substrates prepared via ozonolysis: The following were prepared according to the experimental procedure. All compounds afforded spectral data that was identical to literature values.

5-Acetyl-2-methylcyclohexanone [56893-77-7].[9] R_f= 0.48 (10% EA/hex); (RWC-1-54)

5-Oxohexanal [505-03-3].[10] R_f= 0.33 (30% EA/hex). (RWC-1-71)

6-Oxoheptanal [19480-04-7].[11] R_f= 0. 33 (30% EA/hex). (RWC-1-70)

Octanal (**1b**) [124-13-0].[12] R_f= 0.7 (10% EA/hex). (RWC-3-46)

9-Acetoxynonanal (**2b**) [29541-97-7].[9] R_f= 0.14 (10% EA/hex). (RWC-1-43)

Nonanal [124-19-6].[13] R_f= 0.6 (10% EA/hex). (RWC-1-43)

Methyl-9-oxononanoate [1931-63-1]. R_f= 0.7 (10% EA/hex) (RWC-1-52)

4-(1,1-Dimethylethyl cyclohexanone (**3b**) [98-53-3].[14] R_f= 0.47 (10% EA/hex). (RWC-2-31)

2-Phenylpropanal (**4b**) [1335-10-0].[15] R_f= 0.6 (10% EA/hex). (RWC-1-90)

Nopinone [38651-65-9].[16] R_f= 0.33 (10% EA/hex). (RWC- 3-10)

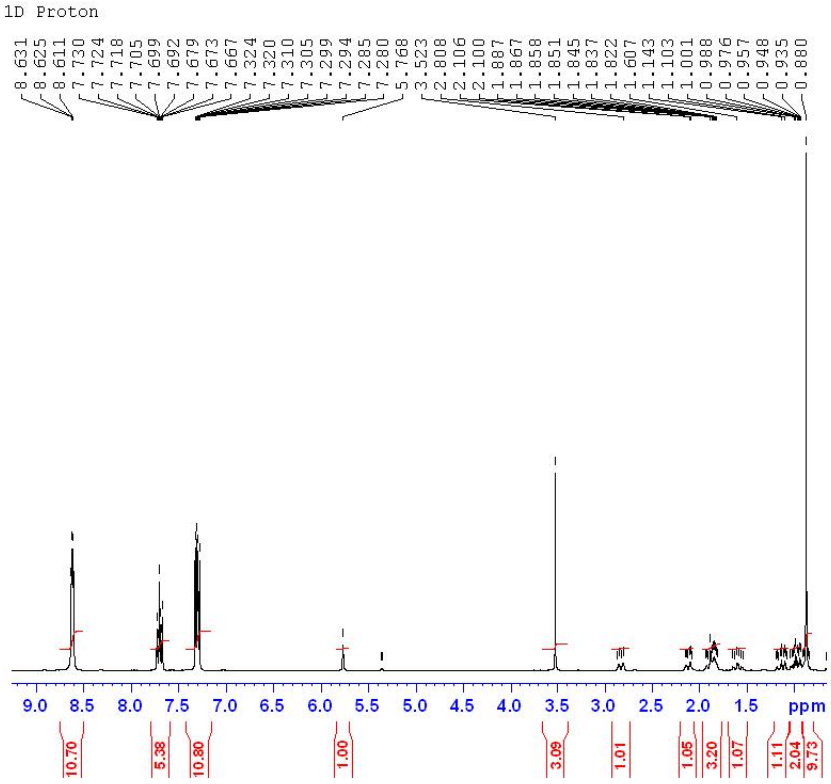
6,6-Dimethyl*spiro*[bicyclo[3.1.1]heptane-2,3'-[1,2,4]trioxolane] [pinene ozonide, 201472-62-0].[17] R_f= 0.8 (10% EA/hex) (RWC-1-77)

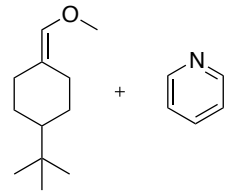
One-pot ozonolysis/organometallic addition: A -78 °C solution of alkene and pyridine in CH_2Cl_2 was subjected to ozonolysis as described above. Once the cleavage of alkene was complete (based upon reaction time and/or TLC analysis), the reaction was sparged with oxygen and the flask was capped with a septa. The internal atmosphere was removed under vacuum and replaced with dry nitrogen. The flask was recooled to 0 °C, whereupon a stoichiometric amount of phenyl or methyl magnesium bromide (nominally 1M solutions in THF) was added. The reaction was monitored by TLC and, when complete, was quenched by dropwise addition of water followed by a few drops of 6M HCl. The mixture was diluted with a volume of saturated aq. NH_4Cl and the separated aqueous layer was extracted with CH_2Cl_2 (3 x). The remainder of the work-up was as for the ozonolysis procedure described above. The combined organic layers were dried and concentrated as described previously.

Decan-2-ol [1120-0605].[18] R_f= 0.20 (10% EA/hex). (RWC-2-82)

1-Phenyldecan-1-ol [256378-51-5].[19] R_f= 026 (10% EA/hex). (RWC-2-95)

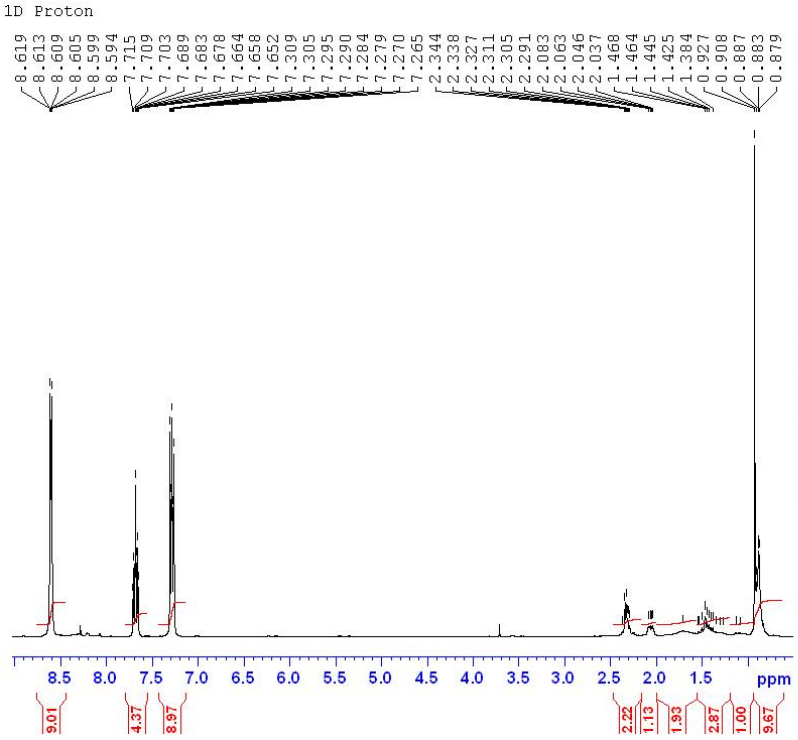
NMR analysis of reaction in CD_2Cl_2





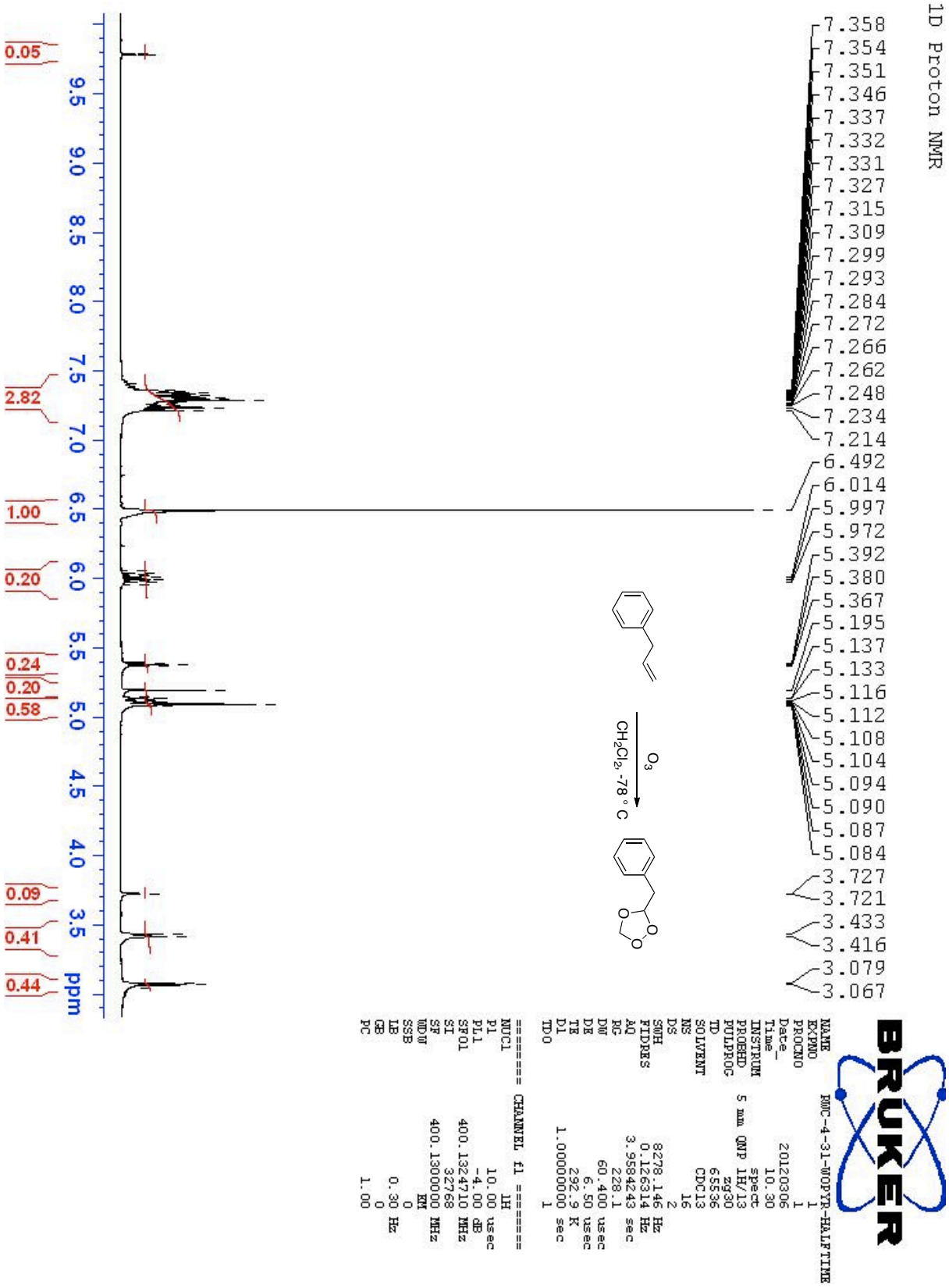
Ran in CD_2Cl_2

Top: Enol ether (3a)plus pyridine in CD_2Cl_2 prior to ozonolysis

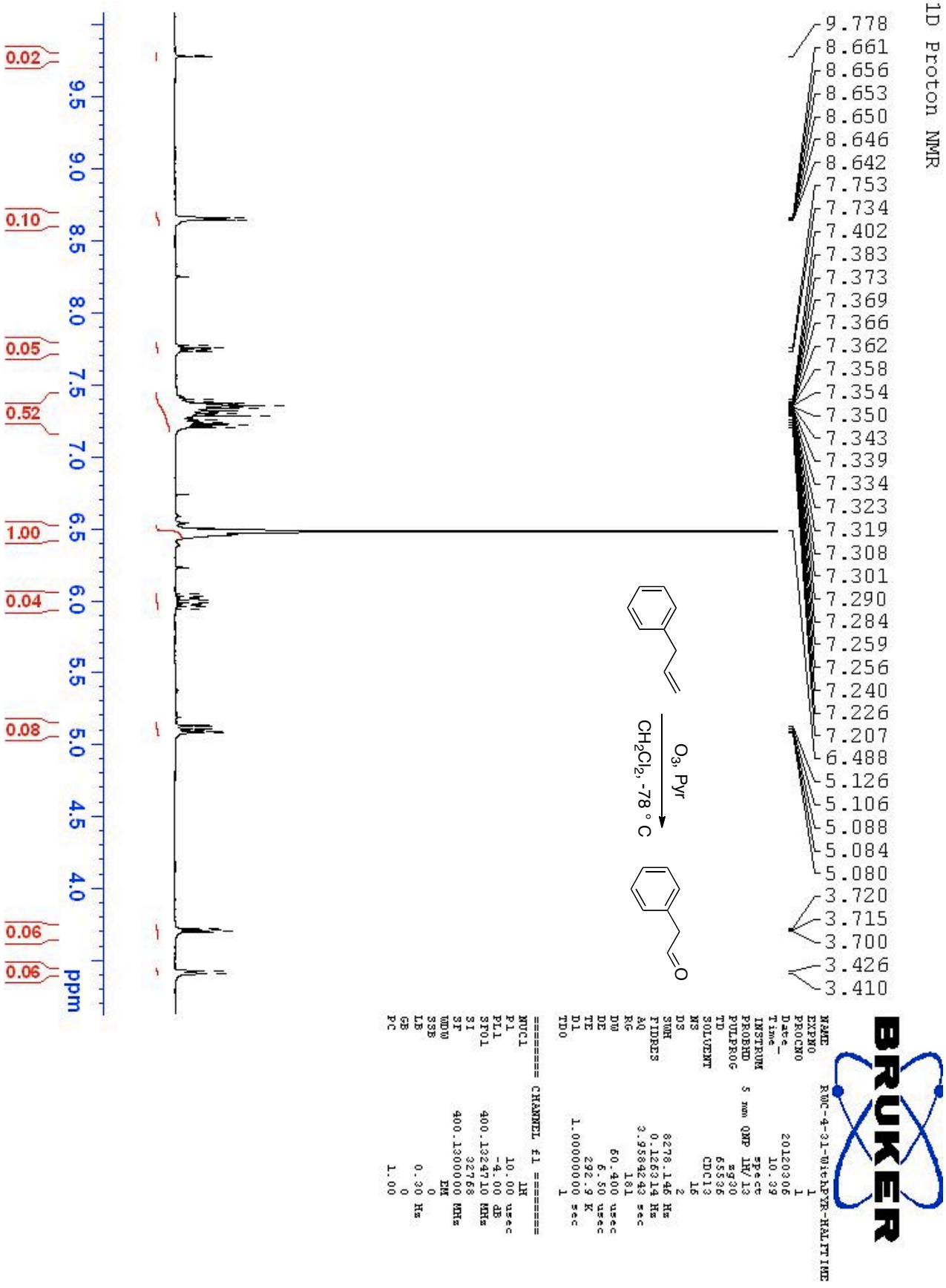


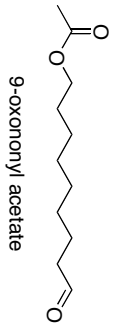
Bottom: Aliquot from ozonolysis of enol ether and pyridine in CD_2Cl_2 immediately following ozonolysis (no work up or concentration).

Delivery of a fixed amount of ozone to an alkene in the absence of pyridine.

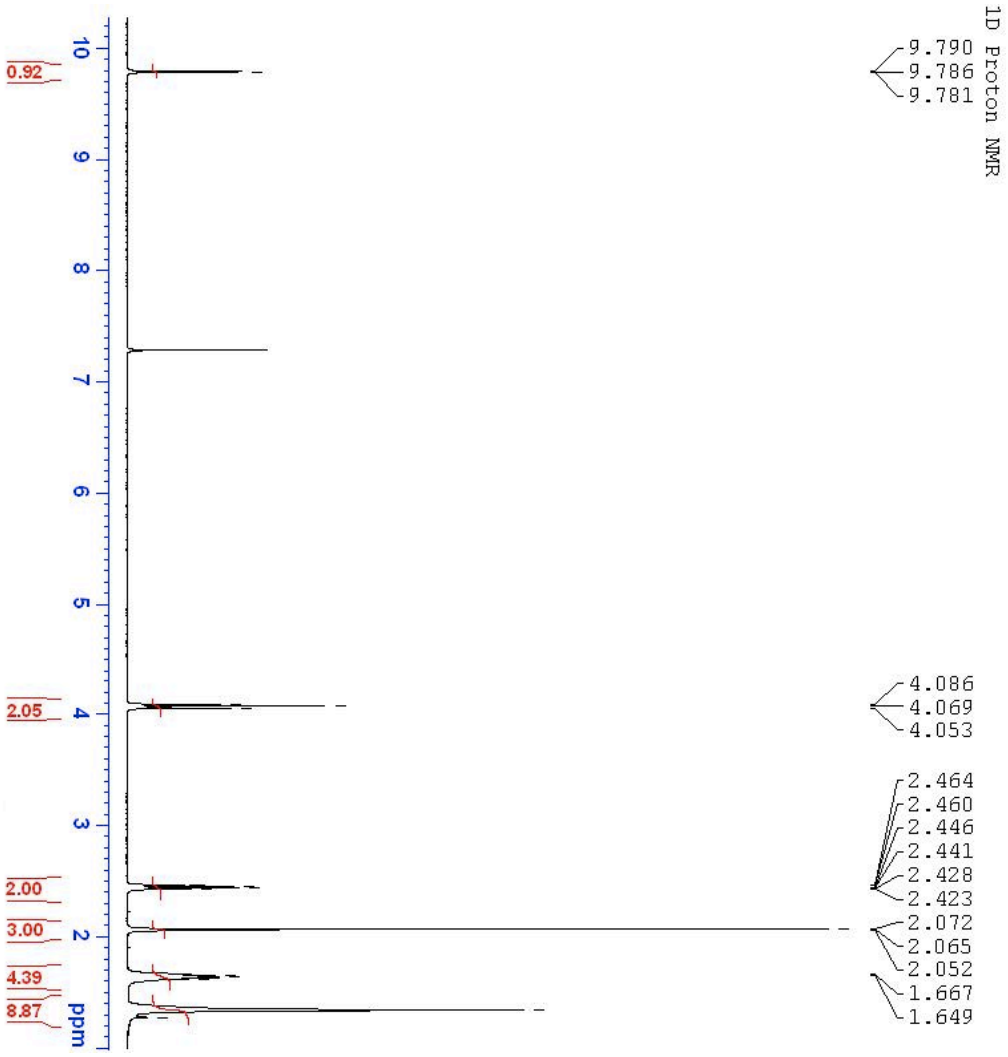


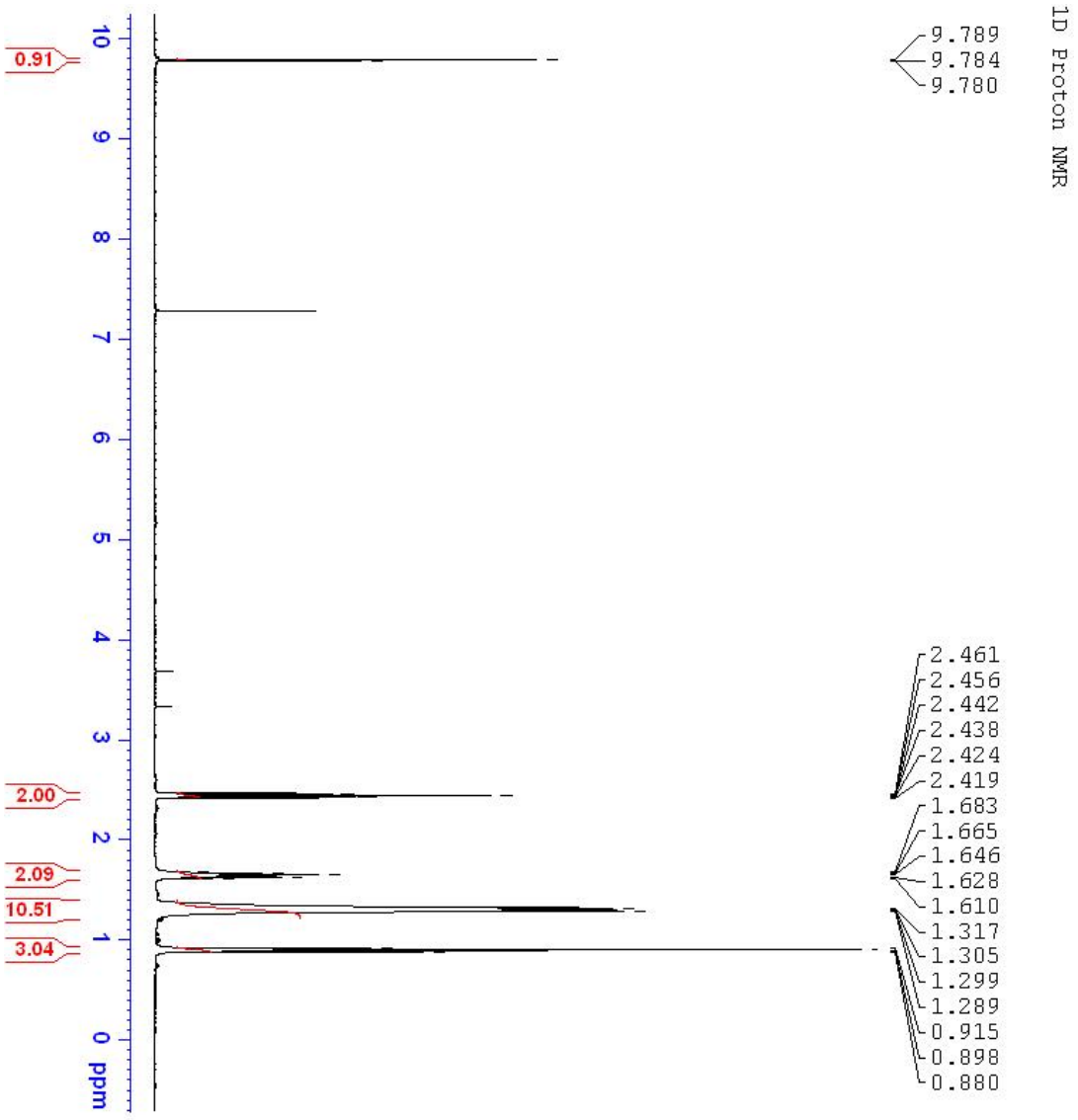
Delivery of a fixed amount of ozone to an alkene in the presence of pyridine.

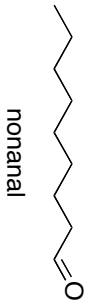



9-oxononyl acetate

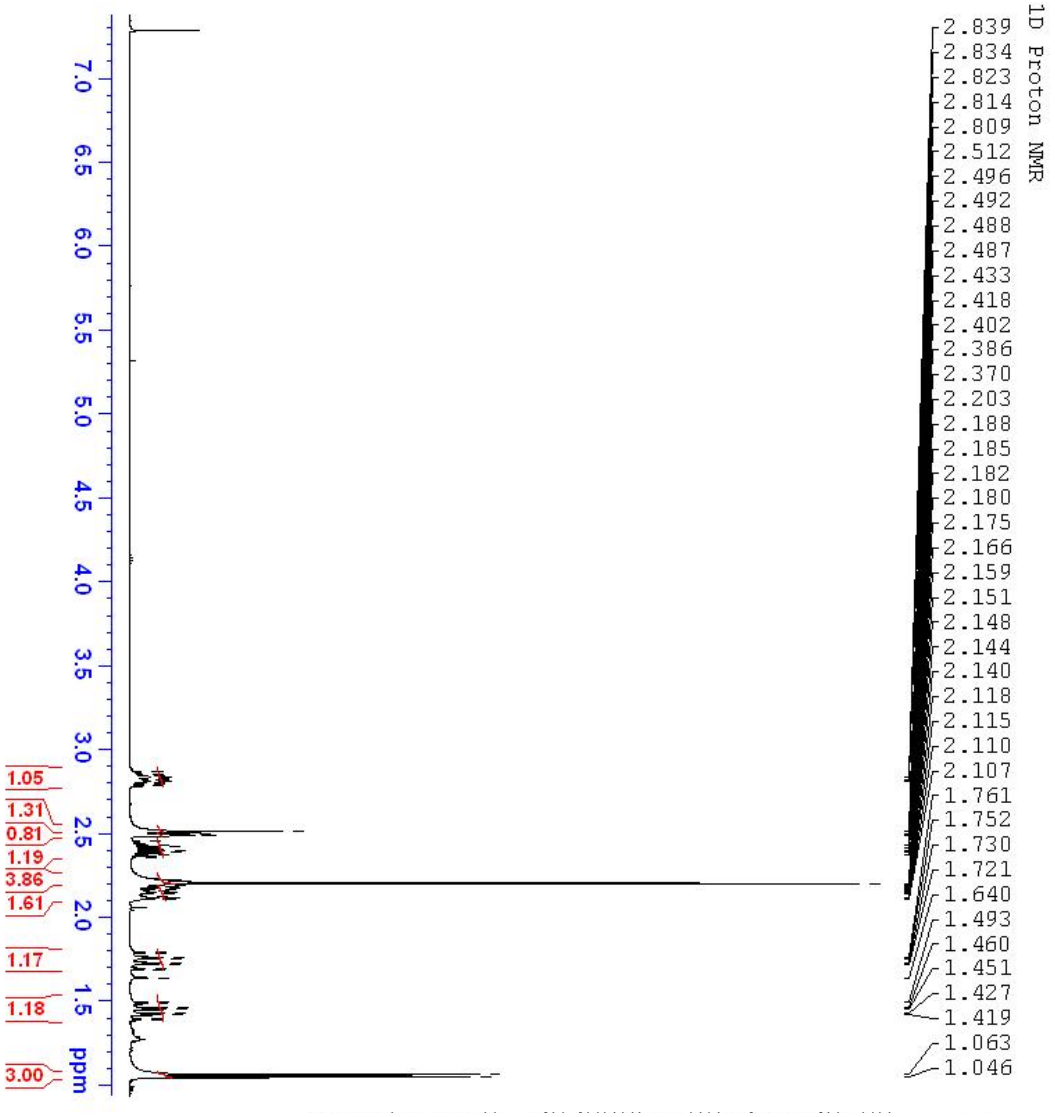
2b


1D Proton NMR
9.790
9.786
9.781
4.086
4.069
4.053
2.464
2.460
2.446
2.441
2.428
2.423
2.072
2.065
2.052
1.667
1.649
0.92
2.05
2.00
3.00
4.39
8.87
ppm

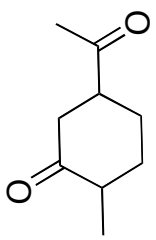

1D Proton NMR
9.789
9.784
9.780
2.461
2.456
2.442
2.438
2.424
2.419
1.683
1.665
1.646
1.628
1.610
1.317
1.305
1.299
1.289
0.915
0.898
0.880
0.91
2.00
2.09
10.51
3.04
ppm

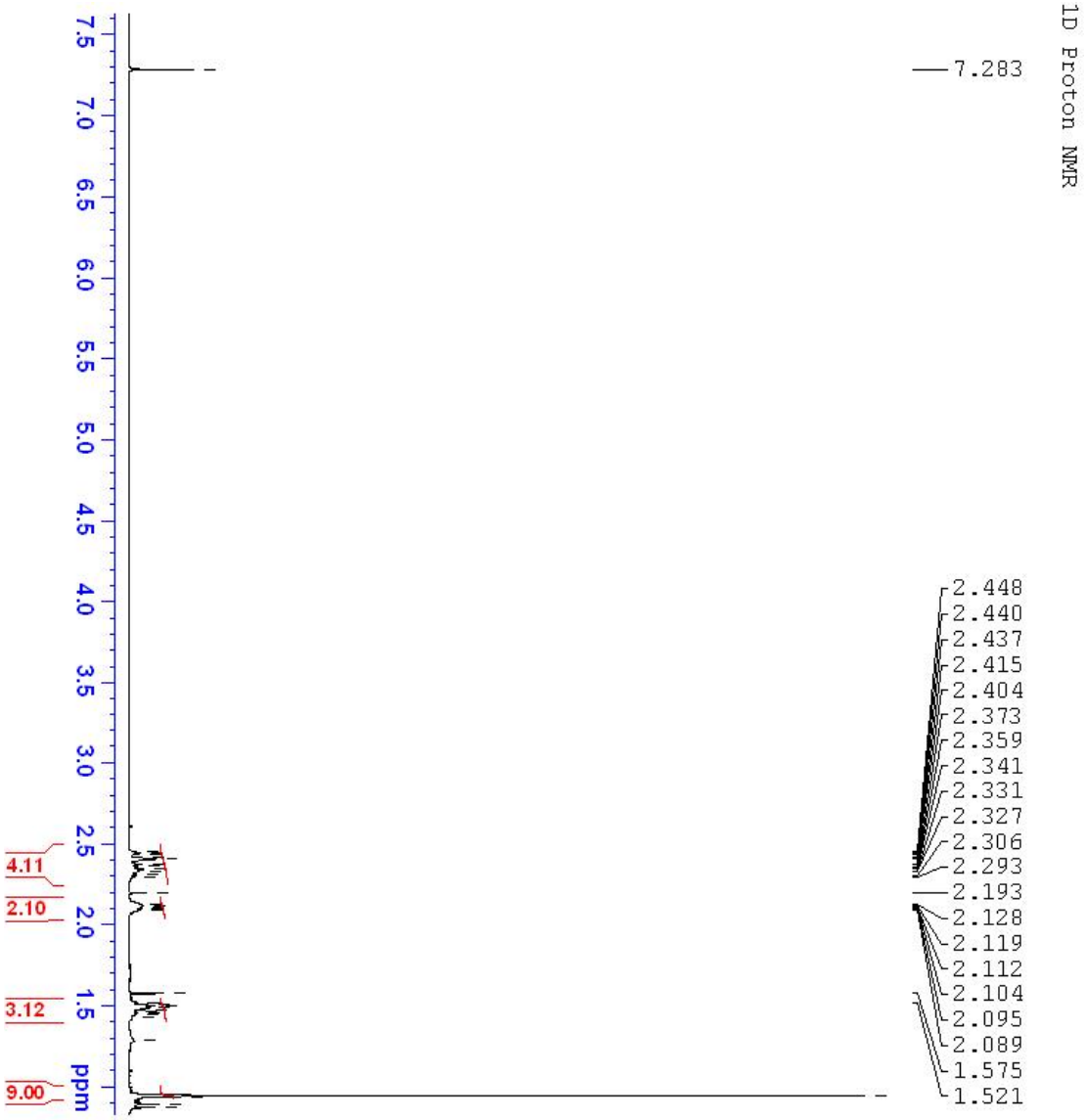

O

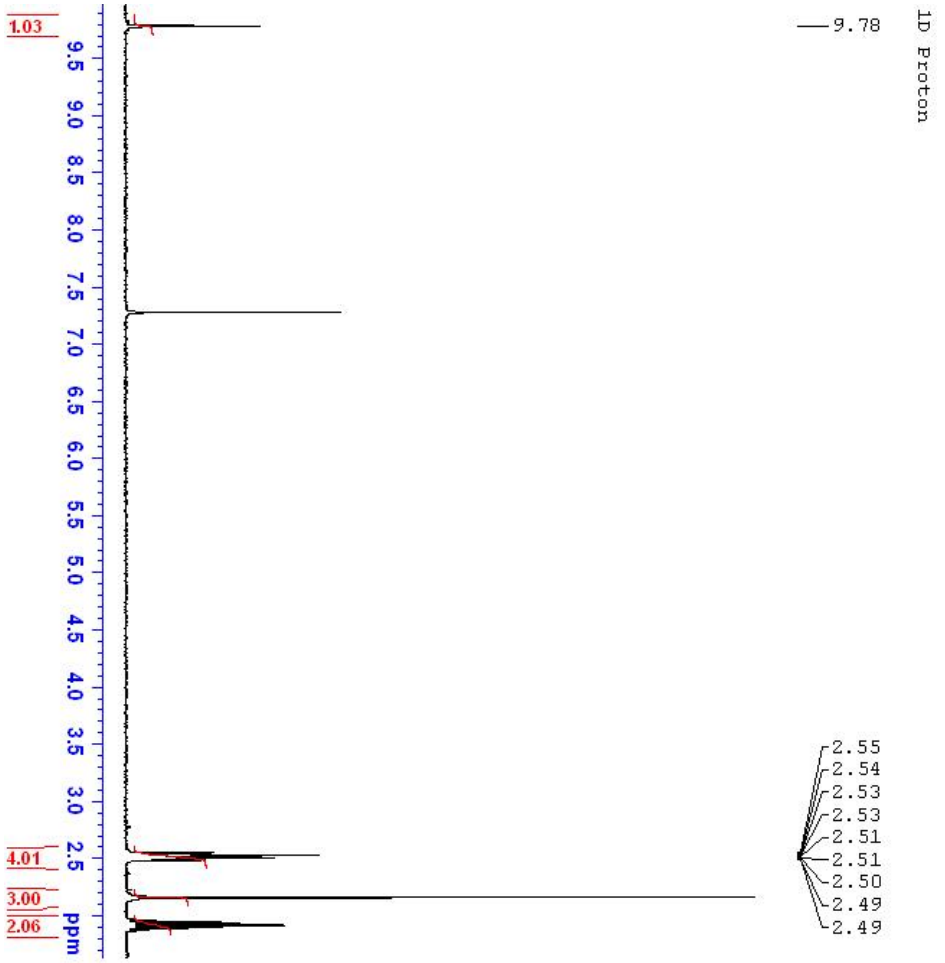
nonanal

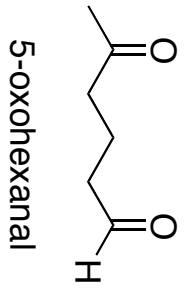


5-acetyl-2-methylcyclohexanone

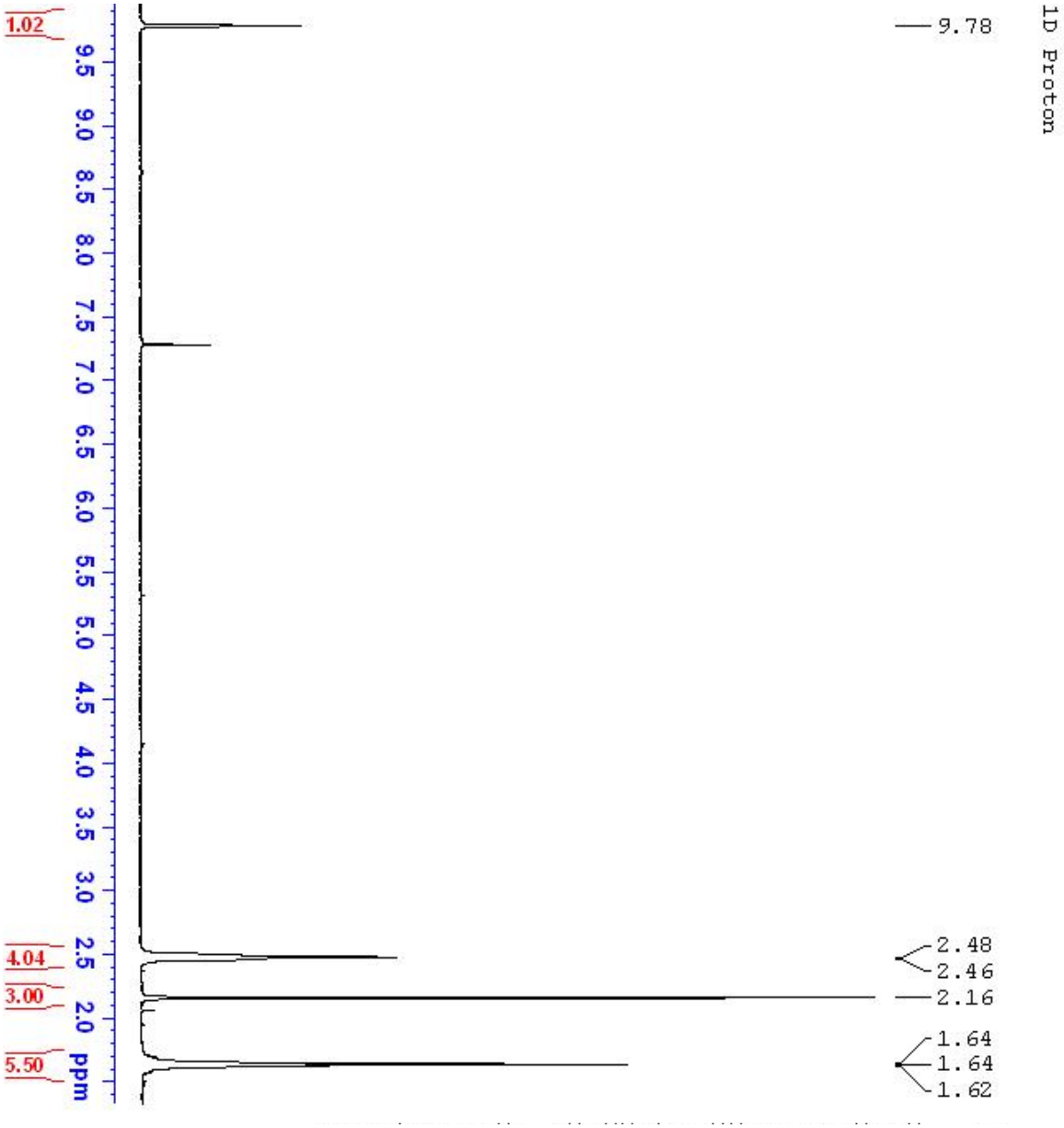


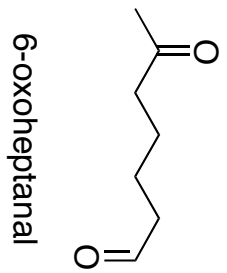

1D Proton NMR
7.283
2.448
2.440
2.437
2.415
2.404
2.373
2.359
2.341
2.331
2.327
2.306
2.293
2.193
2.128
2.119
2.112
2.104
2.095
2.089
1.575
1.521
4.11
2.10
3.12
9.00
ppm
4-(tert-butyl)cyclohexanone
O
3b

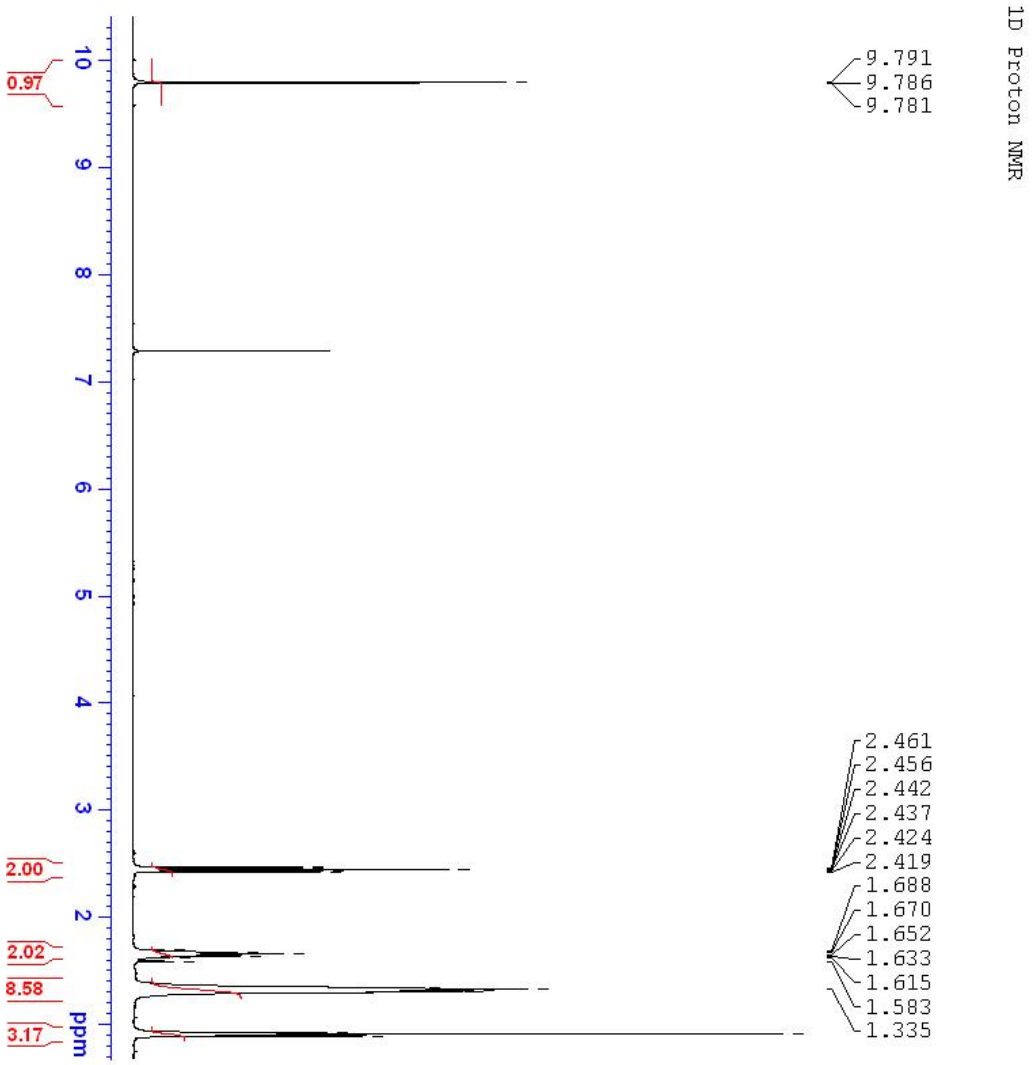


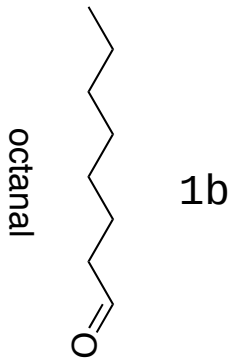


5-oxohexanal

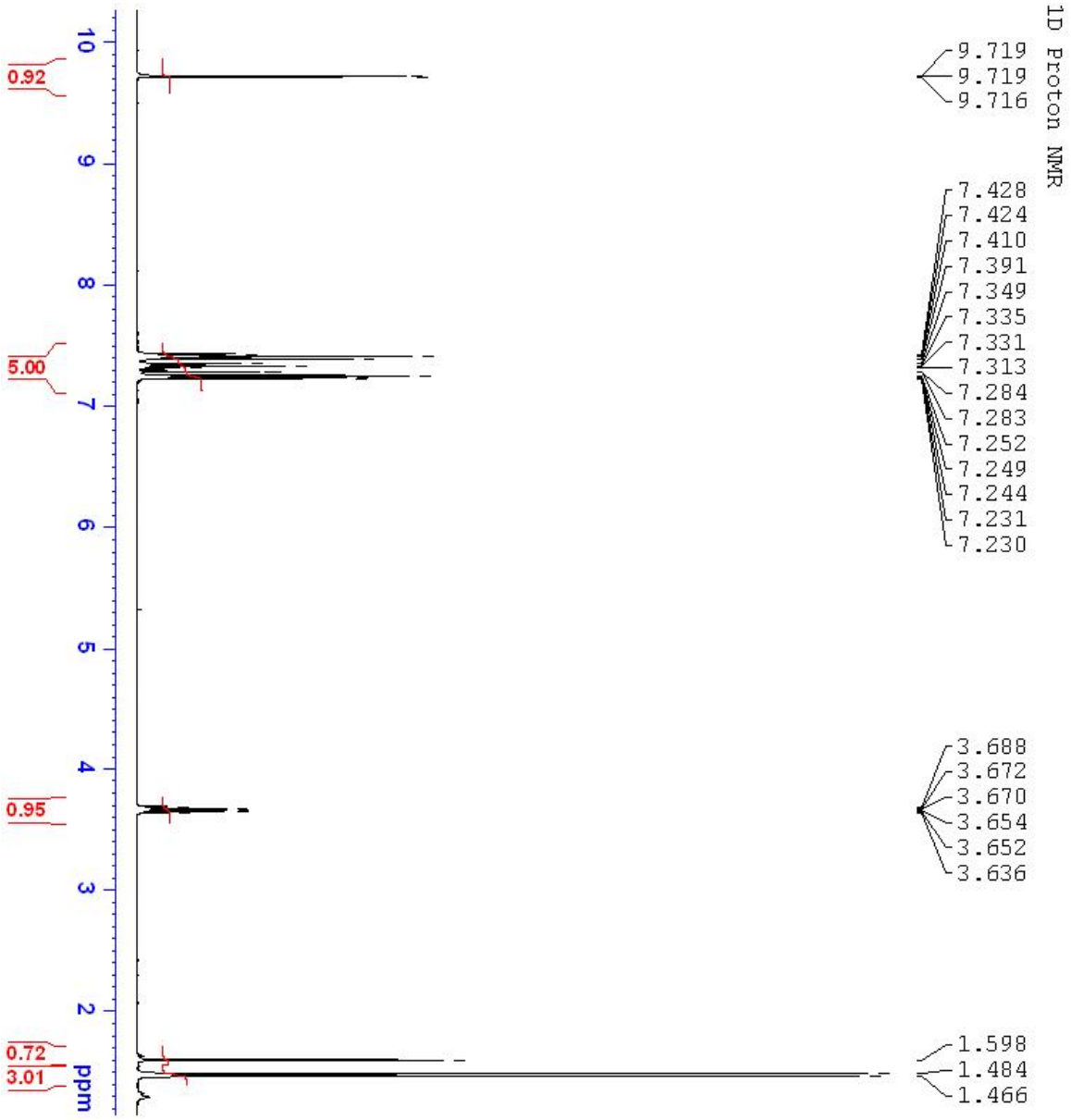

1D Proton
9.78
2.48
2.46
2.16
1.64
1.64
1.62
1.02
4.04
3.00
5.50
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


6-oxoheptanal
O
O

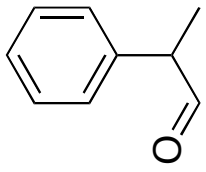

1D Proton NMR
9.791
9.786
9.781
2.461
2.456
2.442
2.437
2.424
2.419
1.688
1.670
1.652
1.633
1.615
1.583
1.335
0.97
2.00
2.02
8.58
3.17
ppm


O

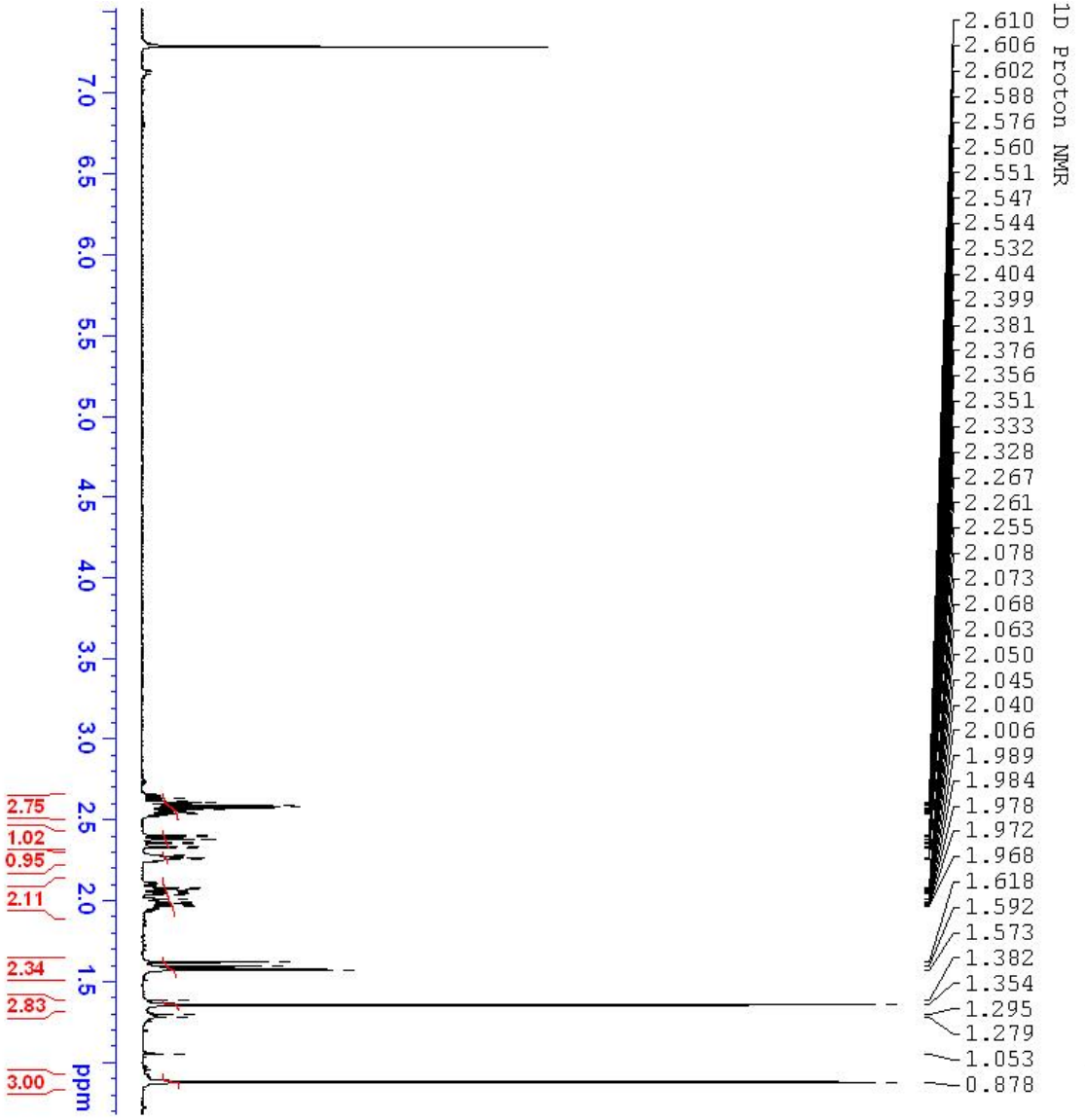
octanal 1b



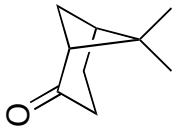
2-phenylpropanal

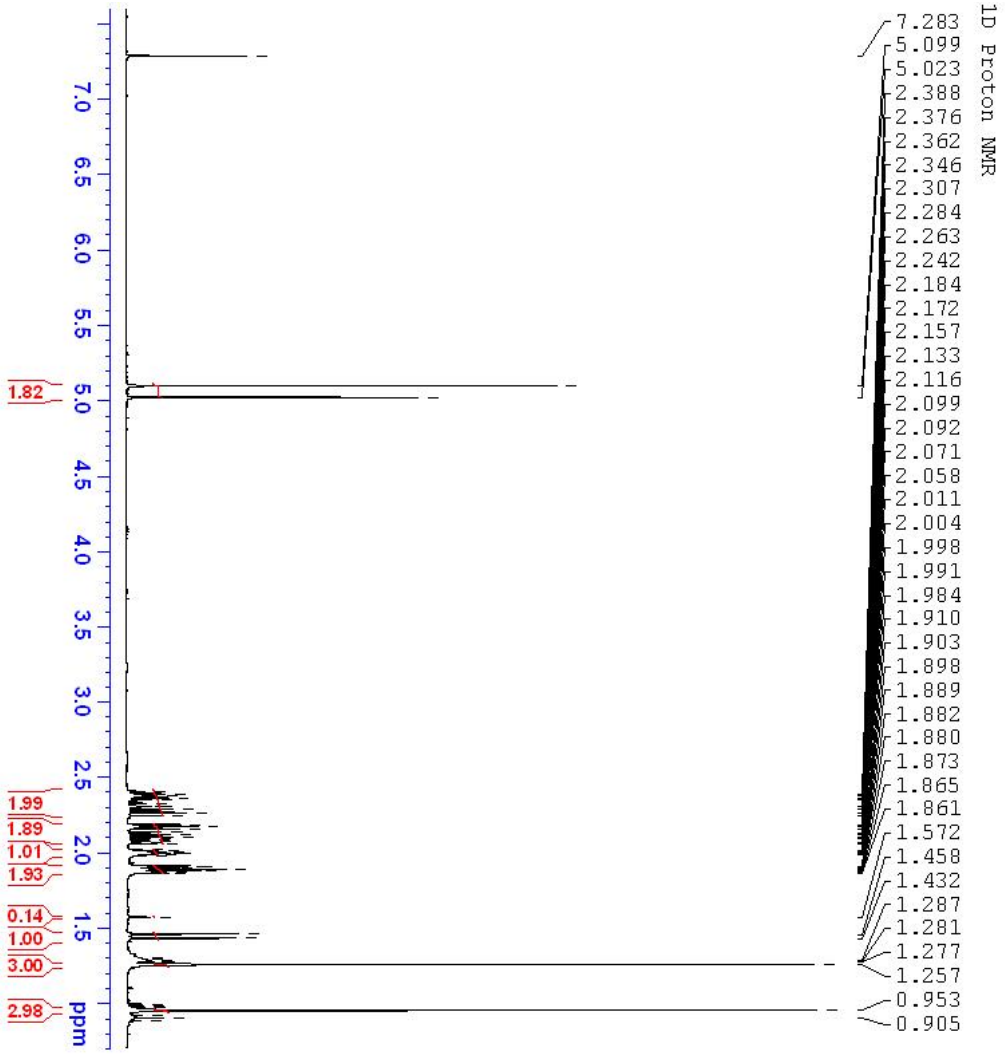


4b

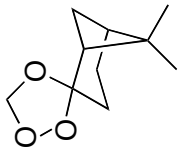


(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-one

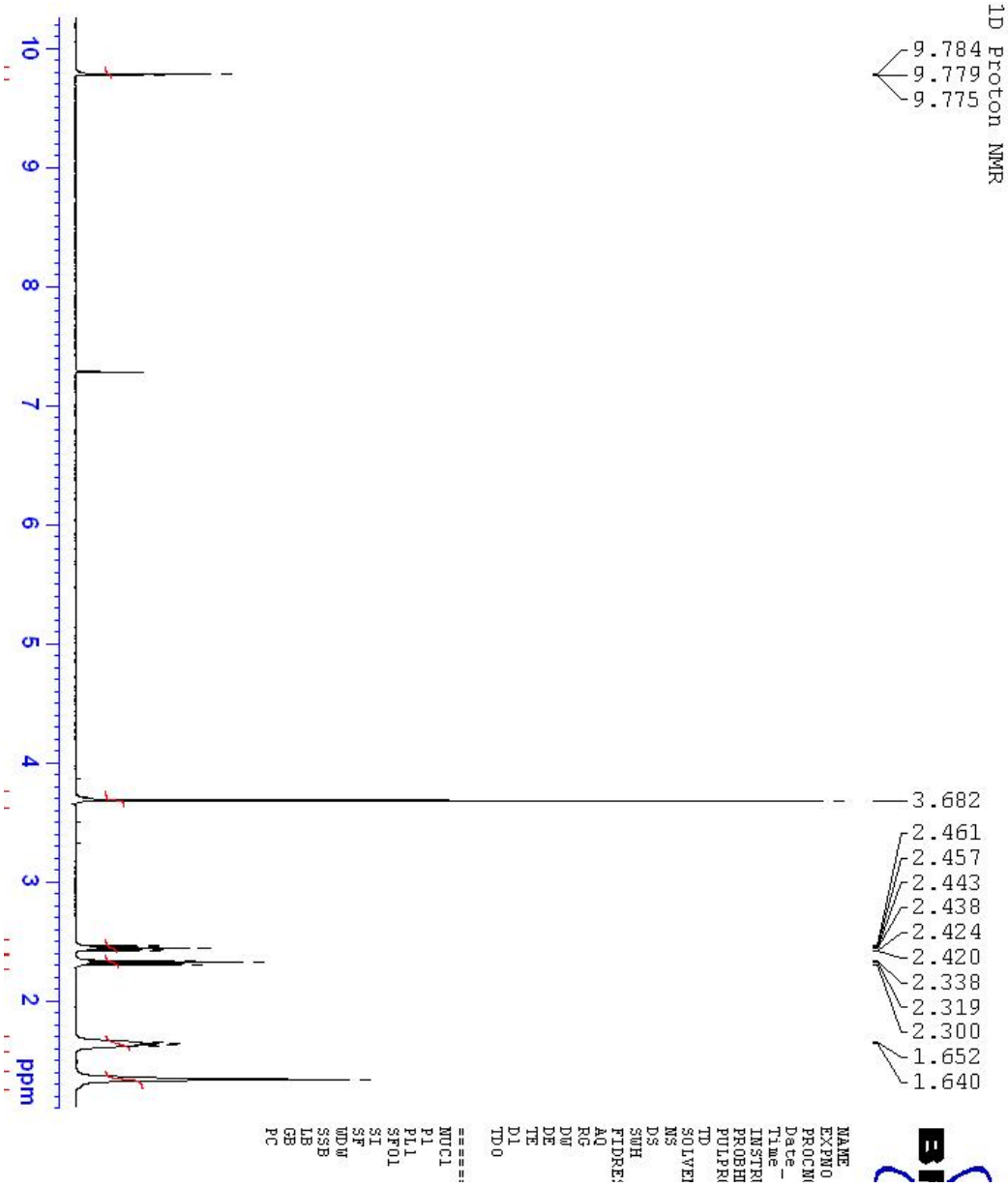


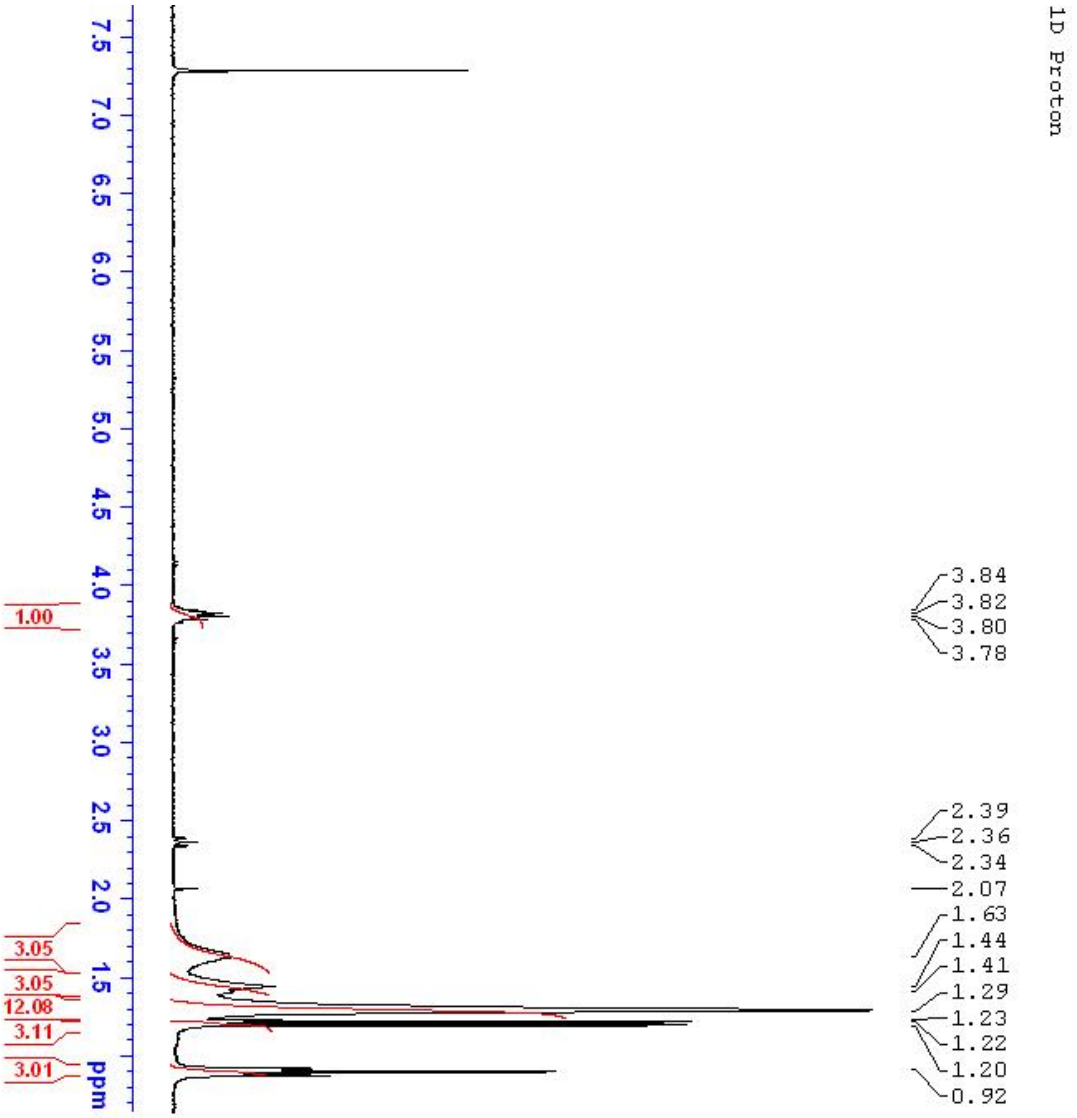


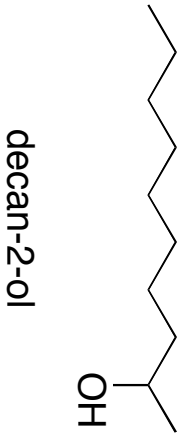
(1*R*,2*R*,5*S*)-6,6-dimethylspiro[bicyclo[3.1.1]heptane-2,3'-[1,2,4]trioxolane]



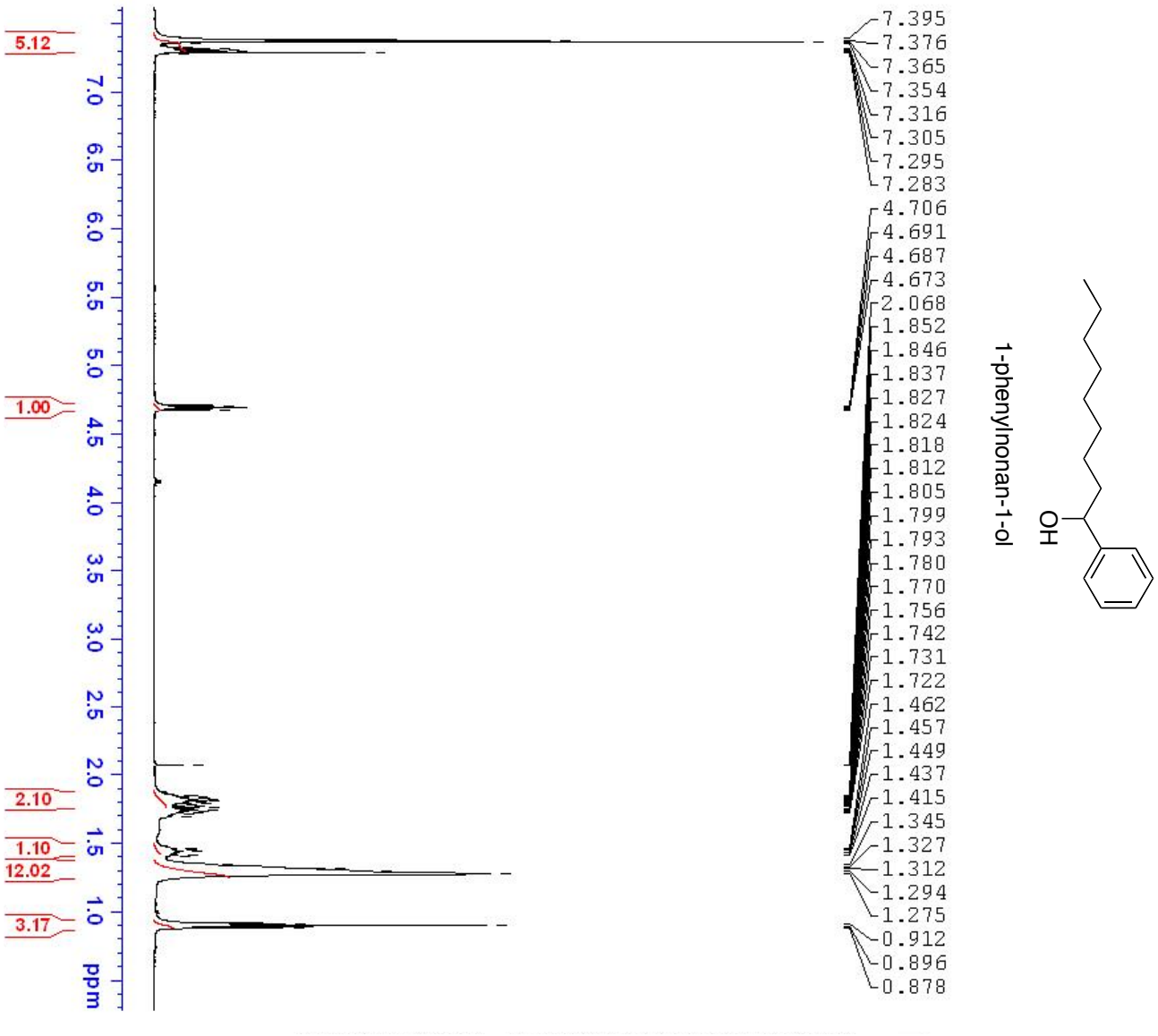
Methyl 9-oxononanoate

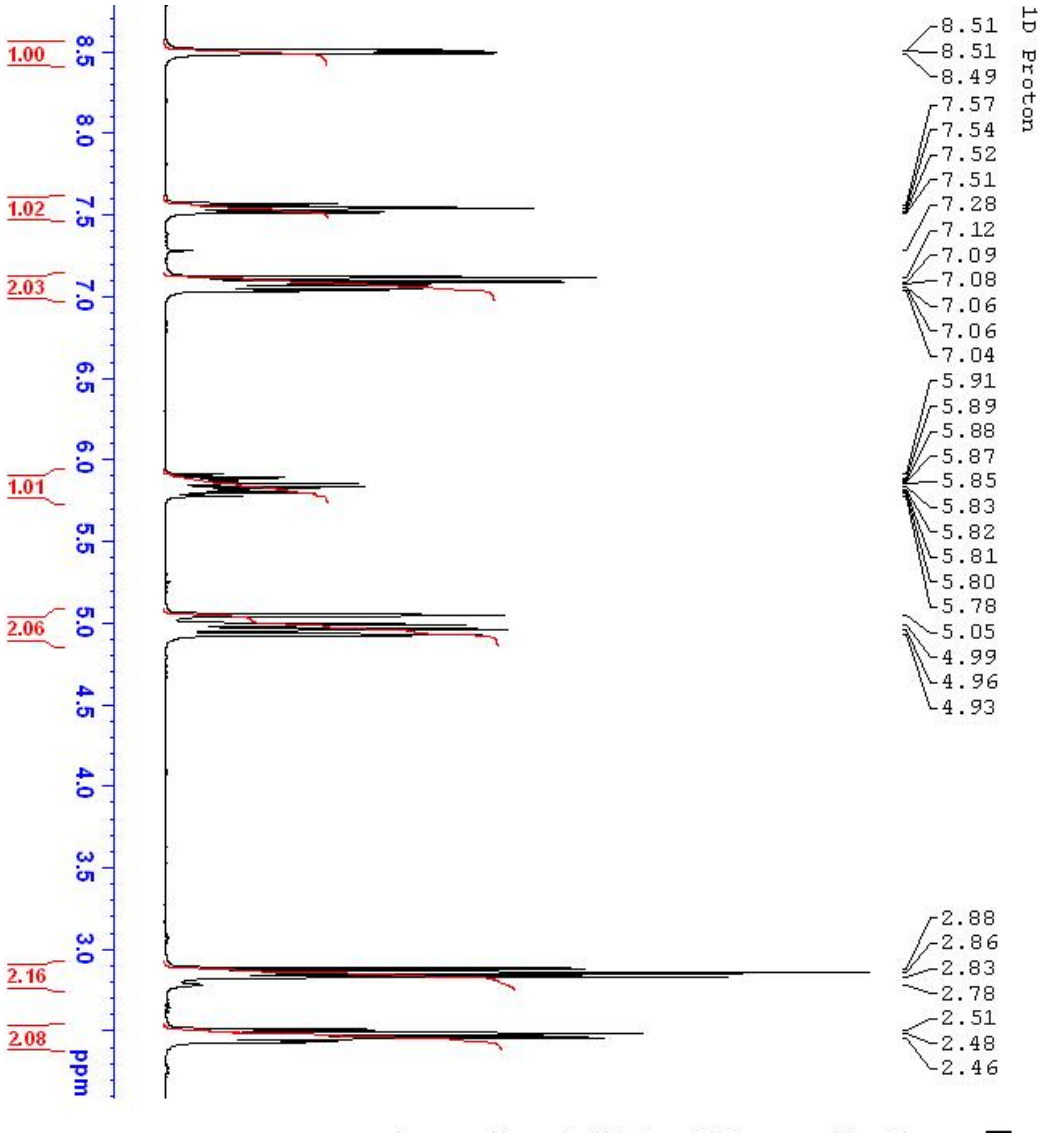



1D Proton
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
3.05
3.05
12.08
3.11
3.01
3.84
3.82
3.80
3.78
2.39
2.36
2.34
2.07
1.63
1.44
1.41
1.29
1.23
1.22
1.20
0.92

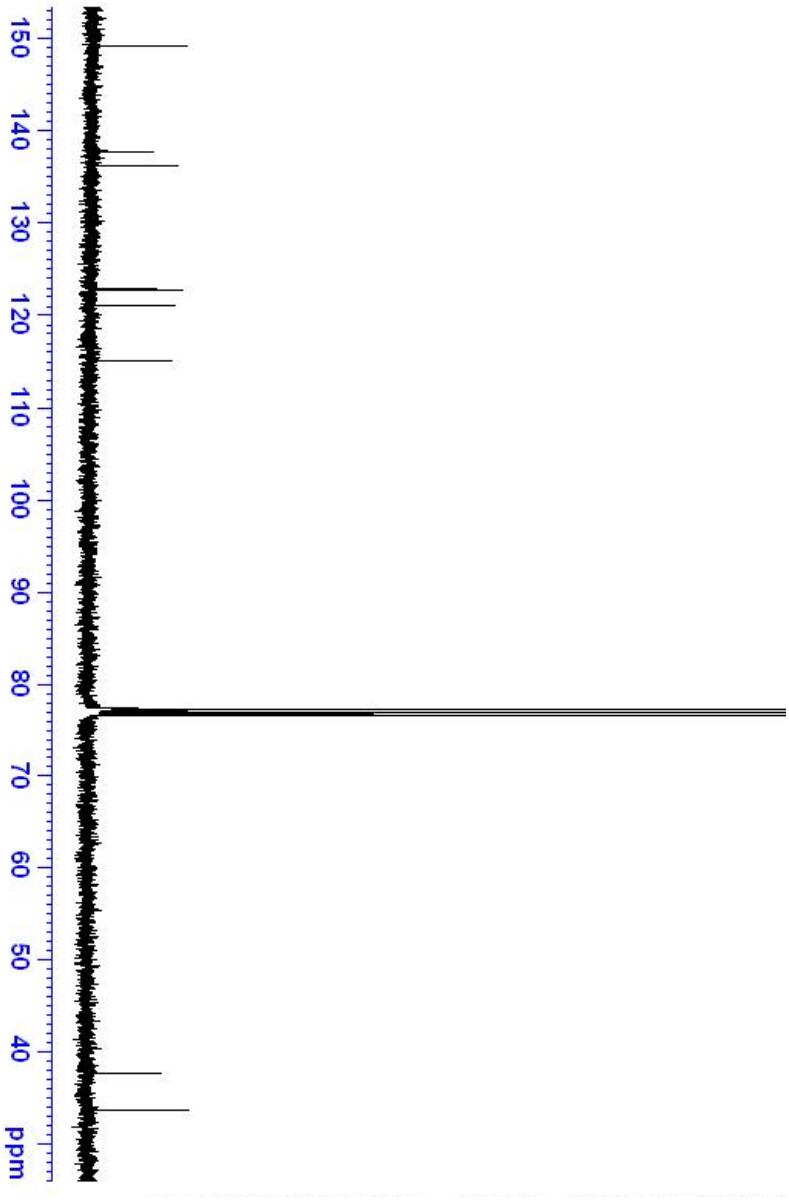

OH

decan-2-ol

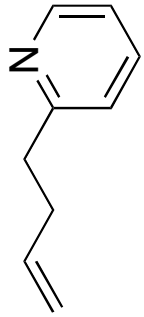

5.12
1.00
2.10
1.10
12.02
3.17
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
7.395
7.376
7.365
7.354
7.316
7.305
7.295
7.283
4.706
4.691
4.687
4.673
2.068
1.852
1.846
1.837
1.827
1.824
1.818
1.812
1.805
1.799
1.793
1.780
1.770
1.756
1.742
1.731
1.722
1.462
1.457
1.449
1.437
1.415
1.345
1.327
1.312
1.294
1.275
0.912
0.896
0.878
1-phenylnonan-1-ol
OH

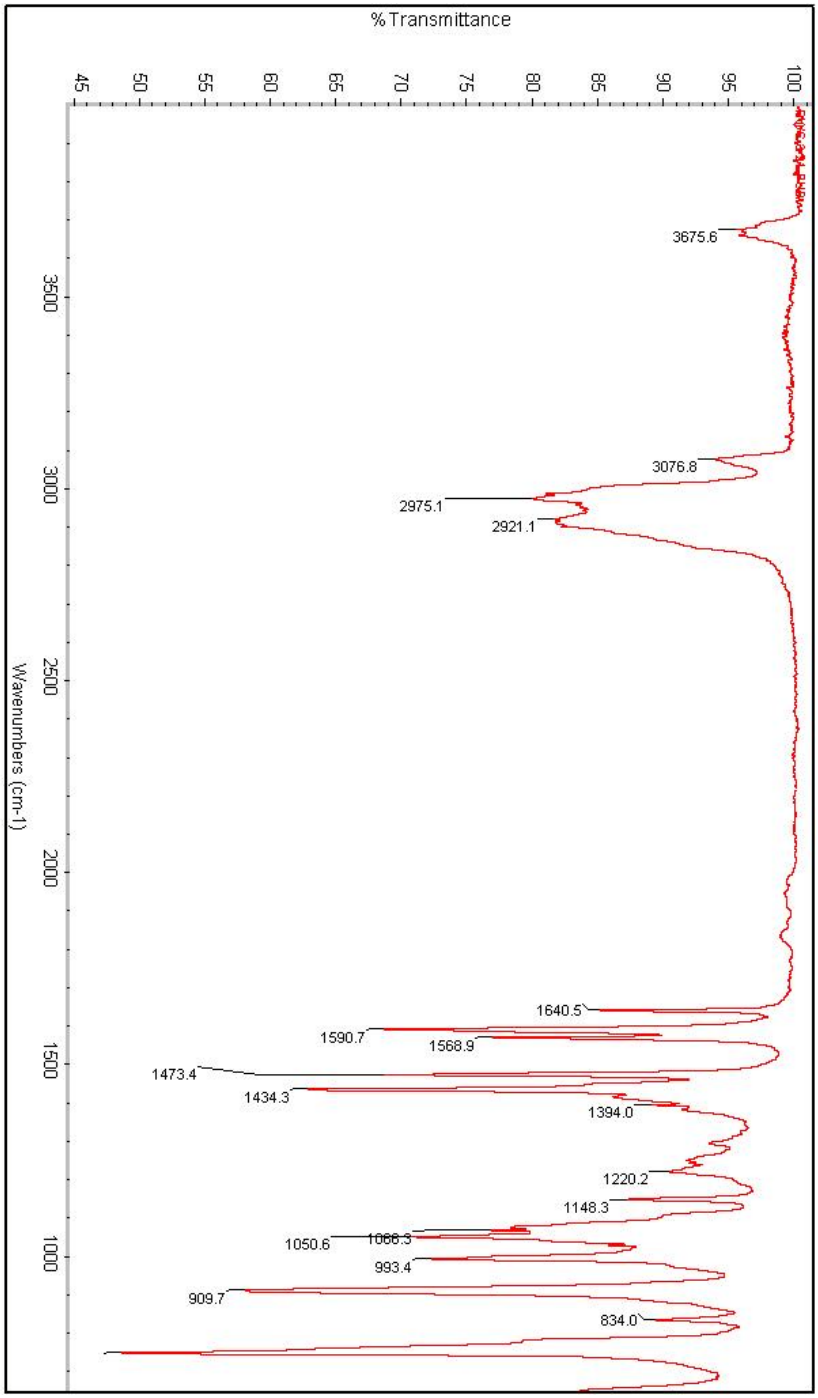


2-(but-3-en-1-yl)pyridine

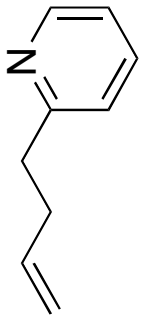


2-(but-3-en-1-yl)pyridine





2-(but-3-en-1-yl)pyridine



References

[1] Murphy, K. E.; Hoveyda, A. H. **2003**, *J. Am. Chem. Soc*. *125*, 4690.
[2] Cren, S., Scha, P., Renaud, P. *J. Org. Chem.* **2009***, 74*, 2942
[3] Rahim, A; Haruhiko, T.; Watanabe, M.; Fujiwara, T.; Takeda, T. *Tetrahedron Lett*. **1998**, *39*, 2153.
[4] Tokunaga, M.; Shirogane, Y.; Aoyama, H.; Obora, Y.; Tsuji, Y. *J. Organomet. Chem.* **2005**, *690*, 5378.
[5] Bae, H. J.; Jeong, W.; Lee, J.H.; Rhee, Y. H.; *Chem. Eur. J.* **2011**, *17*, 1433.
[6] Yoshimitsu, T.; Nakatani, R.; Kobayashi, A.; Tanaka, T. *Org. Lett.* **2011**, *13*, 908.
[7] Israeli, M.; Laing, D. K.; Pettit, L.D. *J. Chem. Soc., Dalton Trans.,* **1974**, 2194.
[8] Smith, L. L.; Hill, F. L. *J. Chrom.* **1972**, *66*, 101.
[9] Schiaffo, C. E; Dussault, P. H. *J. Org. Chem*. **2008**, *73*, 4688.
[10] Jones, R. C. F.; Turner, I.; Howard, K. J *Tetrahedron Lett.*, **1993**, *34*, 6329
[11] Boltukhina, E. V. *Tetrahedron Lett.,* **2011**, *67*, 5382.
[12] Hoover, J.M.; Stahl, S.S. *J. Am. Chem. Soc.,* **2011**, *133*, 16901
[13] Wertz, S. *Adv. Synth. Cat.* **2011**, *353*, 69.
[14] Kamata, K., Yonehara, K., Nakagawa, Y., Uehara, K., Mizuno, N. *Nat. Chem.*, **2010**, 2, 478; Landers, B., Bernini, C., Wang, C., Navarro, O. *J. Org. Chem*. **2011**, *76*, 1390.
[15] Wang, Z., Li, M., Jia, J., Wang, F., Xue, S. *Tetrahedron Lett.*, **2011**, *52*, 5968.
[16] Schaffer, G.W., Boerr, A.B., Purzycki, K.L. *J. Org. Chem.*, **1972**, *37*, 25.
[17] Greisbaum, K.; Miclaus, V.; *Environ. Sci. Technol*. **1998**, *32*, 647.
[18]Nakamura, K.; Matsuda, T. *J. Org. Chem.,* **1998**, *63*, 8957.
[19] Kose, O.; Saito, S. *Org. Biomol. Chem.* **2010**, *8*, 896.