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SUPPORTING INFORMATION

Title: Stereoselective Disposition of the Geminal Dimethyl Group in the Cyclization of Geranyl Acetate under Zeolite Confinement Conditions

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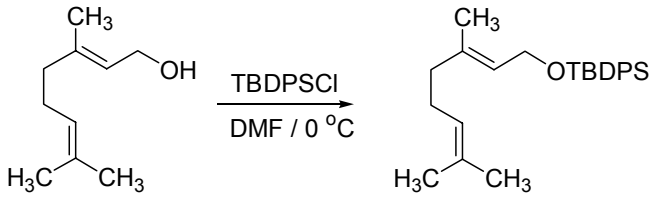
Ref. No.: O200600367

Experimental Section

Nuclear magnetic resonance spectra were obtained on a 500 MHz instrument. Isomeric purities were determined by ^{1}H NMR and by GC analysis on a 60 meters HP-5 capillary column. All spectra reported herein were taken in $CDCl_3$.

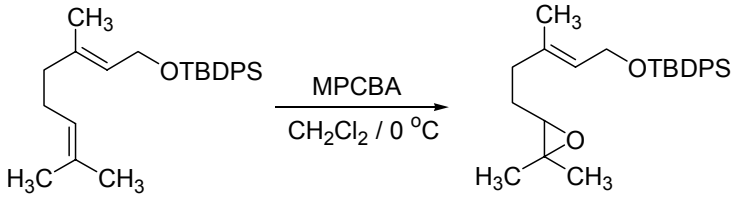
Synthesis of geranyl acetate-d_3 (3)

(*E*)-1-*t*-Butyldiphenylsilyloxy-3,7-dimethyl-2,6-octadiene[1]



To a solution of geraniol (5.09 g, 33 mmol) and imidazole (5 g, 72.6 mmol) in dry DMF (30 mL) were added at 0 °C 10 gr (36.4 mmoles) of *t*-butyldiphenylsilyl chloride (TBDPSCl). The mixture was stirred for 1 h at room temperature, then quenched with water and extracted with diethyl ether (3 x 50 mL). The extract was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford quantitatively the silyl-protected geraniol as a colorless oil. ^{1}H NMR: 7.70 (d, J = 6.5 Hz, 4H), 7.36-7.43 (m, 6H), 5.38 (t, J = 6.5 Hz, 1H), 5.10 (t, J = 6.5 Hz, 1H), 4.23 (d, J = 6.5 Hz, 2H), 2.06 (m, 2H), 1.98 (t, J = 7.0 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.44 (s, 3H), 1.05 (s, 9H).

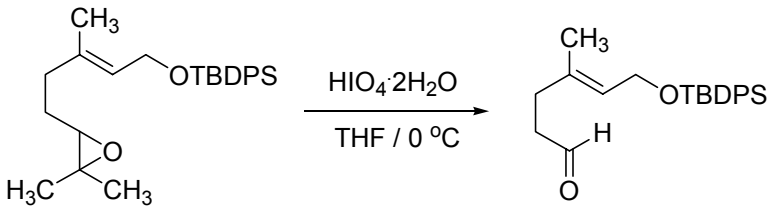
(*E*)-1-*t*-Butyldiphenylsilyloxy-3,7-dimethyl-6,7-epoxy-2-octene[1]



To a solution of (*E*)-1-*t*-butyldiphenylsilyloxy-3,7-dimethyl-2,6-octadiene (12.90 g, 32.9 mmol) in $CHCl_3$ (120 mL) were added at 0 °C 8.9 g (36.2 mmol) of MCPBA (70%) in one portion. The mixture was stirred at 0 °C for 1 h, after which time chloroform was added and the organic layer was washed with water, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed (hexane/ethyl acetate 100:1) to give 9.4 g of the C_6-C_7 epoxide (1-*t*-butyldiphenylsilyloxy-3,7-dimethyl-6,7-epoxy-2-octene) as a colorless oil (70% yield). The rest of the compounds isolated in <10% relative yield were starting material, the regioisomeric C_2-C_3 monoepoxide and the diepoxide as a mixture of distereomers. ^{1}H NMR of (*E*)-1-*t*-butyldiphenylsilyloxy-3,7-dimethyl-6,7-epoxy-2-octene: 7.69 (d, J = 6.5 Hz, 4H), 7.37-

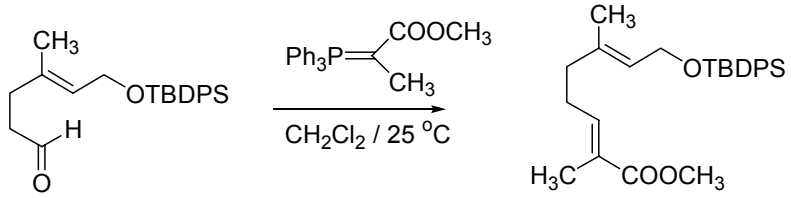
7.44 (m, 6H), 5.42 (t, J = 6.0 Hz, 1H), 4.23 (d, J = 6.0 Hz, 2H), 2.71 (t, J = 6.0 Hz, 1H), 2.06-2.18 (m, 2H), 1.56-1.68 (m, 2H), 1.47 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.05 (s, 9H). ^{13}C NMR: 136.1, 135.6, 134.0, 129.5, 127.6, 124.2, 64.1, 61.1, 58.4, 36.1, 27.2, 26.9, 24.9, 19.2, 18.8, 16.3.

(*E*)-6-*tert*-Butyldiphenylsilyloxy-4-methyl-4-hexanal[1]



A solution of (*E*)-1-*t*-butyldiphenylsilyloxy-3,7-dimethyl-6,7-epoxy-2-octene (9.4 g, 23 mmol) in dry diethyl ether (30 mL) was added to a solution of $HIO_4 \cdot 2H_2O$ (6.3 g, 27.7 mmol) in dry THF (180 mL) at 0 °C under an inert atmosphere. The mixture was stirred for 1 h at 0 °C and then filtered. The filtrate was diluted with diethyl ether, washed with water, saturated aq. $NaHCO_3$, brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford 8.2 g of crude (*E*)-6-*t*-butyldiphenylsilyloxy-4-methyl-4-hexanal, as a colourless oil, which was used in the next step without chromatographic purification. ^{1}H NMR: 9.75 (t, J = 1.2 Hz, 1H), 7.67 (d, J = 6.5 Hz, 4H), 7.38-7.44 (m, 6H), 5.38 (t, J = 6.0 Hz, 1H), 4.22 (d, J = 6.0 Hz, 2H), 2.50 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.45 (s, 3H), 1.04 (s, 9H).

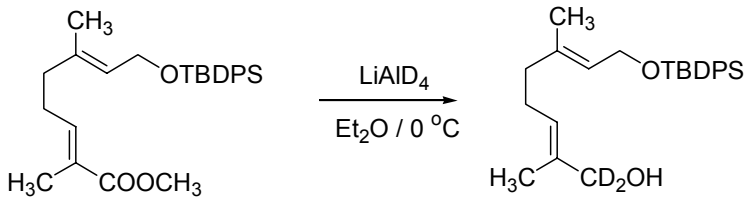
Methyl (2*E*,6*E*)-8-[*t*-butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadienoate[1]



To a solution of crude (*E*)-6-*t*-butyldiphenylsilyloxy-4-methyl-4-hexanal (8.2 g, 22.4 mmol) in CH_2Cl_2 (60 mL) were added 10 g (30 mmol) of the freshly prepared stabilized ylide methyl (triphenylphosphoranylidene)propionate. After stirring for 3 hours at room temperature, the solvent was removed under vacuum and the remaining waxy solids were washed 4 times with 30 mL of hexane each time. The hexane was removed under vacuum, and the residue was chromatographed using hexane/ethyl acetate (10/1 ratio), to afford stereoselectively 7.0 g of the α,β-unsaturated ester methyl (2*E*,6*E*)-8-[*t*-butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadienoate in >95% geometrical purity (70% yield for over two steps). ^{1}H NMR: 7.70 (d, J = 6.5 Hz, 4H), 7.36-7.44 (m, 6H), 6.75 (t, J =

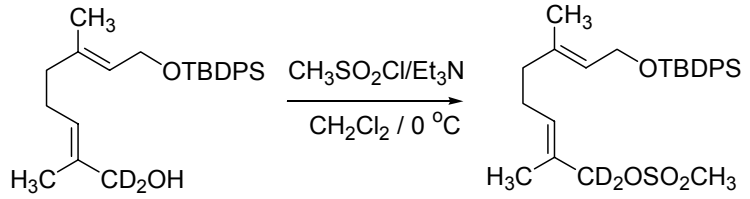
6.5 Hz, 1H), 5.40 (t, J = 6.0 Hz, 1H), 4.23 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H), 2.26 (m, 2H), 2.09 (t, J = 7.5 Hz, 2H), 1.85 (s, 3H), 1.45 (s, 3H), 1.05 (s, 9H). ^{13}C NMR: 168.6, 141.9, 135.9, 135.6, 134.0, 129.5, 127.7, 127.6, 124.8, 61.1, 51.7, 38.0, 27.0, 26.8, 19.2, 16.3, 12.4.

(2*E*,6*E*)-8-[*t*-Butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadien-1-ol–1,1-*d*$_2$



To a slurry of $LiAlD_4$ (0.67 g, 16.0 mmol) in dry diethyl ether (50 ml) were added at 0 ^{o}C, 7.0 g of methyl (2*E*,6*E*)-8-[*t*-butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadienoate (16.1 mmol), under an inert atmosphere. After 30 min the reaction was quenched with water. The ether layer was washed with brine and then dried over $MgSO_4$. The residue was chromatographed (hexane/ethyl acetate 10:1) to afford 4.26 g of (2*E*,6*E*)-8-[*t*-butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadien-1-ol–1,1-*d*$_2$ (65% yield). ^{1}H NMR: 7.71 (d, J = 6.5 Hz, 4H), 7.37-7.45 (m, 6H), 5.40 (t, J = 6.0 Hz, 2H), 4.24 (d, J = 6.0 Hz, 2H), 2.13 (m, 2H), 2.03 (t, J = 7.5 Hz, 2H), 1.68 (s, 3H), 1.46 (s, 3H), 1.06 (s, 9H). ^{13}C NMR: 136.7, 135.6, 134.9, 134.1, 129.5, 127.6, 126.0, 124.3, 124.8, 68.3 (quintet, J = 22 Hz), 61.1, 39.1, 25.9, 19.2, 16.3, 13.7.

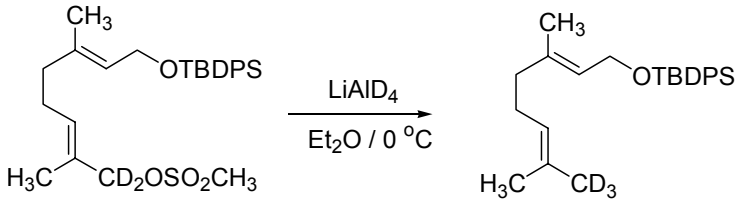
(2*E*,6*E*)-8-[*t*-Butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadienyl-1,1-*d*$_2$ 1-methanesulfonate



To a solution of (2*E*,6*E*)-8-[*t*-butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadien-1-ol-1,1-*d*$_2$ (4.26 g, 10.4 mmol) and triethyl amine (4.4 mL, 31.2 mmol) in 30 mL dry dichloromethane were added dropwise at 0 ^{o}C methanesulfonyl chloride (1.05 mL, 13.5 mmol) under an inert atmoshere. The mixture was stirred 45 min at 0 ^{o}C and then diluted with an aqueous solution of HCl 0.5 N, until pH < 7. The organic layer was dried over $MgSO_4$ and the product was concentrated under reduced pressure to afford 4.66 g (90% yield) of the labile (2*E*,6*E*)-8-[*t*-butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadienyl-1,1-*d*$_2$ 1-methanesulfonate which was used immediately in the next step without purification. ^{1}H NMR: 7.71 (d, J = 6.5 Hz, 4H), 7.37-7.45 (m, 6H), 5.60 (t, J = 6.5 Hz, 1H), 5.39 (t, J =

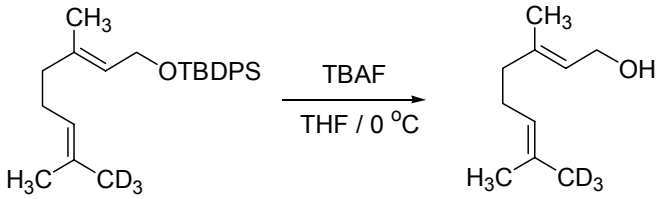
6.0 Hz, 1H), 4.24 (d, J = 6.0 Hz, 2H), 2.97 (s, 3H), 2.17 (m, 2H), 2.04 (t, J = 7.5 Hz, 2H), 1.74 (s, 3H), 1.46 (s, 3H), 1.06 (s, 9H).

(*E*,*E*)-1-*t*-Butyldiphenylsilyloxy-3,7-dimethyl-2,6-octadiene-8,8,8-d_3



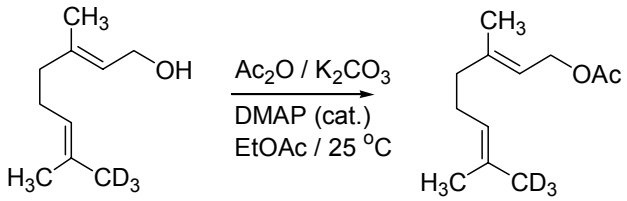
A solution of the crude (2*E*,6*E*)-8-[*t*-butyl(diphenyl)silyl]oxy-2,6-dimethyl-2,6-octadienyl-1,1-d_2 1-methanesulfonate (4.66 g, 9.5 mmol) in dry diethyl ether (5 ml) was added dropwise to a slurry of $LiAlD_4$ (0.24 g, 5.7 mmol) in dry diethyl ether (10 mL) at 0 ^oC, under an inert atmosphere. After 12 h of stirring at room temperature the mixture was quenched with water. The ether layer was washed with brine and dried over $MgSO_4$. The residue was chromatographed (hexane/ethyl acetate 50:1) to afford 2.1 g (56%) of (*E*,*E*)-1-*t*-butyldiphenylsilyloxy-3,7-dimethyl-2,6-octadiene-8,8,8-d_3. ^1H NMR: 7.70 (d, J = 6.5 Hz, 4H), 7.36-7.43 (m, 6H), 5.38 (t, J = 6.5 Hz, 1H), 5.10 (t, J = 6.5 Hz, 1H), 4.23 (d, J = 6.5 Hz, 2H), 2.06 (m, 2H), 1.98 (t, J = 7.0 Hz, 2H), 1.61 (s, 3H), 1.44 (s, 3H), 1.05 (s, 9H). ^{13}C NMR: 137.0, 135.6, 134.1, 129.5, 127.6, 124.1, 124.1, 61.2, 39.5, 26.9, 26.4, 19.2, 17.7, 16.3.

Geraniol-8,8,8-d_3[2]



To a solution of (*E*,*E*)-1-*t*-butyldiphenylsilyloxy-3,7-dimethyl-2,6-octadiene-8,8,8-d_3 (1.4 g, 3.5 mmol) in THF (20 ml) were added dropwise at 0 ^oC 3.9 mL (3.9 mmol) of tetrabutylammonium fluoride (1 M solution in THF). After 3 hours the solution was diluted with diethyl ether, washed with water, and the organic layer was dried over $MgSO_4$. The residue was chromatographed (hexane/ethyl acetate 4:1) to afford 0.5 g of geraniol-8,8,8-d_3 (91% yield) in >95% geometrical purity ^1H NMR: 5.42 (t, J = 6.5 Hz, 1H), 5.09 (t, J = 6.5 Hz, 1H), 4.16 (t, J = 5.5 Hz, 2H), 2.10 (m, 2H), 2.03 (t, J = 7.5 Hz, 2H), 1.68 (s, 3H), 1.64 (br. s, 1H, -OH), 1.60 (s, 3H). ^{13}C NMR: 139.8, 131.7, 123.9, 123.3, 59.4, 39.5, 26.4, 17.6, 16.3.

Geranyl acetate-8,8,8-d_3



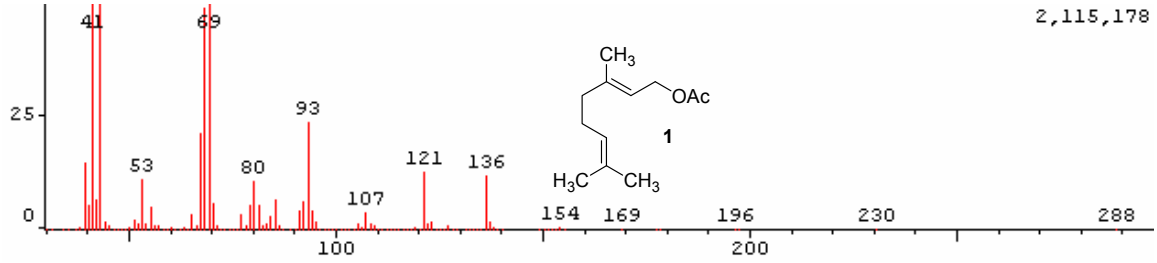
To a solution of geraniol-8,8,8-d_3 (0.18 gr, 1.15 mmol) in ethyl acetate (5 mL) were added 0.23 g of K_2CO_3 (1.7 mmol), acetic anhydride (0.16 mL, 1.7 mmol) and 0.01 g of DMAP. After stirring at 25 ^oC for 1 h, the reaction mixture was filtered and the filtrate was diluted with diethyl ether. The ether layer was washed with saturated aq. $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent afforded 200 mg of pure geranyl acetate-8,8,8-d_3 (87% yield). ^1H NMR: 5.34 (t, J = 7.0 Hz, 1H), 5.08 (t, J = 6.5 Hz, 1H), 4.59 (d, J = 7.0 Hz, 2H), 2.02-2.11 (m, 4H), 2.05 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H). ^{13}C NMR: 171.1, 142.3, 131.8, 123.7, 118.2, 61.4, 39.5, 26.3, 21.1, 17.6, 16.5.

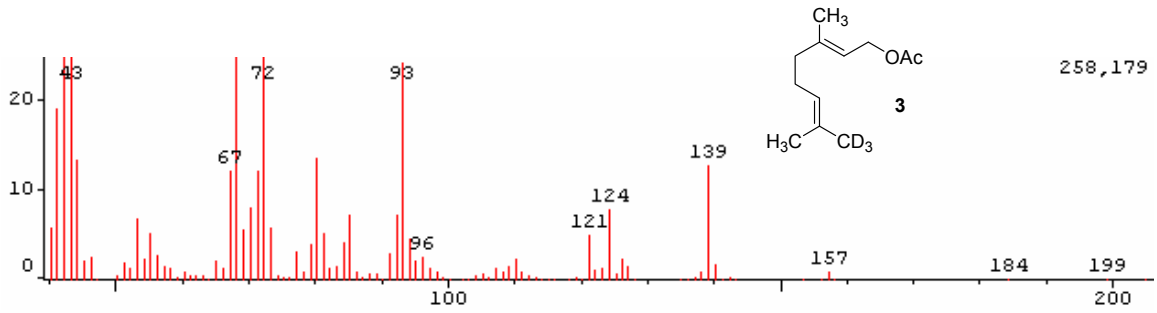
References

[1]. S. Muto, Y. Nishimura, K. Mori, *Eur. J. Org. Chem.* **1999**, 2159.

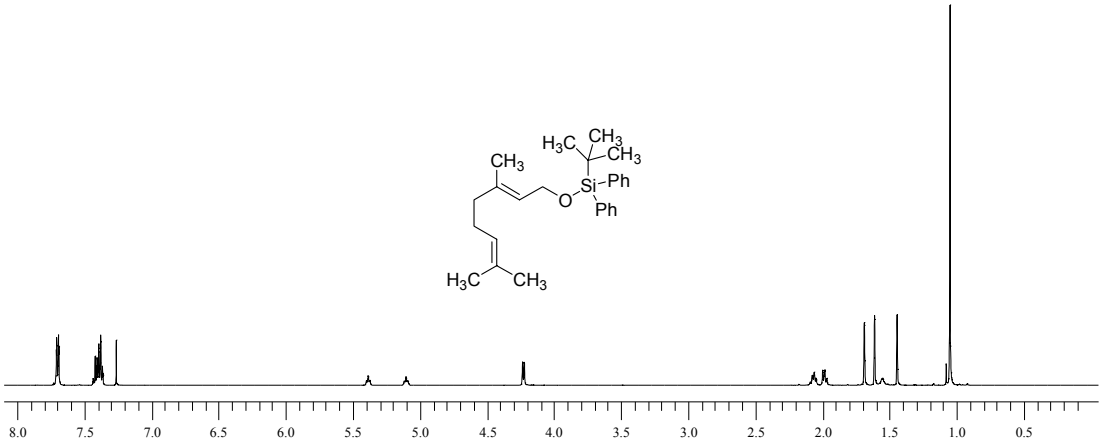
[2] M. L. Wise, H.-J. Pyun, G. Helms, B. Assink, R. M. Coates, R. B. Croteau, *Tetrahedron* **2001**, 57, 5327.

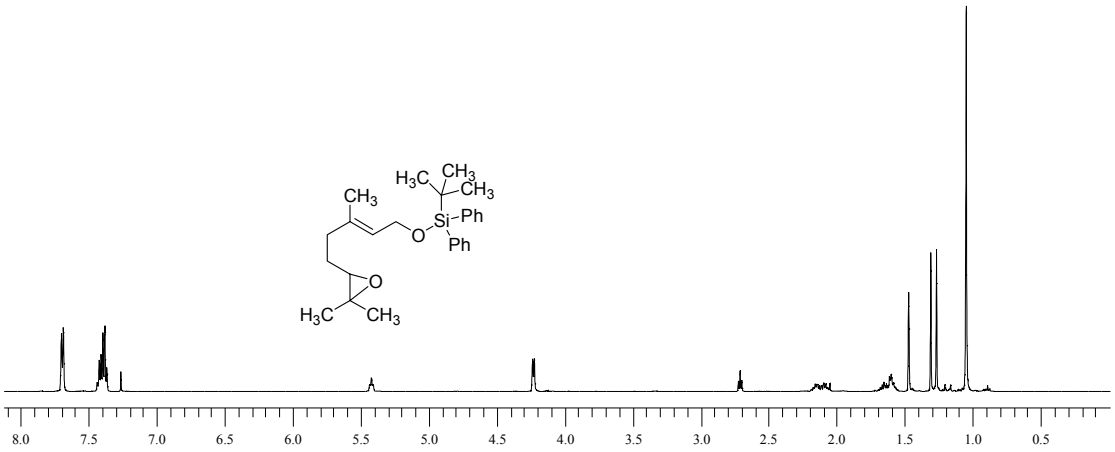
MS spectra of geranyl acetate and geranyl acetate-d_3

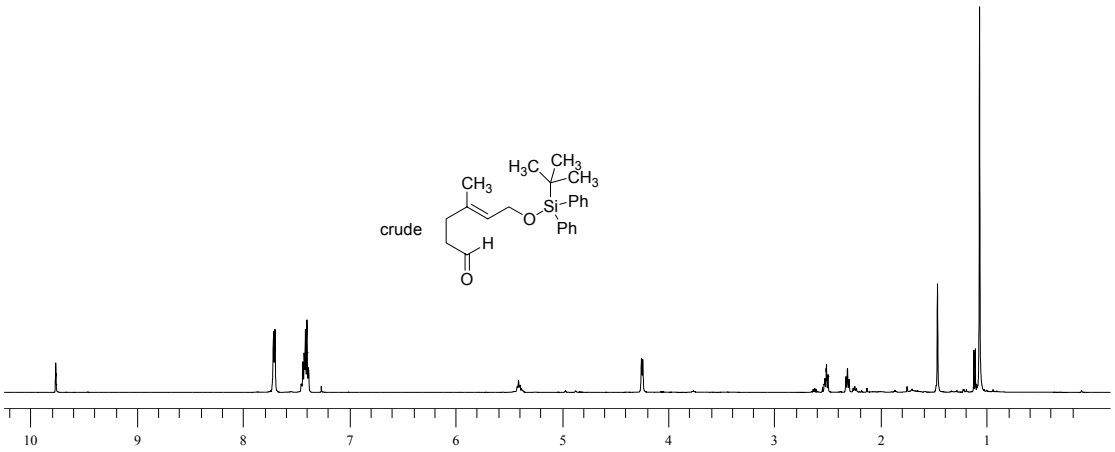


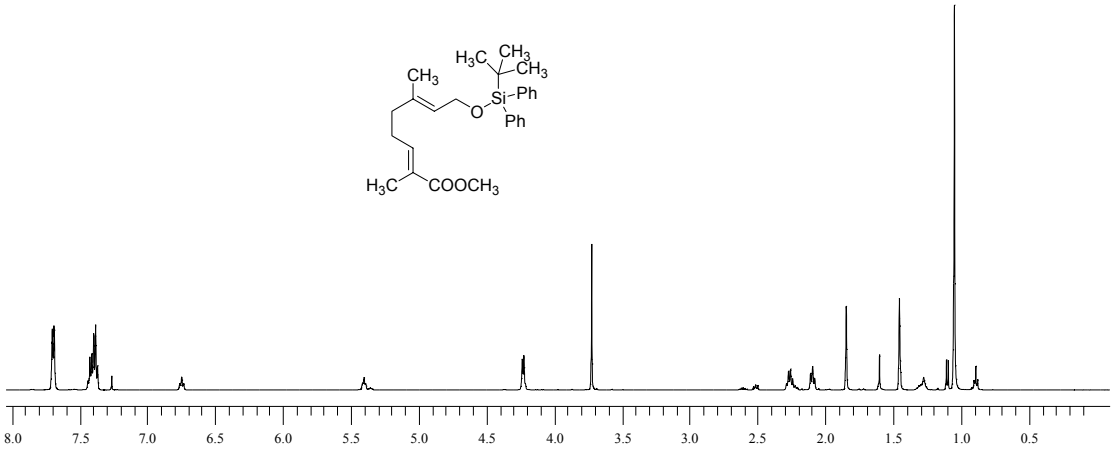


^{1}H and ^{13}C NMR spectra of key compounds and reactions





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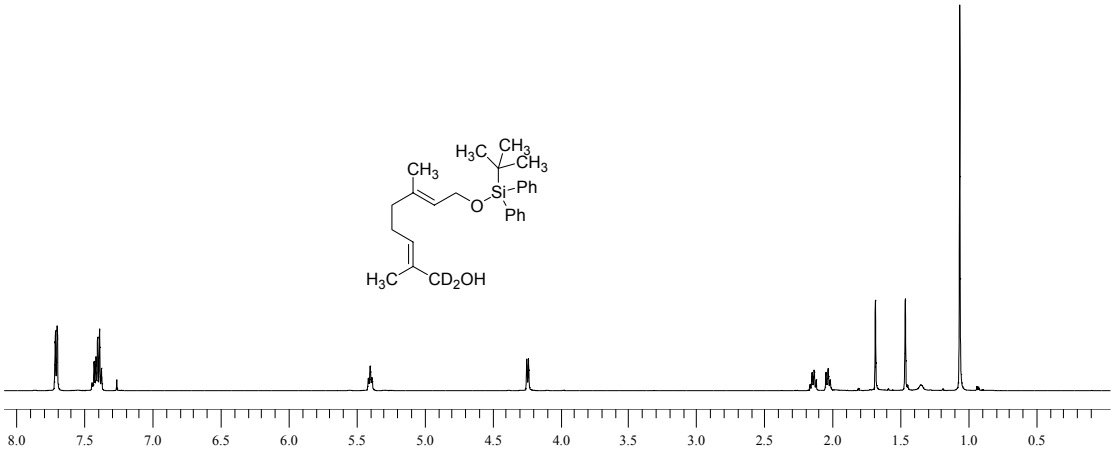
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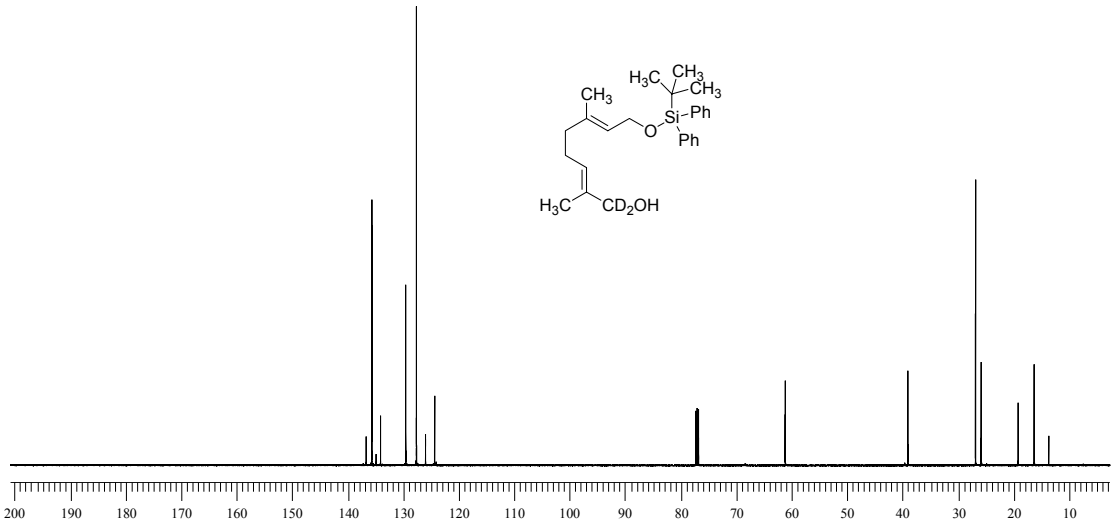
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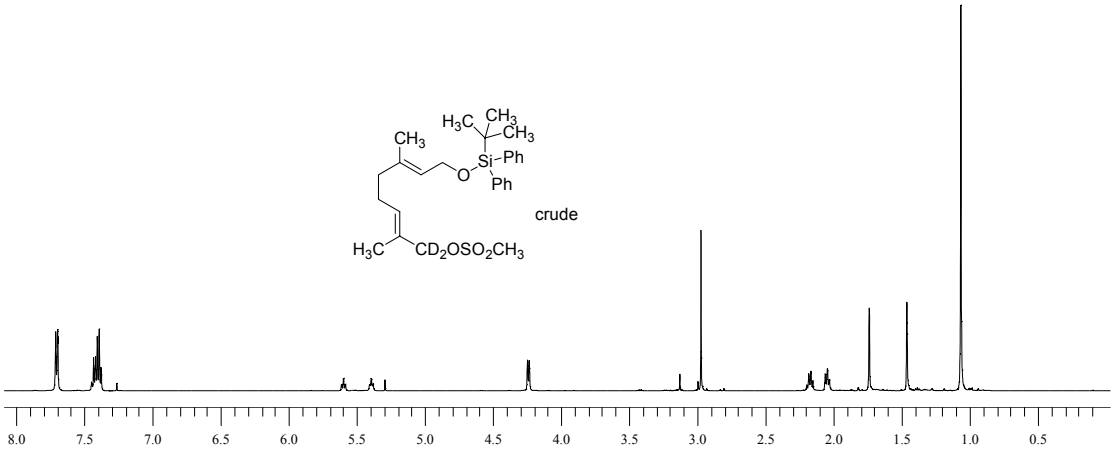
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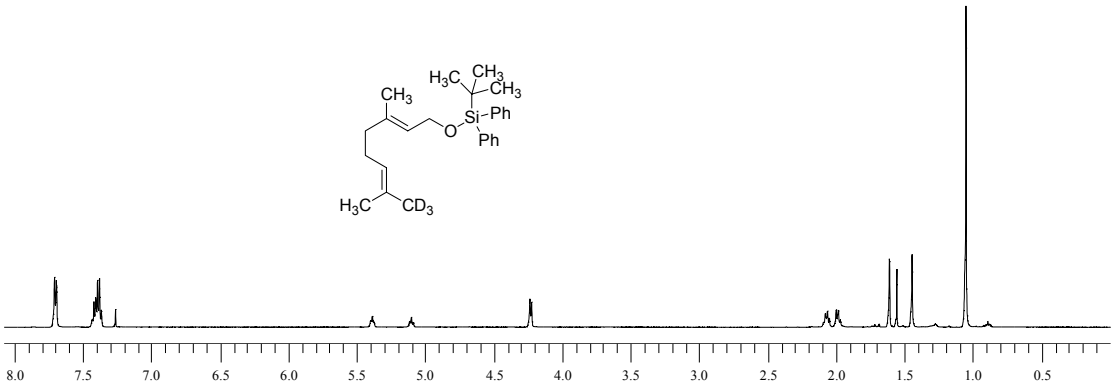
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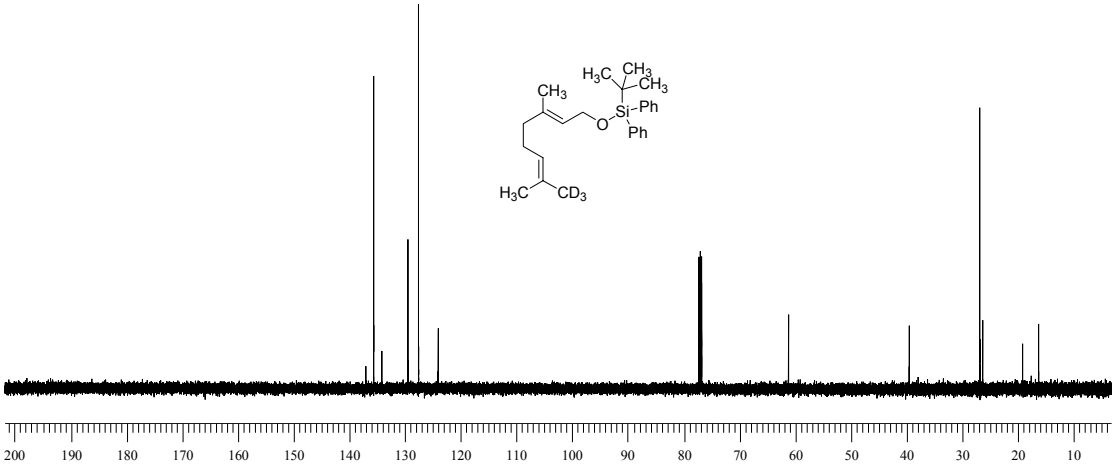
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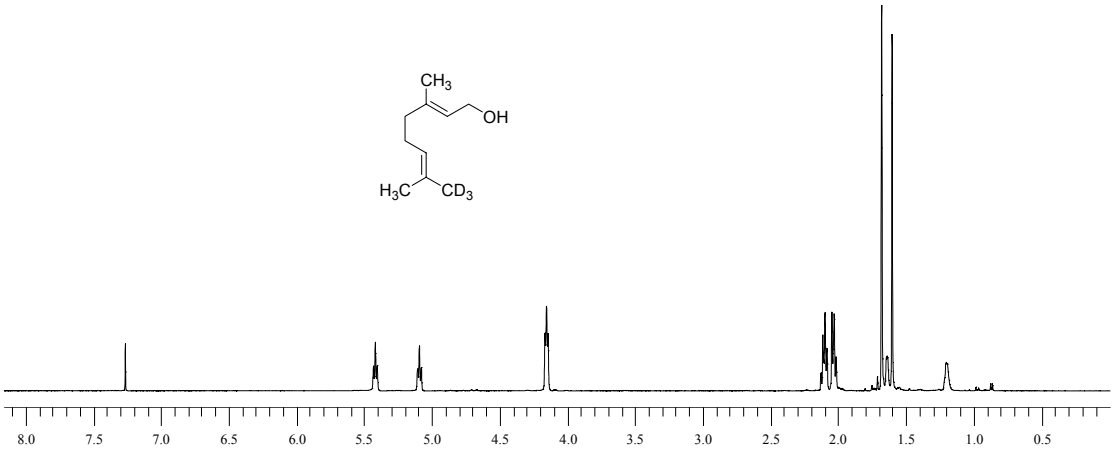
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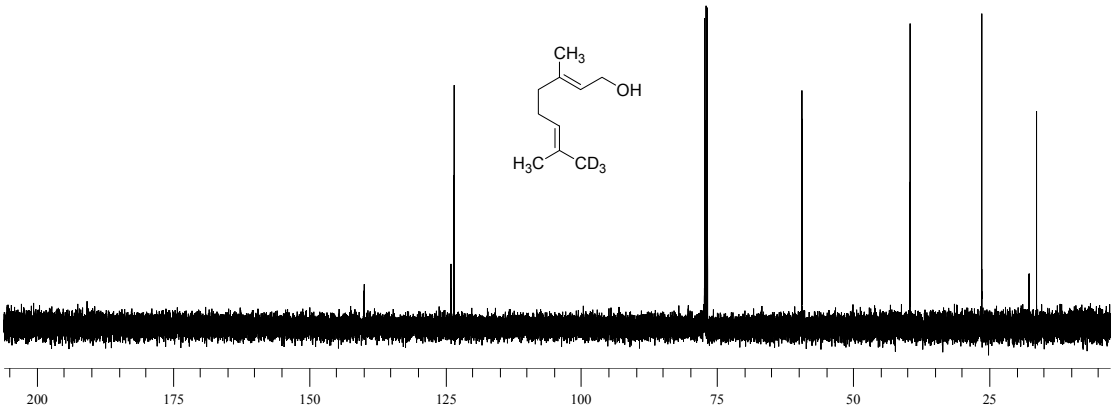
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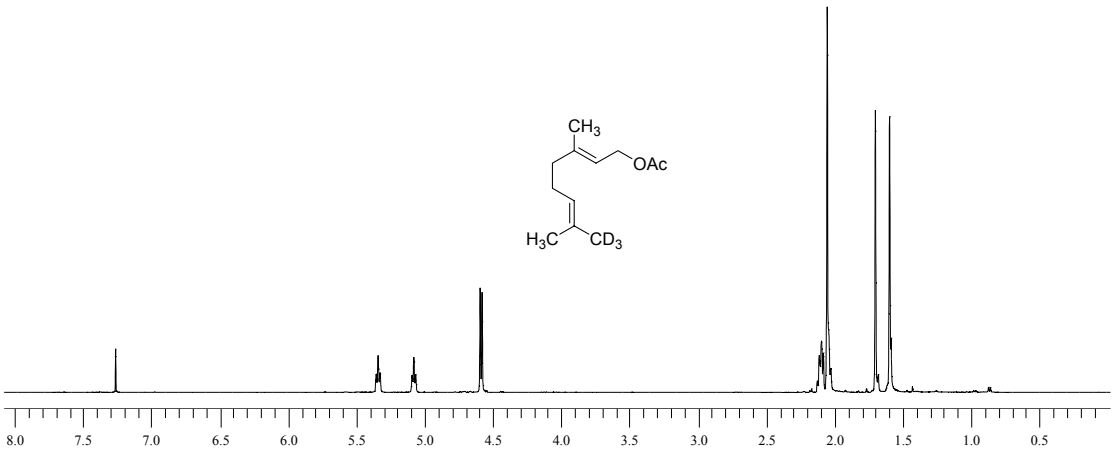
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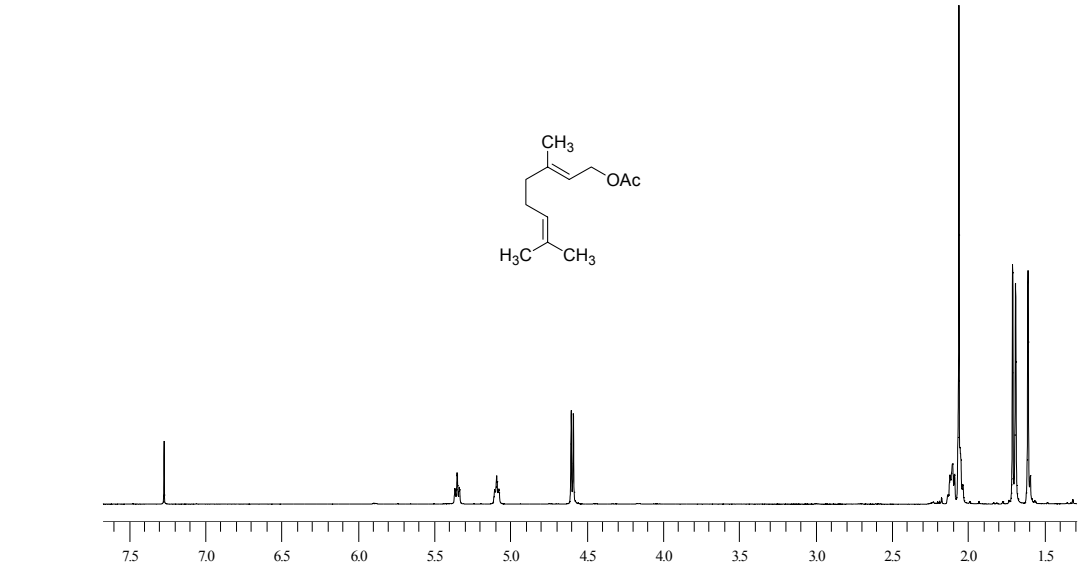
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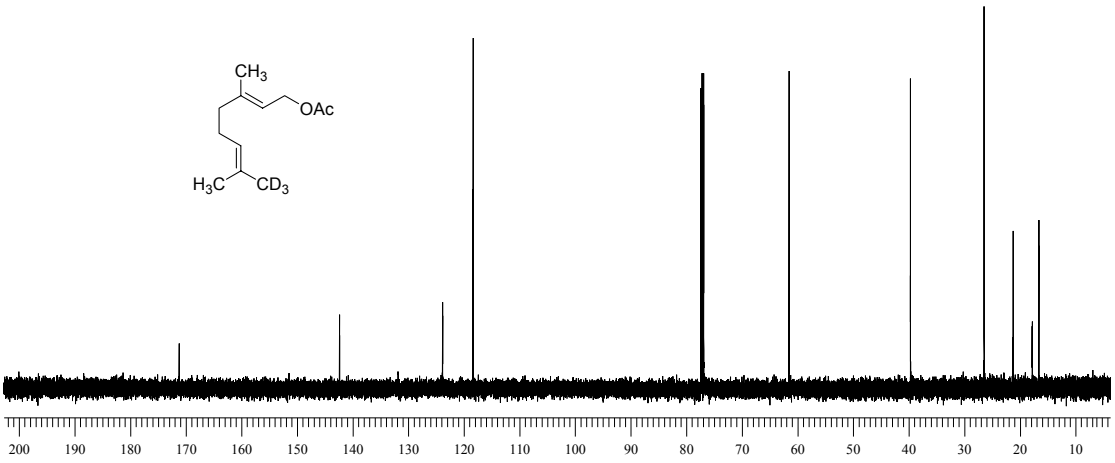
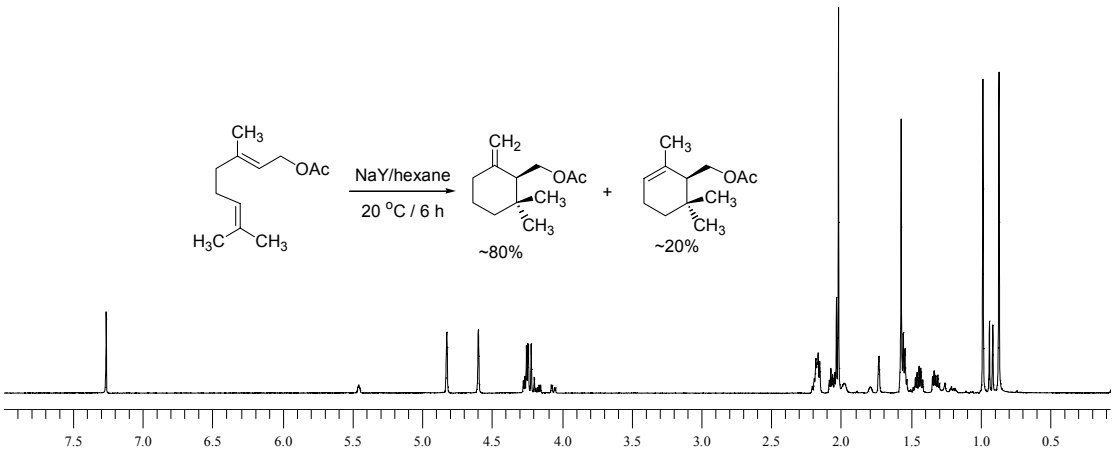
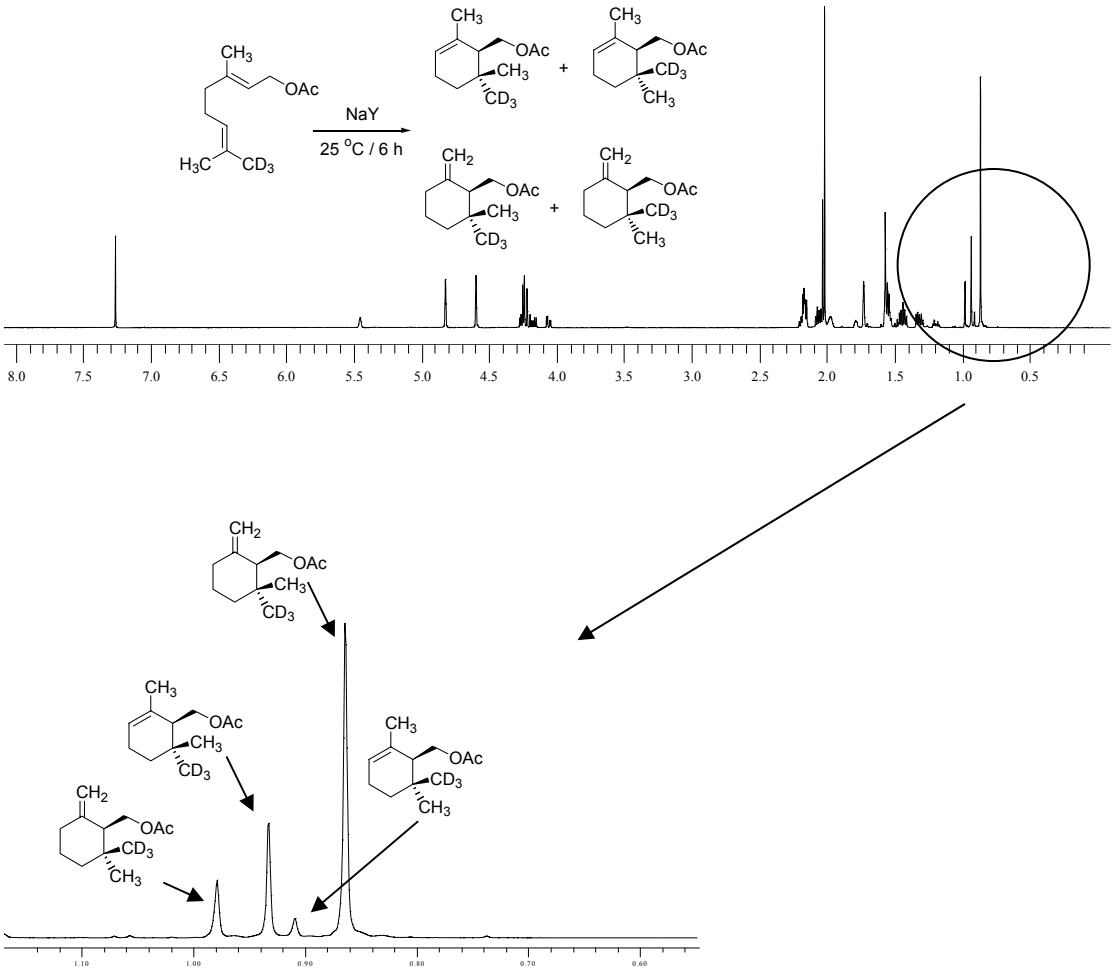
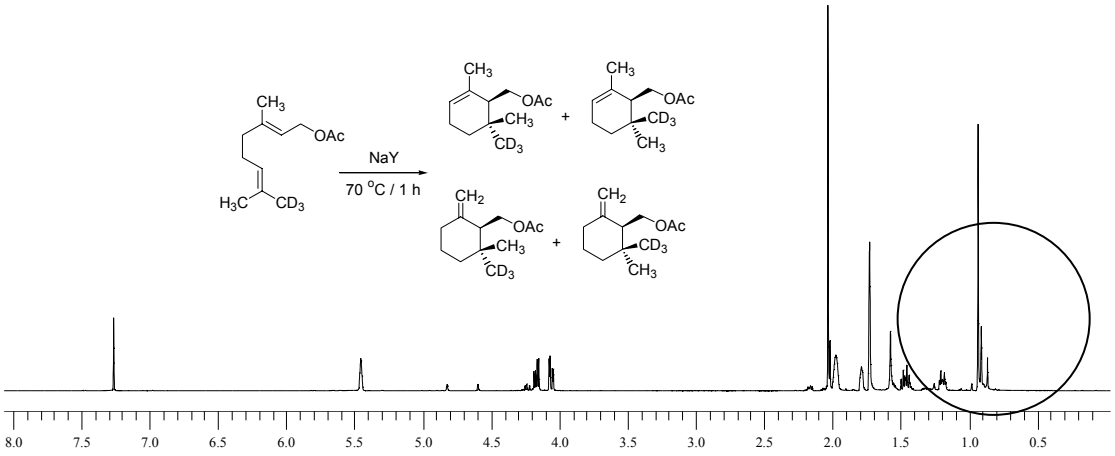
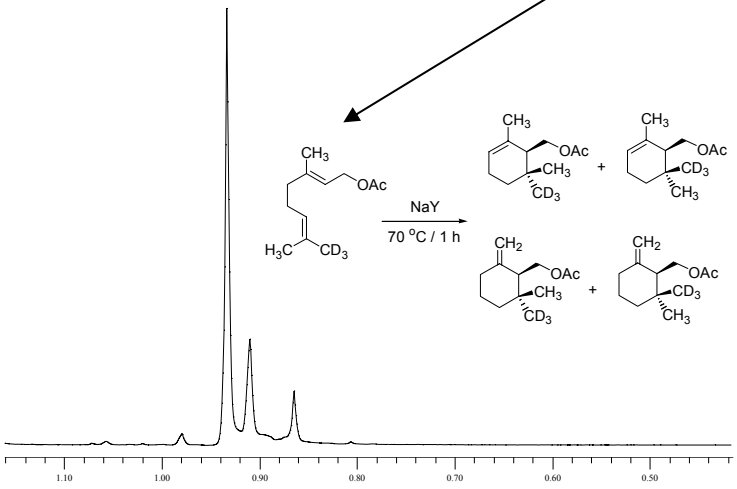
2.5
2.0
1.5

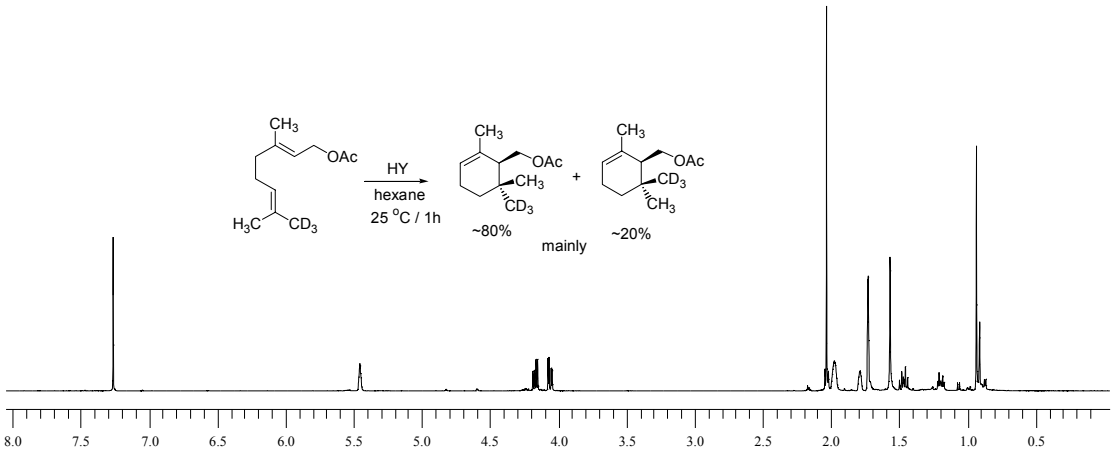

CH3
OAc
H3C
CD3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

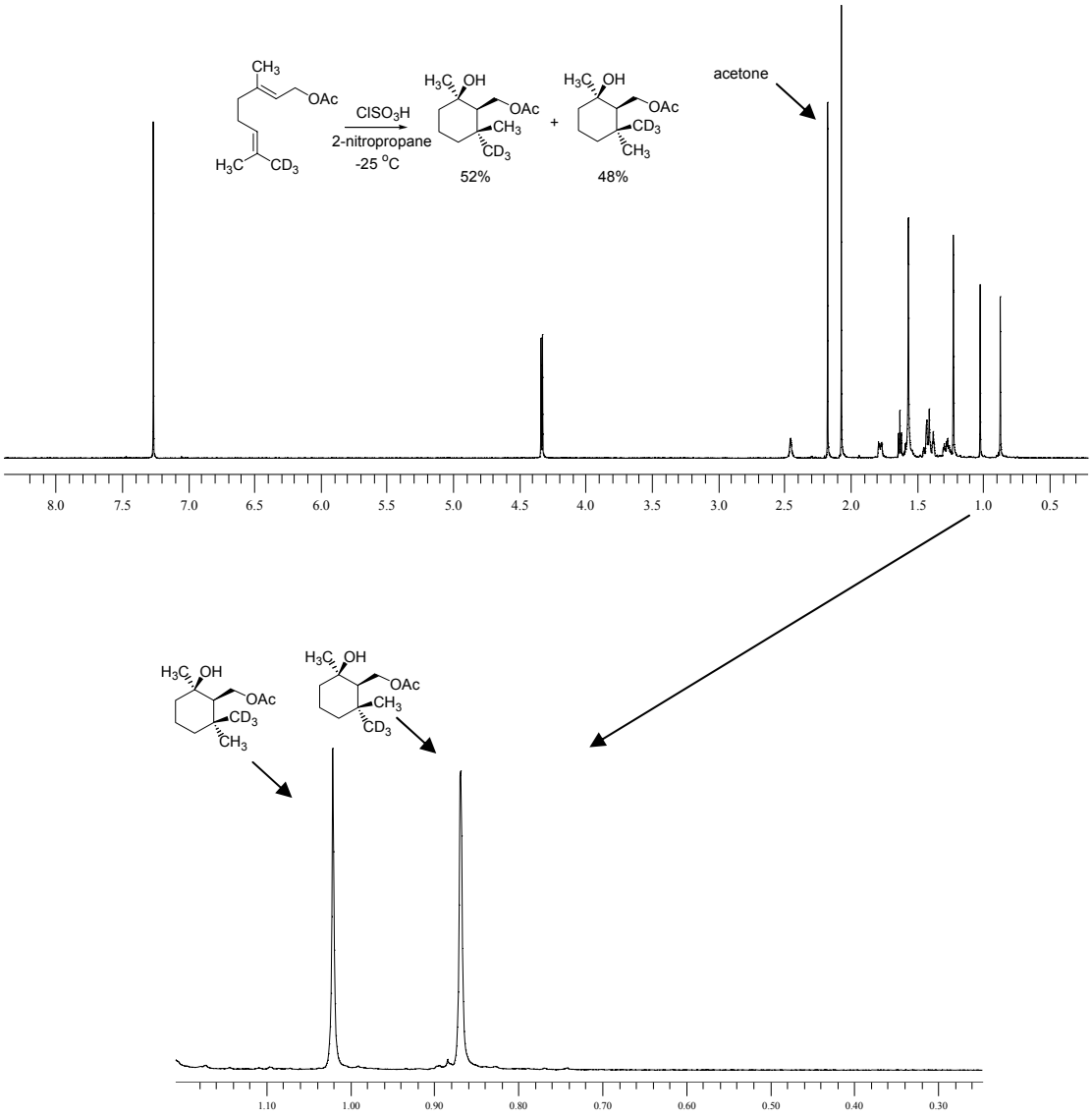

CH3
OAc
H3C
CH3
NaY/hexane
20 °C / 6 h
CH2
OAc
CH3
CH3
~80%
+
CH3
OAc
CH3
CH3
~20%
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


CH3
OAc
H3C
CD3
NaY
25 °C / 6 h
CH2
CH3
CD3
+
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
1.5
1.0
0.5
1.10
1.00
0.90
0.80
0.70
0.60


NaY
70 °C / 1 h
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 1.5 1.0 0.5

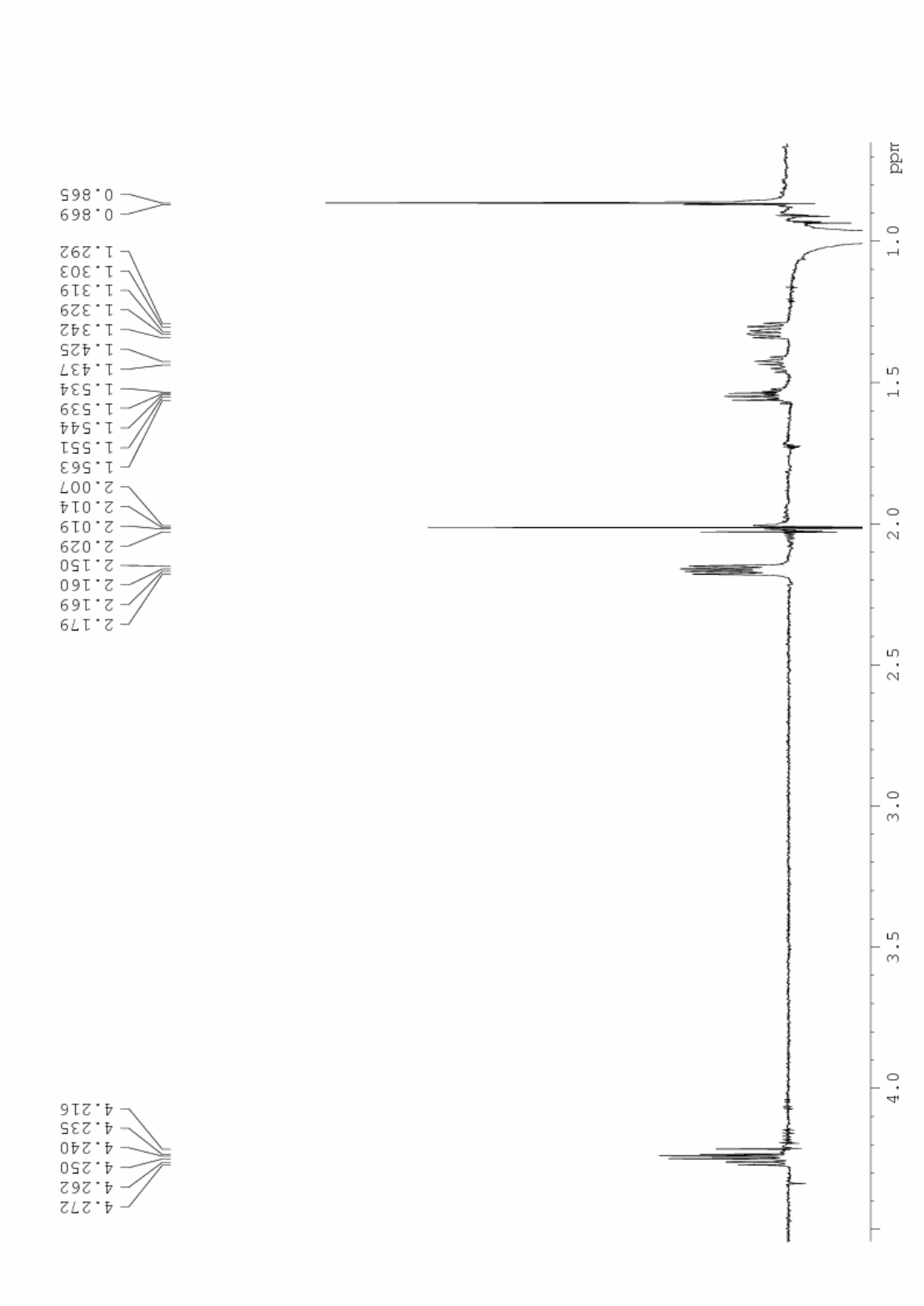

NaY
70 °C / 1 h
1.10 1.00 0.90 0.80 0.70 0.60 0.50


HY
hexane
25 °C / 1h
~80%
mainly
~20%
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 1.5 1.0 0.5

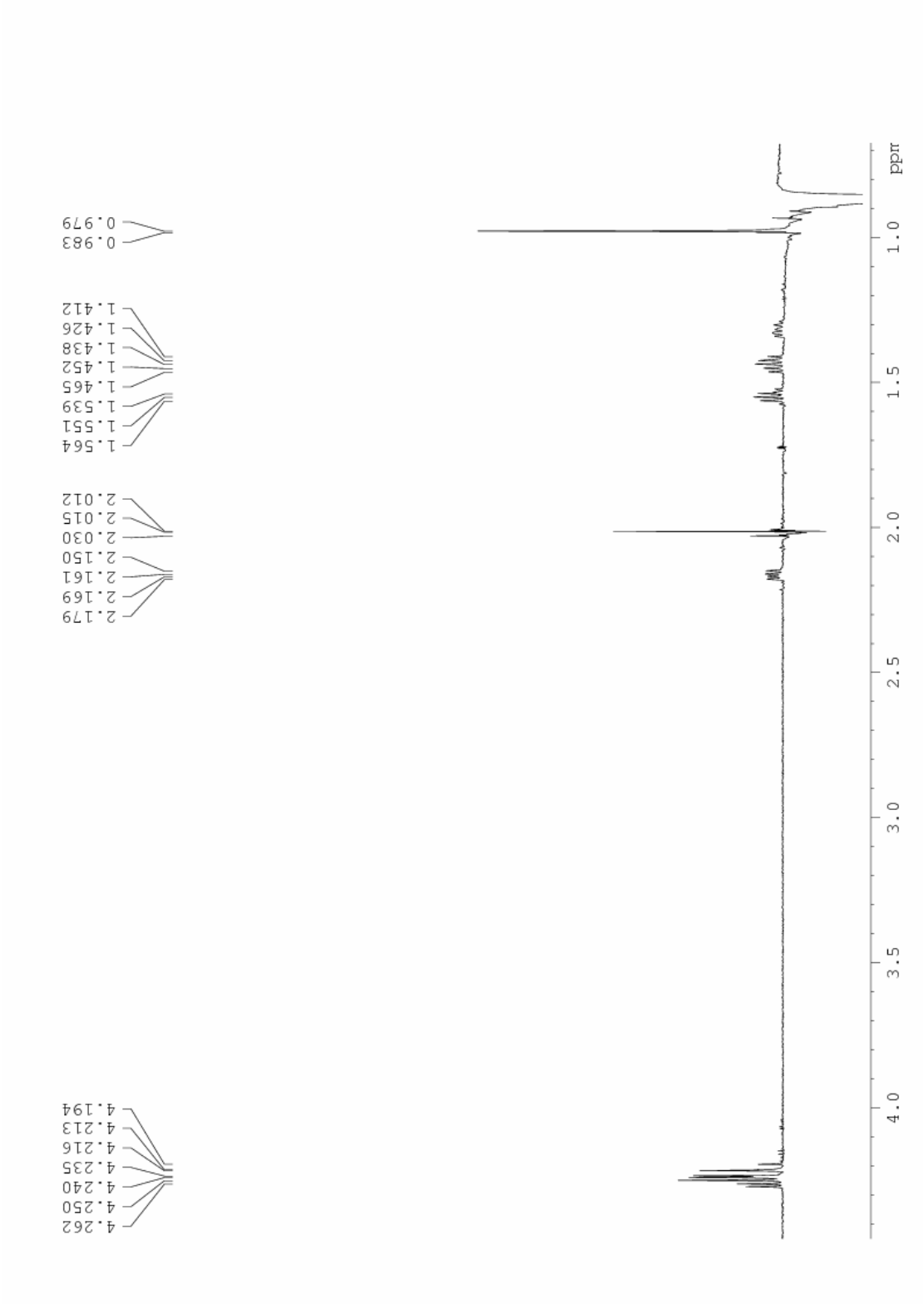

CH3
OAc
H3C
CD3
ClSO3H
2-nitropropane
-25 °C
H3C OH
OAc
CH3
CD3
52%
+
H3C OH
OAc
CD3
CH3
48%
acetone
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
H3C OH
OAc
CD3
CH3
H3C OH
OAc
CH3
CD3
1.10
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30

nOe experiments on γ- and α-cyclogeranyl acetate

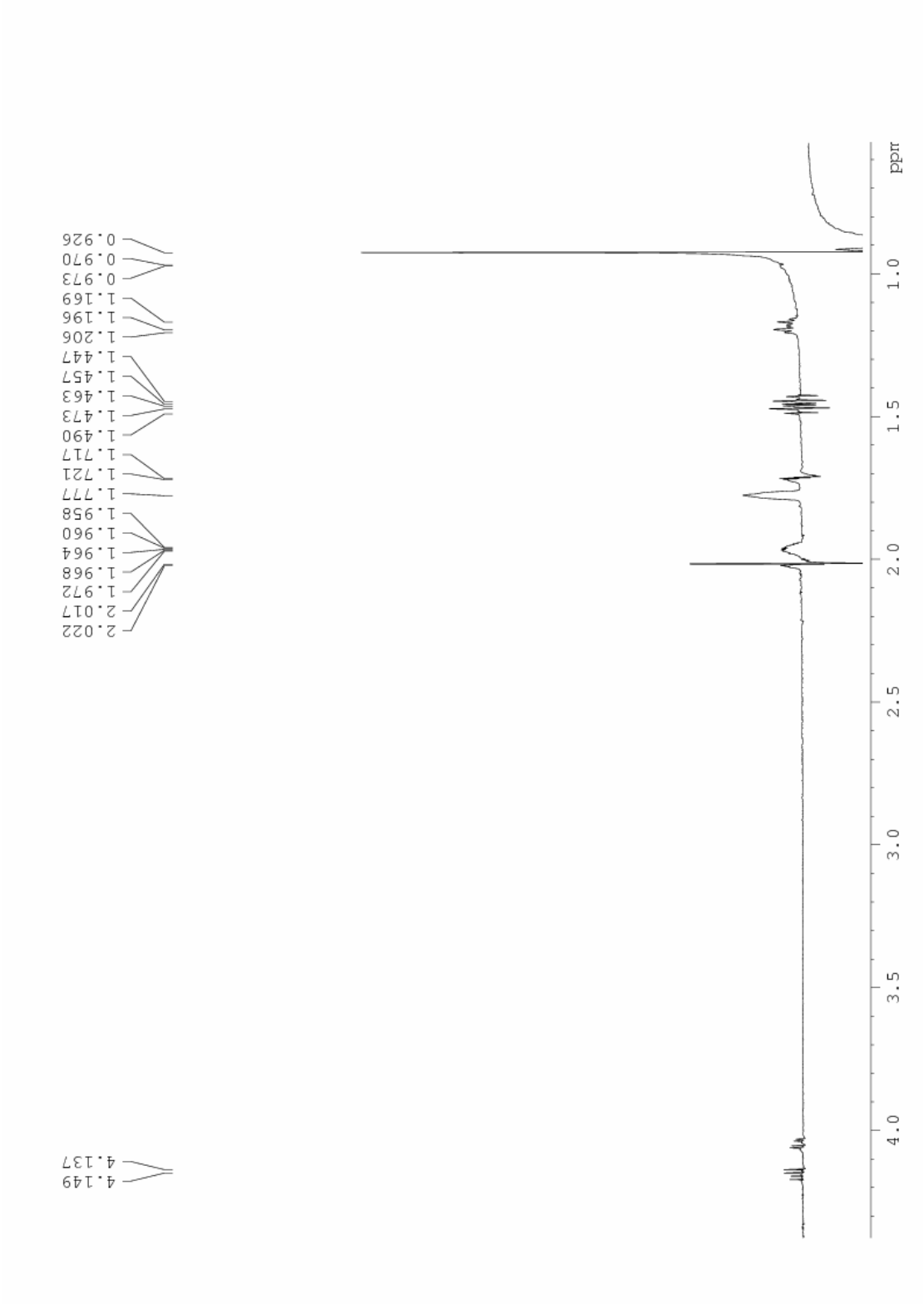
Irradiation of the *gem*-methyl group of γ-cyclogeranyl acetate (**1a**) resonating at 0.99 ppm, which shows significant signal enhancement of the tertiary allylic H atom at 2.17 ppm.



Irradiation of the *gem*-methyl group of γ-cyclogeranyl acetate (**1a**) resonating at 0.87 ppm, which shows lower signal enhancement of the tertiary allylic hydrogen atom at 2.17 ppm.



Irradiation of the *gem*-methyl group of α-cyclogeranyl acetate (**1b**) resonating at 0.92 ppm, which shows significant signal enhancement of the tertiary allylic H atom at 1.72 ppm.



Irradiation of the *gem*-methyl group of α-cyclogeranyl acetate (**1b**) resonating at 0.94 ppm which shows moderate signal enhancement of the tertiary allylic H atom at 1.72 ppm.